4/24/24

Buprenorphine for OUD and Pain

Megan Buresh, MD, DFASAM, AAHIVM
Assistant Professor, Division of Addiction Medicine

Learning Objectives

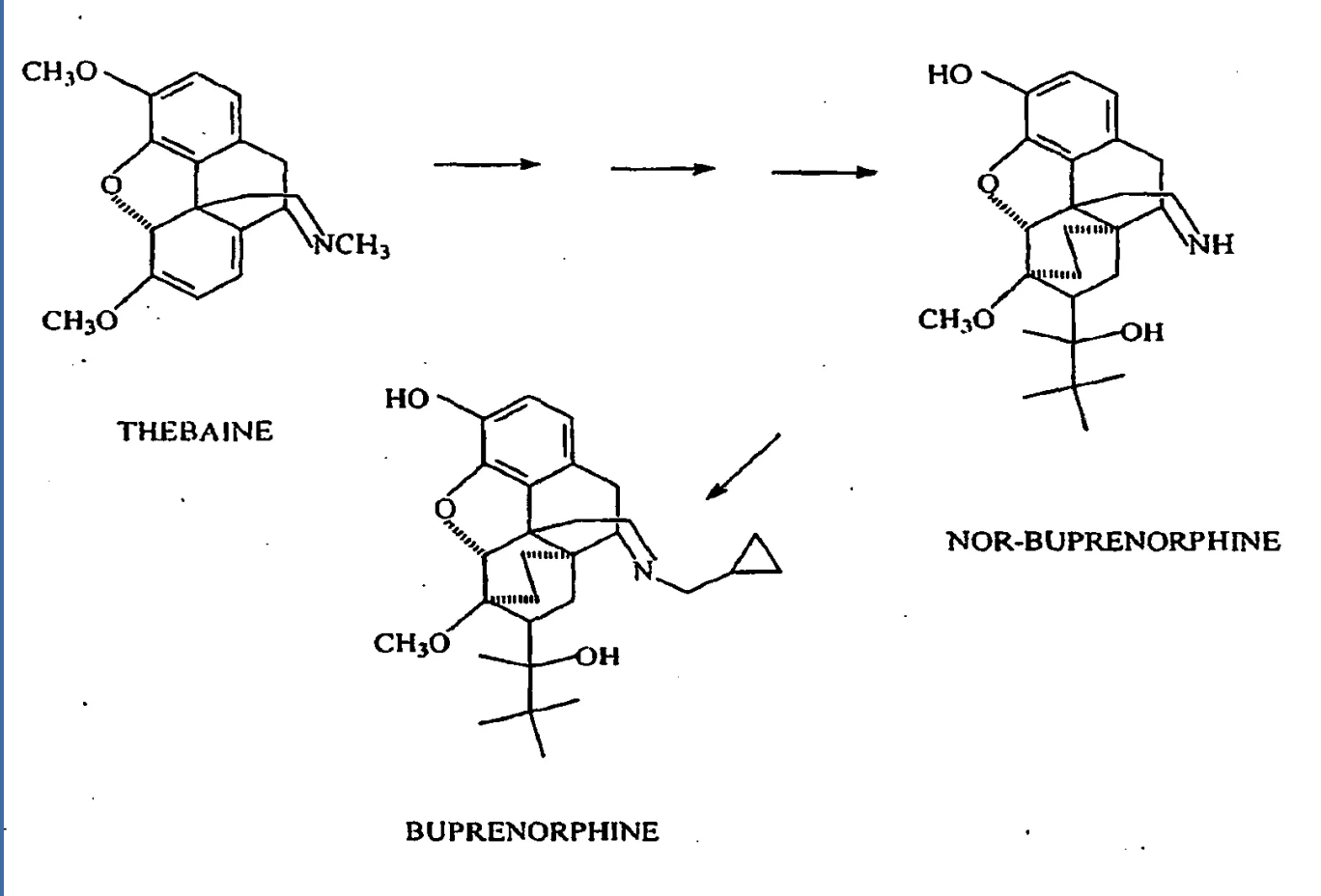
- To understand pharmacology of buprenorphine
- To understand updates in U.S. regulations for prescribing buprenorphine
- To use buprenorphine for both OUD and chronic pain

Financial Disclosures/Unapproved Use

- I have no financial relationships with a commercial entity that is relevant to the content of this presentation.
- I will not reference unlabeled or unapproved uses of drugs or other products.

HISTORY AND PHARMACOLOGY OF BUPRENORPHINE

Buprenorphine



Buprenorphine: History

- 1966: Developed by Reckitt & Colman
- 1978: First marketed in UK
- 1995: First sublingual version developed
- 2000: DATA
- 2002: Suboxone and Subutex approved.
- 2003: RCT - Fudala PJ et al. NEJM.
- 2022 – Elimination of X-waiver

Who can prescribe buprenorphine?

- Since Dec. 2022, ALL prescribers with DEA license can now prescribe buprenorphine for OUD
- There was never X-waiver requirement for buprenorphine formulations approved for pain

thebmj

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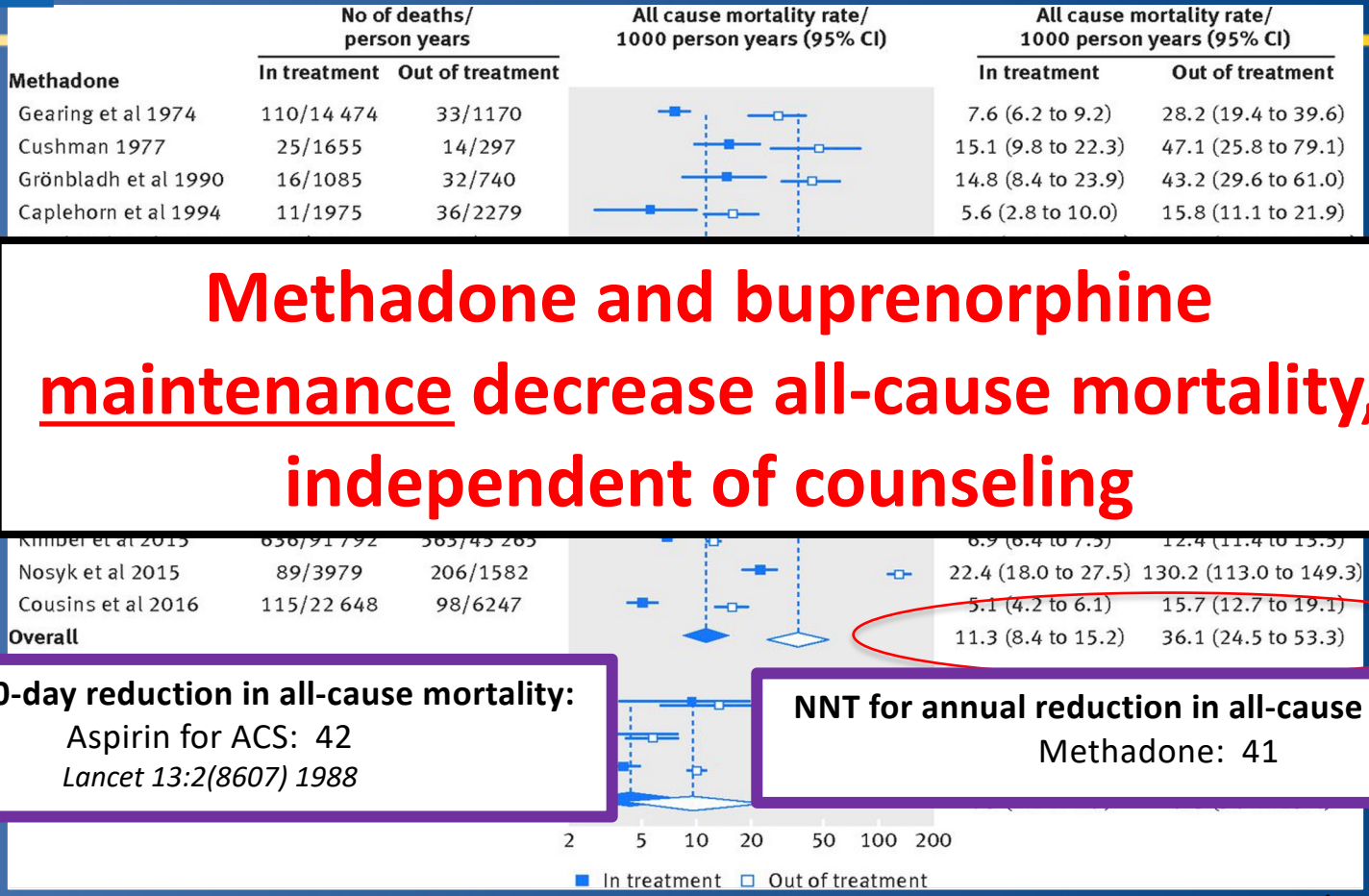


Methadone and buprenorphine maintenance decrease all-cause mortality, independent of counseling

NNT for 30-day reduction in all-cause mortality:
Aspirin for ACS: 42
Lancet 13:2(8607) 1988

NNT for annual reduction in all-cause mortality:
Methadone: 41

Sordo et al. BMJ 20

Buprenorphine:
Available formulations

For opioid use disorder:

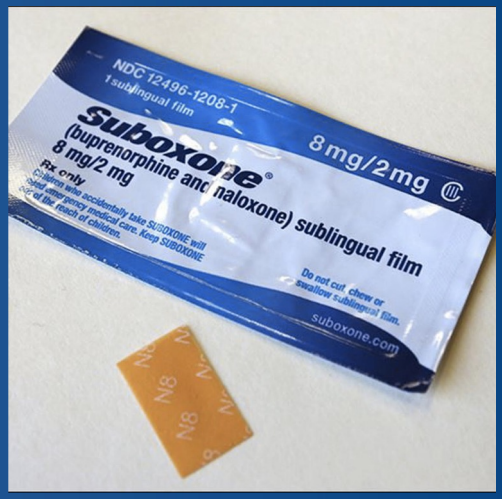
1. Sublingual tablet (buprenorphine & bup/naloxone)
2. Sublingual film (Suboxone)
3. Rapidly dissolving, high-bioavailability tablet (Zubsolv)
4. Buccal film (Bunavail)
5. Implant (Probuphine)
6. Long-acting injectable (Sublocade, Brixadi)

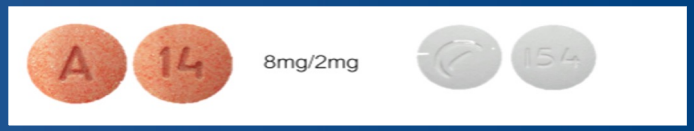
For pain:

1. Injectable (Buprenex)
2. Transdermal (Butrans)
3. Buccal film (Belbuca)

What is buprenorphine?

1. Long-acting opioid
2. Partial agonist: extremely low chance of overdose from bup alone
3. High affinity for mu-opioid receptor: *displaces other opioids!*
   - *Buprenorphine can precipitate withdrawal*
   - Higher risk with fentanyl





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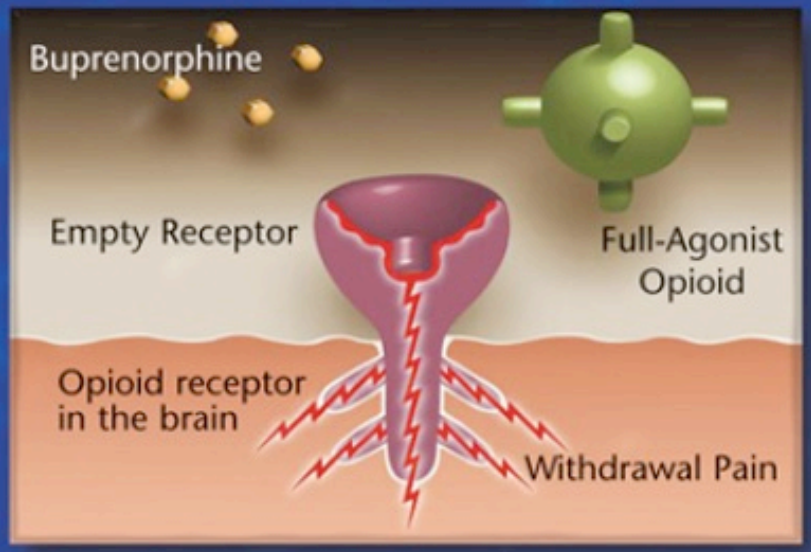
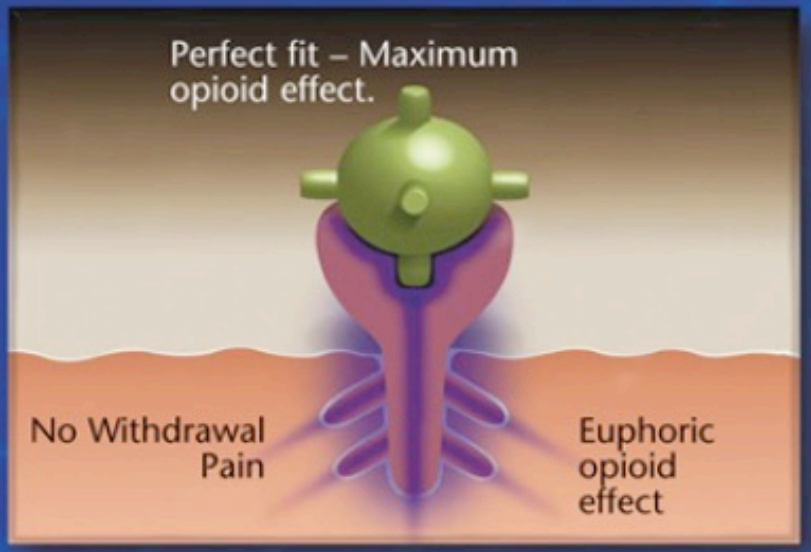
How Buprenorphine Works



Opioid receptor is empty. As someone becomes ***tolerant*** to opioids, they become less sensitive and require more opioids to produce the same effect. Whenever there is an insufficient amount of opioid receptors activated, the patient feels discomfort. This happens in withdrawal.



Opioid receptor filled with a full-agonist. The strong opioid effect of heroin and painkillers can cause euphoria and stop the withdrawal for a period of time (4-24 hours). The brain begins to crave opioids, sometimes to the point of an uncontrollable compulsion (addiction), and the cycle repeats and escalates.

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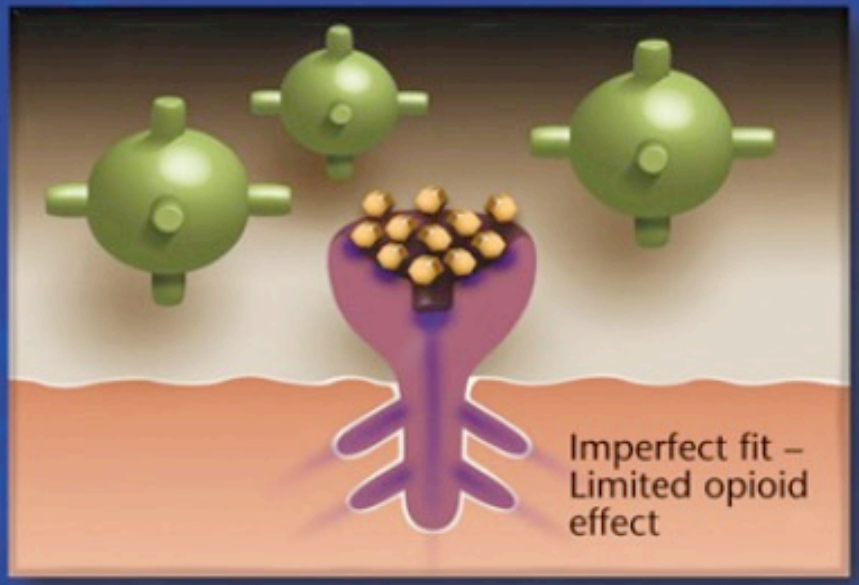
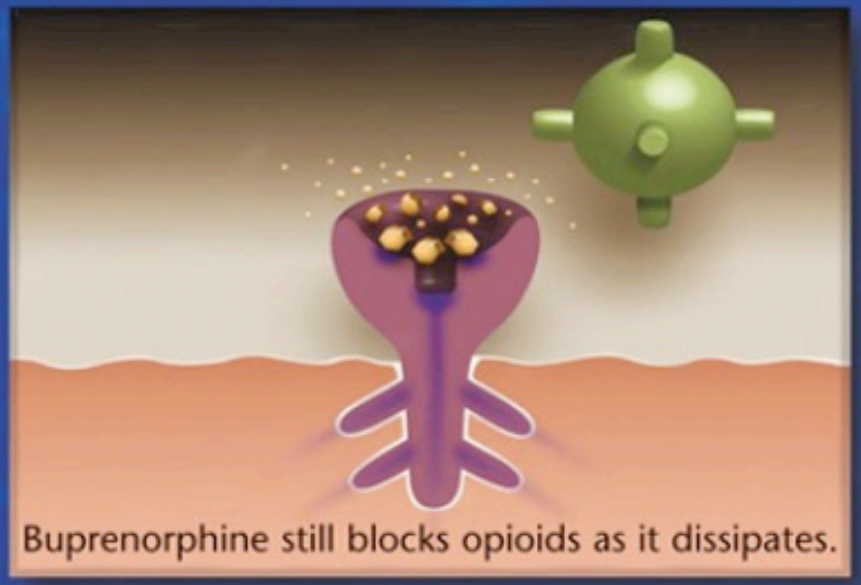
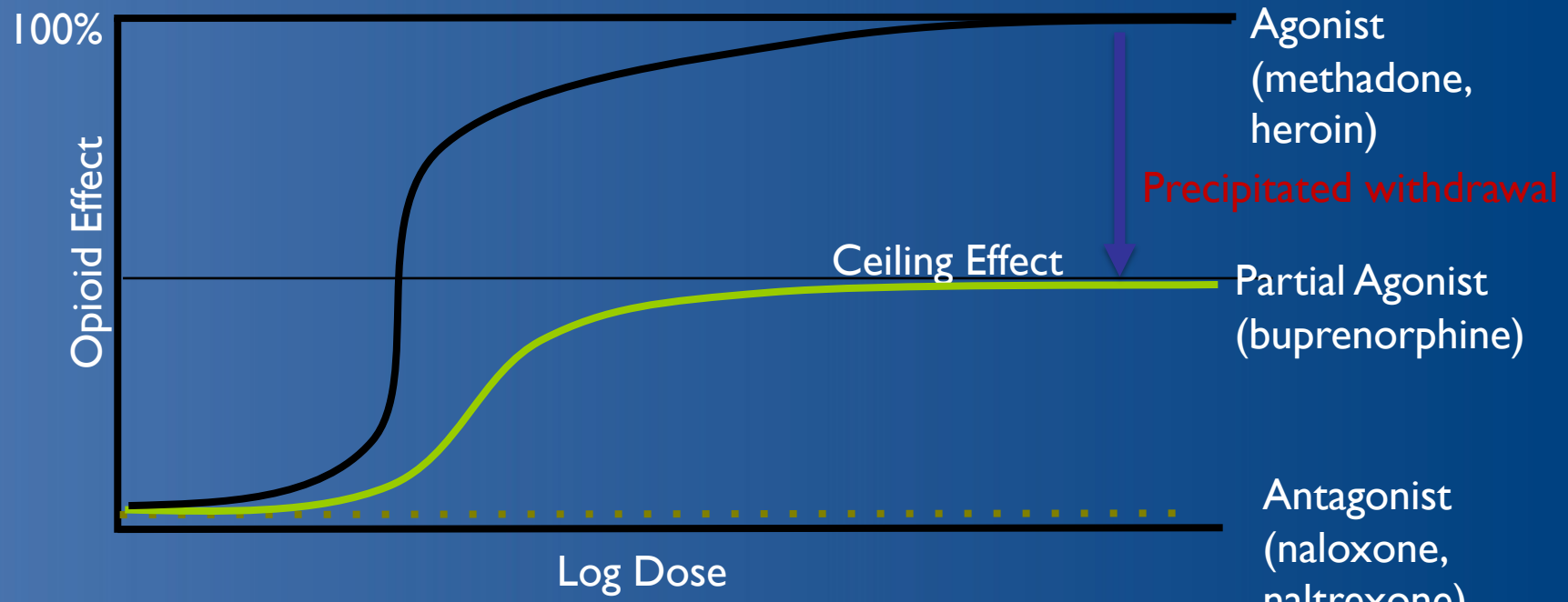


Opioids replaced and blocked by buprenorphine. Buprenorphine competes with the full agonist opioids for the receptor. Since buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect, enough to stop withdrawal but not enough to cause intense euphoria.



Over time (24-72 hours) buprenorphine dissipates, but still creates a limited opioid effect (enough to prevent withdrawal) and continues to block other opioids from attaching to the opioid receptors.

Precipitated withdrawal



Adapted from slide courtesy of Project SHOUT

BUPRENORPHINE AND ACUTE PAIN

Buprenorphine and acute pain

British Journal of Anaesthesia 96 (5): 627–32 (2006)
doi:10.1093/bja/ael051 Advance Access publication March 17, 2006

BJA

Buprenorphine induces ceiling in respiratory depression but not in analgesia

A. Dahan[1]*, A. Yassen[2], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]

[1]*Department of Anesthesiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands.* [2]*Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Gorlaeus Laboratory, Leiden, The Netherlands*

20 volunteers
Received buprenorphine 0.2 mg/70 kg or 0.4 mg/70 kg IV
Measured respirations and pain tolerance afterward

Buprenorphine and acute pain

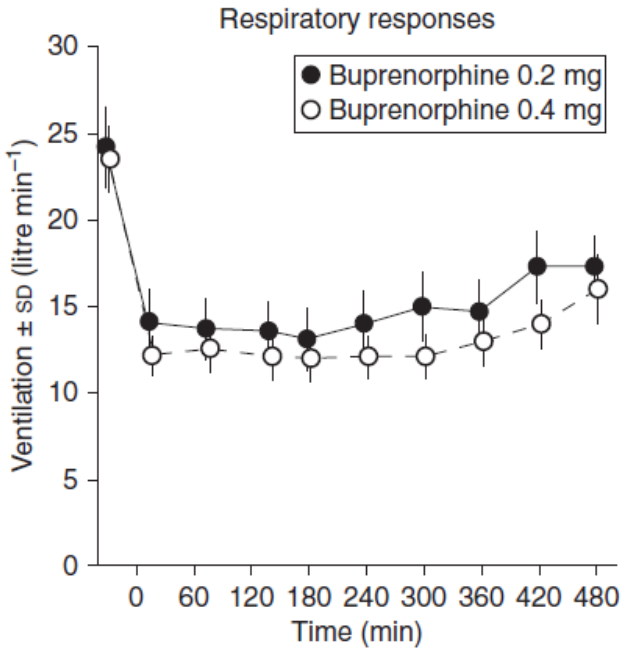


Fig 1 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on inspired minute ventilation at a fixed end-tidal P_{CO_2} of 7 kPa in healthy volunteers. The influence of the two buprenorphine doses is similar with respect to peak respiratory depression and duration of effect.

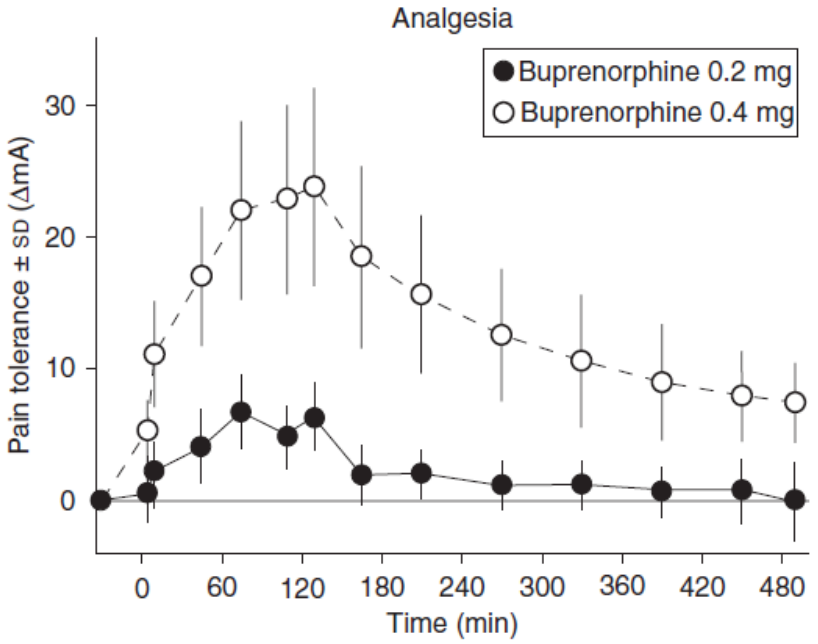


Fig 2 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on pain tolerance in healthy volunteers. Values are the increase in currents to achieve pain tolerance relative to baseline pain tolerance currents (ΔmA). A significant increase in analgesia is observed going from buprenorphine 0.2 to 0.4 mg.

BUPRENORPHINE FOR OUD AND CO-MORBID PAIN

Case 1

- Mr. S, 65M with OUD on SL buprenorphine is admitted to hospital for TKR and home buprenorphine dose is continued.
- Surgery goes well and patient is discharged to post-acute care unit of your SNF on POD#3. RN contacts you that his pain is uncontrolled. Chart review shows pt is receiving acetaminophen 1000mg Q8hrs and ibuprofen 800mg PO Q8hrs.
- **How do you manage his acute pain?**
  A. Continue current medications – buprenorphine should control his pain
  B. Add oxycodone 5mg PO Q8hrs
  C. Add oxycodone 10-15mg PO Q4hrs prn for pain
  D. Start MS Contin for long-acting relief

Principles of Pain Management for Patients with OUD

- Higher opioid tolerance → will need higher doses of short-acting opioids
- Baseline buprenorphine won't treat acute pain
- For moderate to severe pain, will likely need short-acting full agonist opioids
- Acknowledge stigma and practice patient-centered care

Management of Mild Pain

- Start with non-opioid analgesics (e.g., NSAIDs, acetaminophen) and multimodal therapy
- Buprenorphine:
  - consider splitting buprenorphine dose into Q6-8 hour dosing (ex. 4-8mg SL Q6 hours)
  - Can increase total daily dose up to 32mg for better pain coverage

Management of Moderate to Severe Pain

1) Add **one** short-acting full agonist opioid (e.g., oxycodone or hydromorphone) for breakthrough pain. Given underlying tolerance, higher doses will be required compared to opioid-naïve patients (e.g., oxycodone 15-20mg PO instead of 5-10mg or hydromorphone 4mg).
2) Non-opioid analgesia should be maximized (NSAIDs, acetaminophen, lidocaine patches, etc)
3) Some evidence for duloxetine in acute pain[1]
4) Exercise caution with gabapentinoids and other sedating medications (benzos, muscle relaxers)

Yuan et al., 2022.

Buprenorphine and Pain w/OUD
Give more buprenorphine?

Journal of Substance Abuse Treatment 104 (2019) 128–134

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

journal homepage: www.elsevier.com/locate/jsat

Effects of ascending buprenorphine doses on measures of experimental pain: A pilot study

S. Nielsen[a,b,c,*], C. Rivas[c], A. Demirkol[c], N. Lintzeris[c,d,e]

Seven volunteers on buprenorphine 4-16 mg/day
Received usual dose or 150%/200% of usual dose (DB)
Tested for pain threshold and tolerance (cold pressor)

Buprenorphine dose and pain

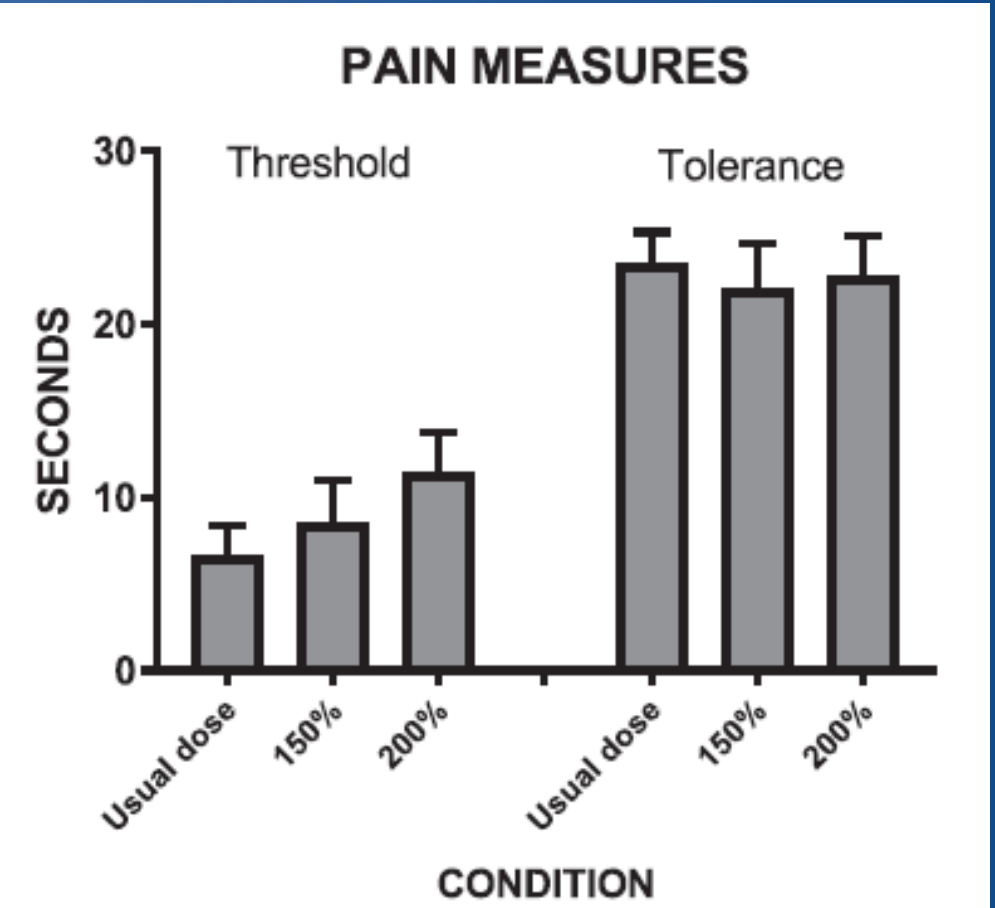


Fig. 2. Effect of buprenorphine dose condition on pain threshold and tolerance. All values represent mean ± SEM.

Acute pain on OAT

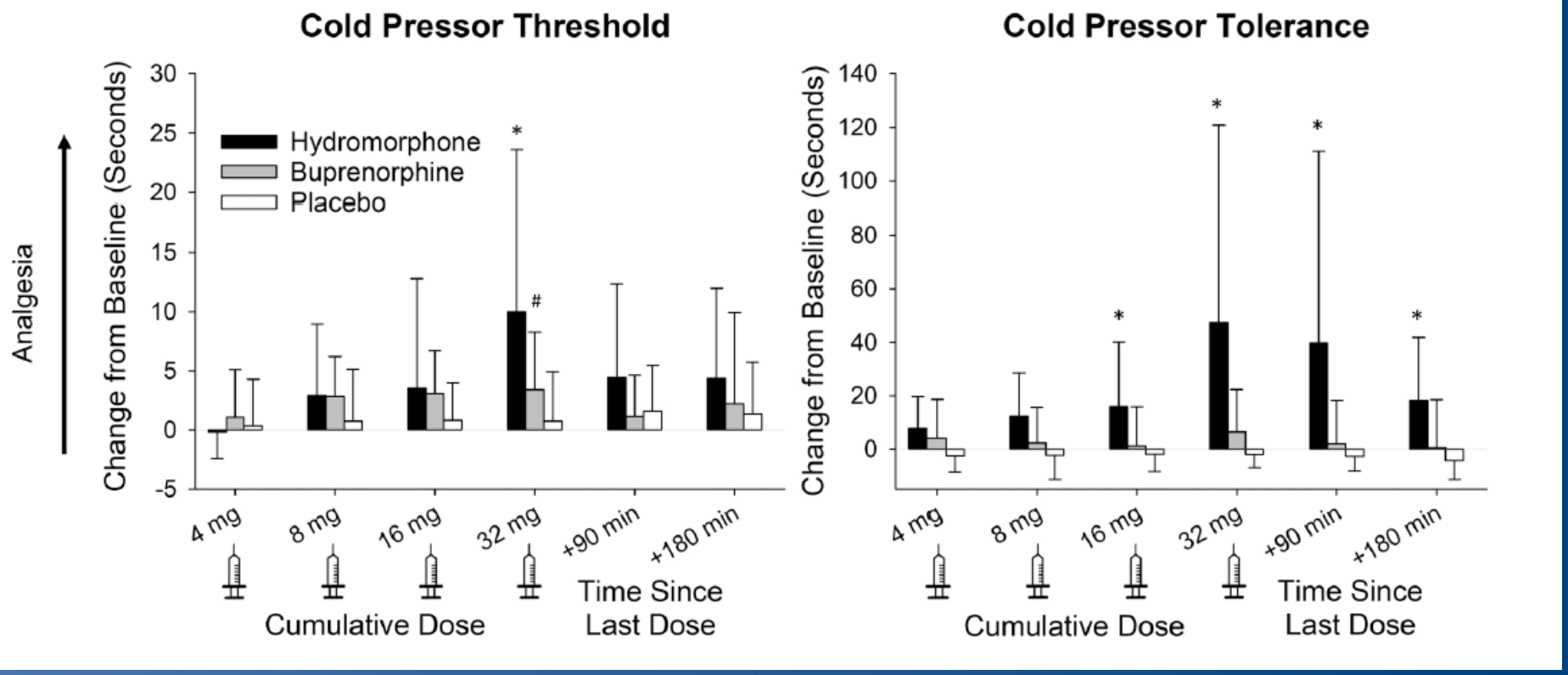
Anesthesiology. 2019 January ; 130(1): 131–141. doi:10.1097/ALN.0000000000002492.

Analgesic Effects of Hydromorphone versus Buprenorphine in Buprenorphine-Maintained Individuals

Andrew S. Huhn[1], **Eric C. Strain**[1], **George E. Bigelow**[1], **Michael T. Smith**[1], **Robert R. Edwards**[2], and **D. Andrew Tompkins**[3]

- 13 subjects on 12-16 mg of buprenorphine daily
- Given 4, 4, 8 and 16 mg of hydromorphone IV or buprenorphine IV 90 minutes apart
- Cold pressor testing done after each dose

Acute Pain on OAT



Buprenorphine and acute pain with OUD: Summary

- For patients on buprenorphine, the best strategy is to continue and add full agonists.
- High doses of full agonists will be needed to have an effect.

Buprenorphine for chronic pain with OUD

Design: Secondary analysis of 12 wk RCT followed by 36 wk open label phase.

Subjects: 81 adults with OUD and mild-moderate chronic pain (out of 159 in study)

Intervention: buprenorphine vs extended release injectable naltrexone

Outcomes: McGill pain questionnaire scores

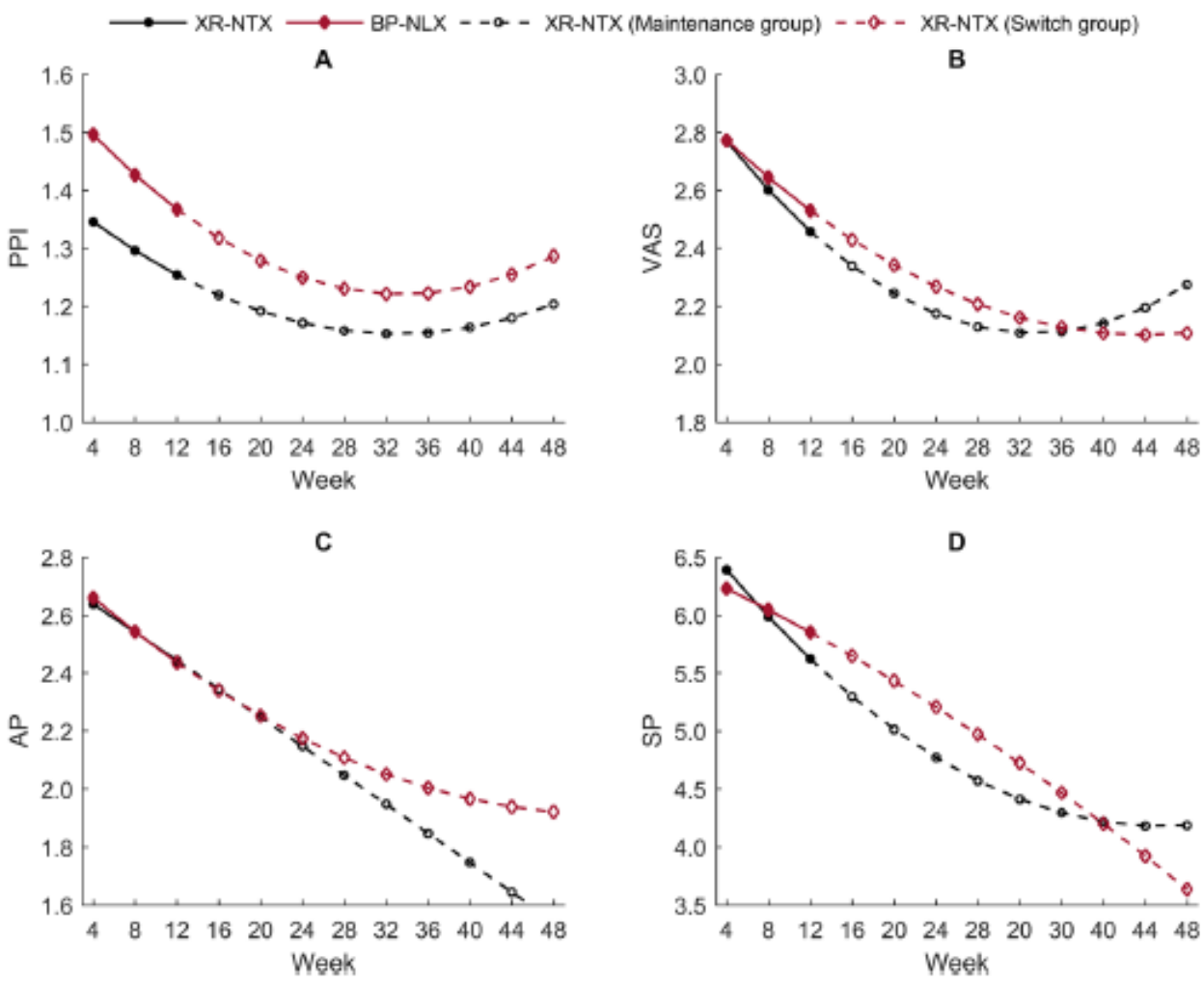


FIGURE 1. Changes in the pain score among study participants both in the randomization period and follow-up period of the study. Changes in the pain score measured by 4 components of McGill pain questionnaire, A: Present Pain Intensity (PPI), B: Visual Analogue Scale (VAS) C: Affective Pain Score (AP), D: Sensory Pain Score (SP) among participants randomized to XR-NTX (black line) or BP-NLX (red line) treatment from week 4 to week 12 and between participants continuing on XR-NTX (red line) and participants switching from BP-NLX to XR-NTX (black line) from week 16 to week 48 in the follow-up period.

Buprenorphine and Chronic Pain with OUD

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

Buprenorphine/Naloxone Dose and Pain Intensity Among Individuals Initiating Treatment for Opioid Use Disorder

William C. Becker, M.D. [a,b,*], Dara Ganoczy, M.P.H. [c], David A. Fiellin, M.D. [b], Amy S.B. Bohnert, Ph.D. [c,d]

[a] VA Connecticut Healthcare System, 950 Campbell Avenue, Mail Stop 151B, West Haven, CT 06516, USA
[b] Yale University School of Medicine, E.S. Harkness Building A, 367 Cedar Street, Suite 406A, New Haven, CT 06510, USA
[c] Serious Mental Illness Treatment Research and Evaluation Center (SMITREC), Department of Veterans Affairs, 2215 Fuller Road (11H), Ann Arbor, MI 48105, USA
[d] Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI 48109, USA

Buprenorphine and Chronic Pain with OUD

Observational study of 1,106 VA patients started on buprenorphine for OUD who had a pain intensity score measured within 30 days of initiation and 15-90 days later; 71% had a chronic pain diagnosis.

Results: 70% had a significant improvement in pain scores (change in NRS≥2). Improvement was not associated with dose.

Case 2

- 35 year old with OUD admitted for injection-related osteomyelitis of cervical spine with epidural abscess requiring surgery. She is started on buprenorphine 8mg SL QID during hospitalization and acute pain is managed with hydromorphone 4-6mg PO Q4hrs standing. She is discharged to SNF on POD#10 for IV antibiotics.

- **How do you manage their opioids while at SNF?**

How to manage opioid tapers for acute pain …

- Length of opioid depends on pain indication
  - Ex. reasonable to require short-acting opioids for several weeks after major surgery
- Involve patient in taper discussion and plan of care – focus on larger goal rather than day to day battles (ex. to taper off hydromorphone prior to dc from facility)
- Make one change at a time – decrease dose or increase frequency
- Distinguish acute vs. chronic pain
- Close outpatient follow-up → ideally no more than 1-2 week Rx for opioids if going home
- May continue opioid taper post-SNF if there is continuity provider (ex. PCP or pain management) – ONLY if agreed to by outpatient provider

Case 3

- 70M with chronic pain 2/2 osteoarthritis back and knees, now living in ALF. Has been prescribed oxycodone 20mg Q6hours for pain. Starting to have sedation with oxycodone. Also noting that it is not controlling his pain and asks for dose increase.
- **What do you do about his pain?**

Opioids for Chronic Pain

2018 systematic review of 96 RCTs:

Opioids compared to placebo:

- Modest pain relief (-0.8 points on 10-point scale)
- Studies with longer duration reported less pain relief (none longer than 6 months).
- Modest improvement in physical functioning (2 points on a 100-point scale)

Studies comparing opioids with NSAIDs:

- No difference in pain relief or physical functioning

None of the studies assessed for development of OUD

Busse JW, et al. JAMA 2018;320:2448.

Buprenorphine for chronic pain

Vol. 42 No. 6 December 2011 Journal of Pain and Symptom Management

Original Article

Efficacy and Safety of the Seven-Day Buprenorphine Transdermal System in Opioid-Naïve Patients with Moderate to Severe Chronic Low Back Pain: An Enriched, Randomized, Double-Blind, Placebo-Controlled Study

Deborah J. Steiner, MD, Steve Sitar, MD, Warren Wen, PhD, Gosford Sawyerr, MA, Catherine Munera, PhD, Steven R. Ripa, MD, and Craig Landau, MD

Purdue Pharma L.P. (D.J.S., W.W., G.S., C.M., S.R.R., C.L.), Stamford, Connecticut, and Orange County Clinical Trials (S.S.), Anaheim, California, USA

Buprenorphine for chronic pain

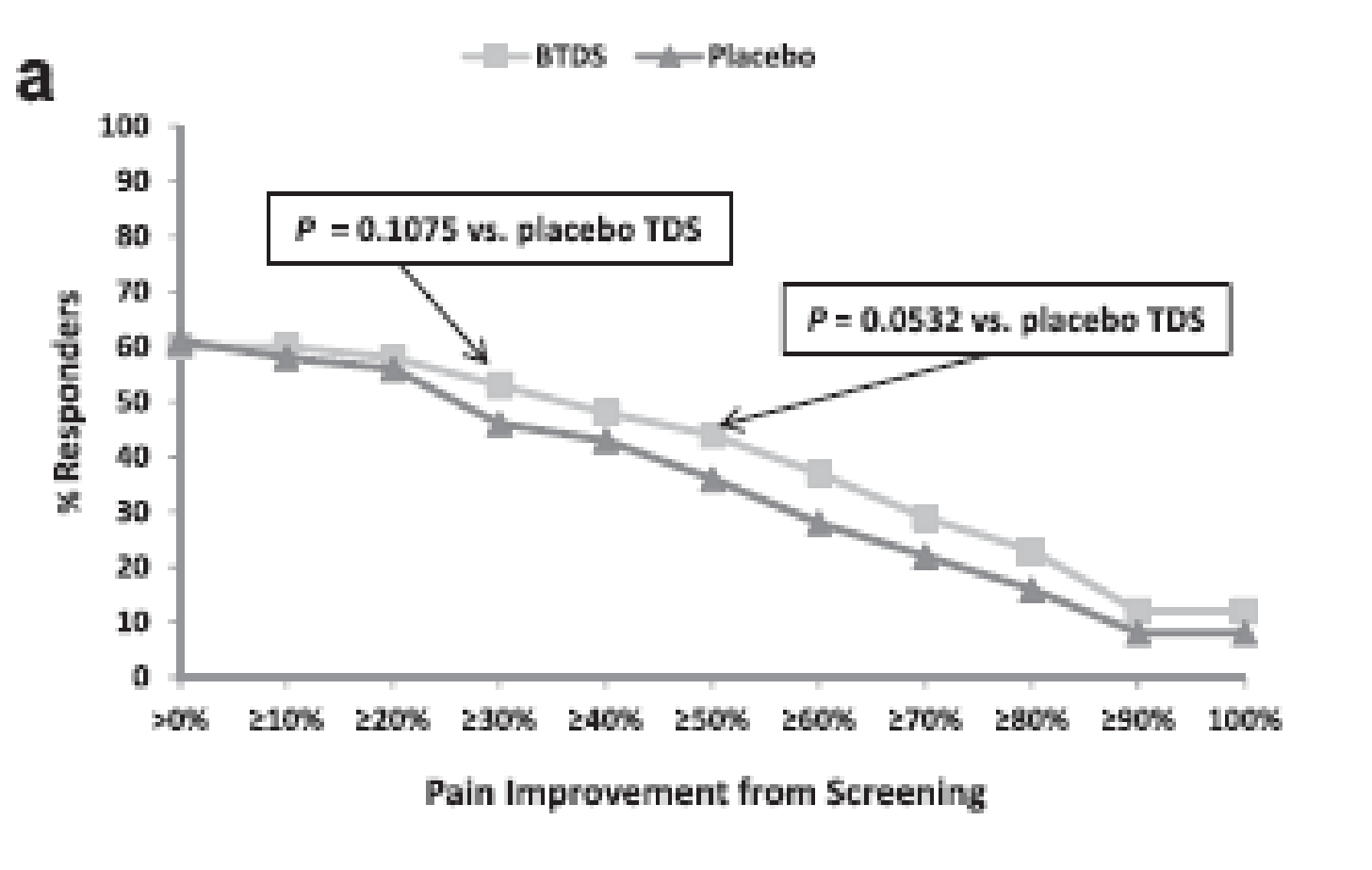
Design: Double-blind RCT

Subjects: 541 opioid-naïve adults with mod-severe low back pain for >3 mos, who tolerated and responded to transdermal bup during a run-in phase (53%)

Intervention: transdermal bup 10 or 20 mcg/hr vs placebo for 12 weeks

Outcomes: average pain over the last 24 hours at week 12 (0-11).

Buprenorphine for chronic pain



Av pain in past 24 hours at week 12: 3.8 vs. 4.4 (p=0.01)

Buprenorphine for chronic pain

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Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain

Richard L. Rauck, Jeffrey Potts, Qinfang Xiang, Evan Tzanis & Andrew Finn

To cite this article: Richard L. Rauck, Jeffrey Potts, Qinfang Xiang, Evan Tzanis & Andrew Finn (2016) Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain, Postgraduate Medicine, 128:1, 1-11, DOI: 10.1080/00325481.2016.1128307

To link to this article: https://doi.org/10.1080/00325481.2016.1128307

Buprenorphine for chronic pain

Design: Double-Blind RCT

Subjects: 462 opioid-naïve adults with chronic low back pain for ≥6 months

Intervention: buccal buprenorphine 75-450 mcg twice daily vs placebo for 12 weeks

Outcomes: average daily pain intensity (0-11).

Buprenorphine and chronic pain

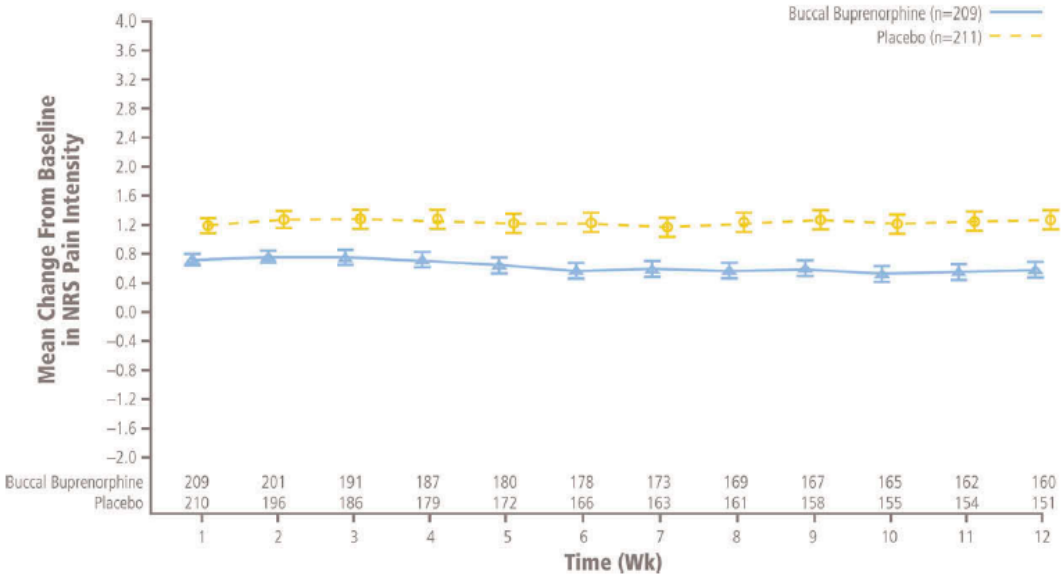


Figure 3. Mean (± SE) of weekly change from baseline in NRS pain intensity in double-blind treatment phase, observed cases only (ITT efficacy population; patients at one site excluded). ITT: Intent-to-treat; NRS: Numerical rating scale.

Percentage with >30% reduction in pain intensity:
63% (BUP) vs 47% (PLA); p=0.001

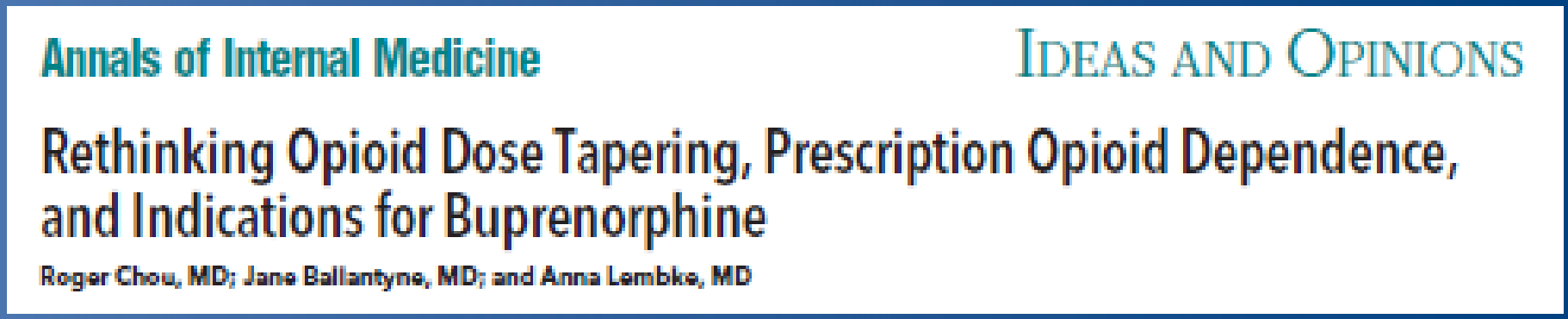
Buprenorphine for chronic pain?

Systematic review:

"Preliminary trials suggest a plausible role; however, due to a paucity of high-quality trials, the current evidence is insufficient to determine the effectiveness of sublingual buprenorphine for the treatment of chronic pain. Rigorous further trials are warranted."

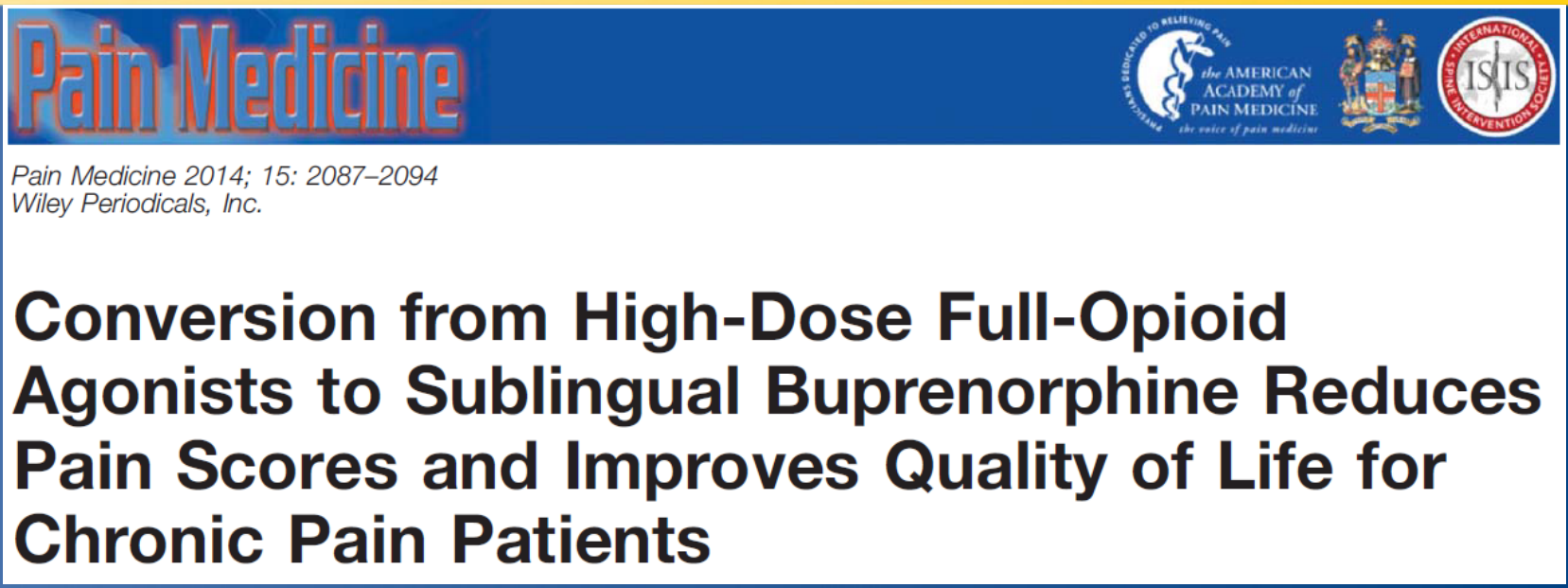
Cote J. Pain Med 2014;15:1711.

Buprenorphine for chronic pain and opioid dependence (not OUD)?



Ann Intern Med 2019;171:427-29..

Buprenorphine for chronic pain and opioid dependence (not OUD)?



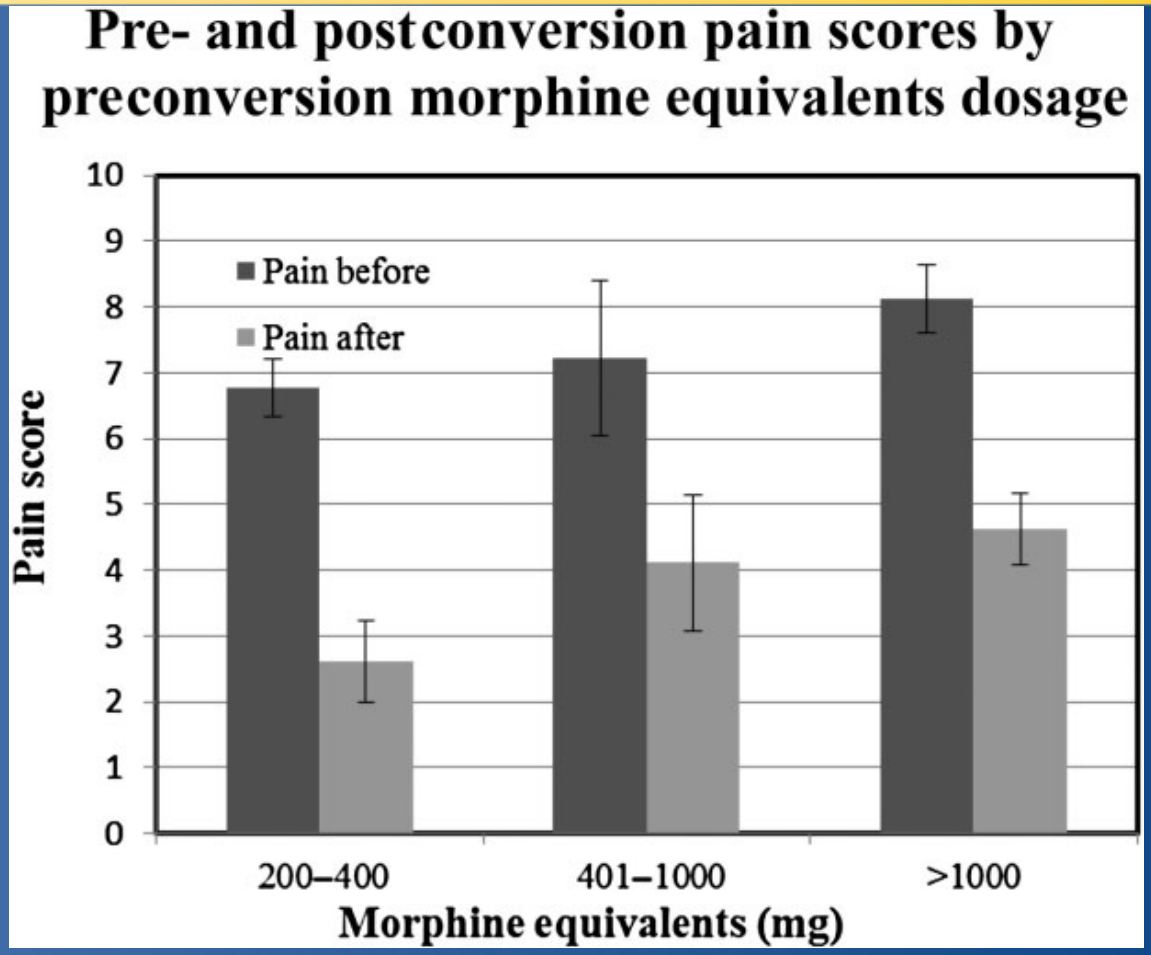
Pain Medicine

Pain Medicine 2014; 15: 2087–2094
Wiley Periodicals, Inc.

Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients

- 35 subjects on high-dose opioids (mean morphine equivalent 550 mg/day) with continuous or worsening pain
- Converted to buprenorphine (mean dose 28 mg/day)
- Pain and quality of life scores measured at baseline and after 2 months

Buprenorphine for chronic pain and opioid dependence (not OUD)?



Daitch D. Pain Med 2014;15:2087-94.

Why use bup for chronic pain?

- Due to superior safety profile, buprenorphine is preferred opioid in the elderly.
- Good option for patients with physical dependence on opioid (even without OUD).
- Can use Butrans transdermal patch or Belbuca buccal buprenorphine for pain
- With comorbid opioid dependence (F11), can also use SL buprenorphine

Who to consider for buprenorphine

- Patients receiving opioids for chronic pain who are developing tolerance or having side effects/safety concerns (ex. sedation, falls)
- Patients with potential misuse of opioids, even if they don’t meet criteria for OUD

Transitioning from Full-Agonist Opioids to Buprenorphine

- If pt on multiple opioids, transition to one short-acting opioid (ex. oxycodone or hydromorphone)
- Need to stop all full-agonist opioids for 8-12 hours prior to starting buprenorphine (or risk precipitated withdrawal)
- Usually most comfortable to do transition overnight
- Write for as needed adjunctive medications for withdrawal

Precipitated Withdrawal

- Sudden-onset severe withdrawal that occurs from giving buprenorphine when other opioids still in system
- Rule of thumb for starting bup:
  - 8-12 hours after short-acting opioids (heroin, oxycodone)
  - 24 hours after long-acting Rx opioid (MSContin, Oxycontin)
  - 3-7 days after methadone use
  - ?? For fentanyl (likely longer – 1-3 days – start with 2mg)

Back to our patient …

- After shared-decision making with patient, plan was made to transition from oxycodone to SL buprenorphine
- Last dose of oxycodone given at midnight
- Overnight, pt was given as needed ondansetron, hydroxyzine and loperamide for withdrawal. Non-opioid analgesia (NSAIDs, acetaminophen, lidocaine patch) was continued.
- At 8am the next morning, pt was in mild withdrawal (COWS 4) and given buprenorphine 4mg SL x 1, which he tolerated without precipitated withdrawal or sedation.
- Patient was then given buprenorphine 4mg SL four times daily.

Case continued …

- 2 weeks later, patient reports that pain is generally well-managed and not having sedation, but having some ongoing pain.
- You increase buprenorphine to 6mg SL QID (24mg/day) and he reports improvement in pain and function.

Practical Tips on Bup Prescriptions and Prior-Auths

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- Default prescription “buprenorphine-naloxone 8-2mg films SL BID”
- Include X-number on prescription
- Write “ok to substitute tab or film”
- Any quantity over 60 tabs/films per 30 days will require PA from Maryland Medicaid
- Some Medicare plans require prior-auth

Maintenance Dosing

- 8 - 32mg per day, divided per patient preference (usually BID – TID)
  - Increase by 4-8 mg if experiencing withdrawal
  - Decrease by 4mg if over-sedated
- Most effective at doses >/ 16mg/day
- Divide dose Q6-Q8hr for patients with chronic pain (maximizes analgesia)

Buprenorphine and pain

Conclusions:

1. Effective for acute pain
2. Modestly effective for chronic pain
3. Safer than full agonists, particularly for those with OUD or at risk for OUD
4. Anyone can prescribe!

Resources

- **ASAM eLearning** (many courses satisfy 8-hour DEA training req): https://elearning.asam.org/
- **PCSS**: https://pcssnow.org/
- **Maryland Addiction Consult Service (MACS):** 1-855-337-MACS (6227)
  - https://www.marylandmacs.org/

References

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Questions?

JOHNS HOPKINS MEDICINE

- mburesh2@jhmi.edu