Penn State College of Medicine
Continuing Education

16th Annual Focus on Pharmacology Conference

Saturday, April 11, 2026

Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

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PennState College of Medicine

1

BUPRENORPHINE and *SUZETRIGINE*

(2 pain medications we should all know about)

David M Giampetro, MD

2

Disclosures

- NONE
- I will mention using buprenorphine formulations for chronic pain that are FDA-approved only for OUD
- I will suggest uses for suzetrigine that are not yet FDA approved

3

Introduction

- Quick update on the Opioid epidemic
- Buprenorphine
  - Background
  - Pharmacology
  - Clinical utility in pain management
  - Perioperative notes
- Suzetrigine
  - Pharmacology
  - Current evidence
  - Prescribing info

4

CONTEXT

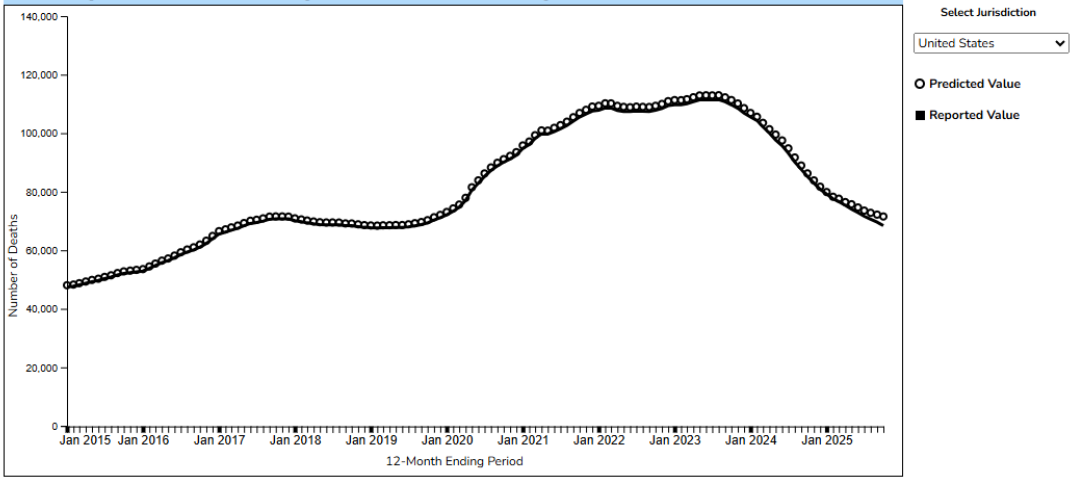
- 10% to 30% of people experience chronic pain
  - Up to 100 million US adults experience chronic pain
- Chronic pain incurs a direct and indirect cost of **$84.1 to $624.8 billion annually**
- Opioid-related overdoses:
  - 2022 ≈ 82,000
  - 2023 ≈ 75,000
  - 2024 ≈ 54,000

5

GOOD NEWS!!! It is still in decline

Based on data available for analysis on: March 1, 2026

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data

6

BIG PICTURE STATEMENTS

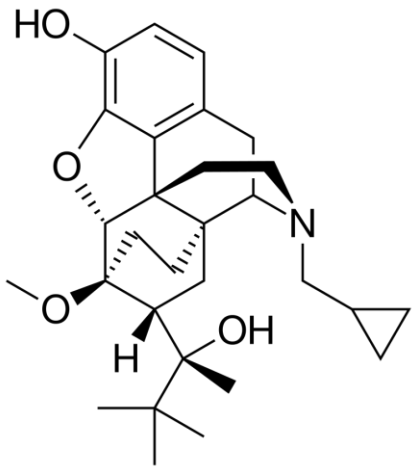
- Chronic pain is a problem
- Opioid related mortality is a problem
- We need:
  - Safer opioids = Buprenorphine
  - Better non-opioid treatments = Suzetrigine

NO DUH

7

Buprenorphine - $C_{29}H_{41}NO_4$

- **Semi-synthetic** derivative of thebaine
- (2S)-2-[(5R,6R,7R,14S)-17-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol



By Harbin, https://commons.wikimedia.org/w/index.php?curid=5685393

8

BUPRENORPHINE

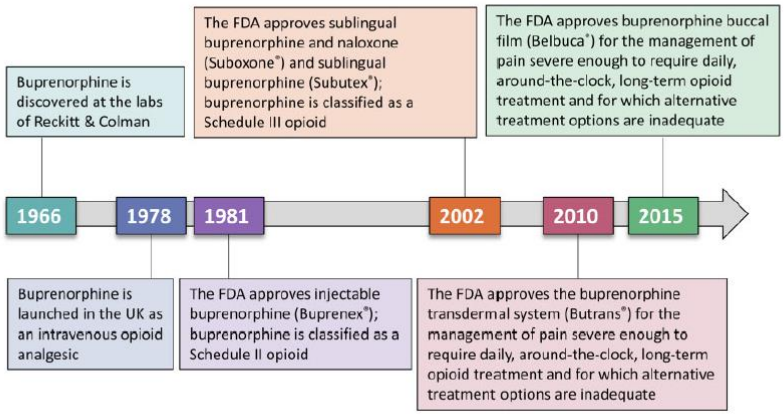


Figure 1. The history of buprenorphine. Buprenorphine was originally developed as an analgesic and was subsequently used for OUD before novel delivery systems allowed for approval in chronic pain management [8,9,12,13]. FDA=Food and Drug Administration; OUD=opioid use disorder.

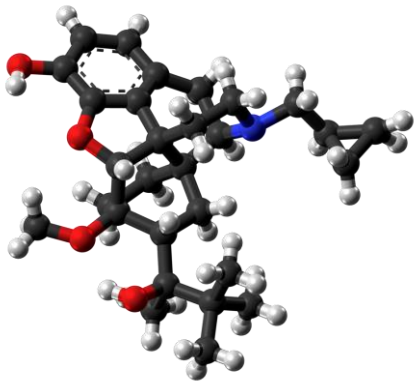
9

KEY TAKE HOME POINTS

- **No X-waiver is needed anymore!** *(it never was for pain)*
- **Unique BUP pharmacology:**
  - Fewer adverse effects
  - Lower risk of overdose
- **BUP in chronic pain**
  - It works (for pain and OUD)!
  - Induction
    - Easy to start in opioid-naïve patients
    - Induction options for those dependent on opioids
  - Keep on BUP in perioperative period

10

BUPRENORPHINE PHARMACOLOGY



By Jynto, Buprenorphine molecule, https://en.wikipedia.org/wiki/Buprenorphine#/media/File:Buprenorphine_molecule_from_xtal_ball.png

11

Buprenorphine

Unique pharmacology makes this a better opioid

- Fewer adverse effects
  - including constipation, hyperalgesia, and falls in the elderly
  - no need to adjust for kidney function
  - ↓ overdose risk
- Analgesia on par with full agonist opioids
- ↓ ADRBs (Aberrant Drug-Related Behaviors)
- Treatment of opioid use disorder (↓ death by 50%)

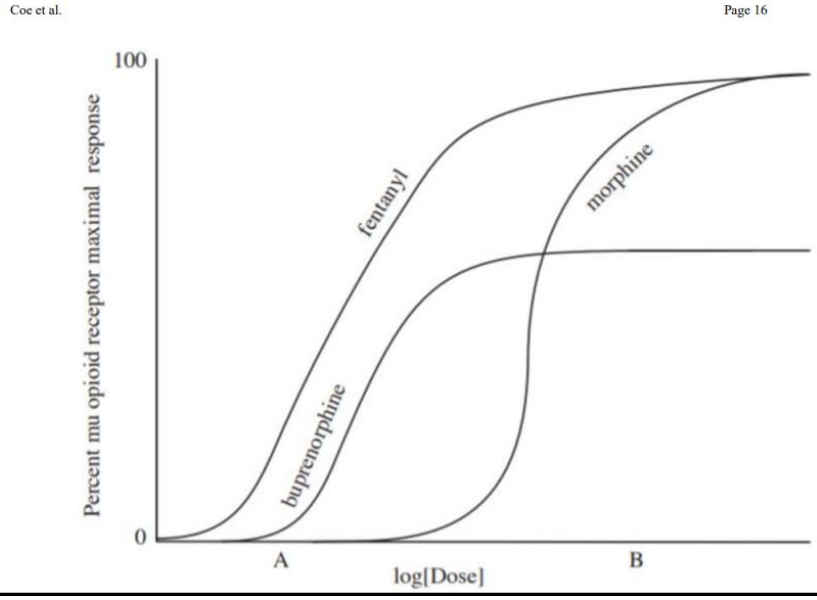
12

Buprenorphine

- Pharmacologic characteristics and implications
  - **Partial μ-opioid receptor agonist**
    - Low intrinsic activity
    - Ceiling Effect = SAFETY
    - ***But it still works!***
  - **Biased ligand**
    - Less tolerance
    - Less respiratory depression
    - Less constipation

13

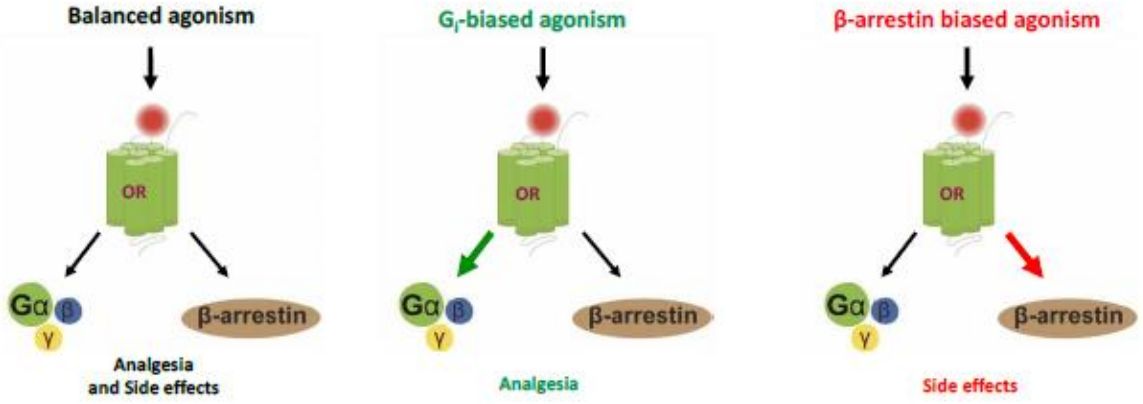
Buprenorphine: a partial μ-opioid receptor agonist



14

Biased Agonism

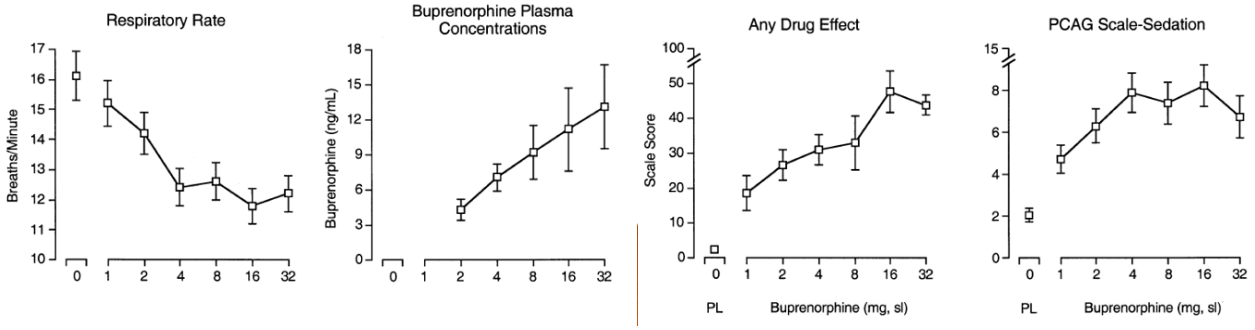
Molecules **2020**, *25*, 4257



Faouzi A, Varga BR, Majumdar S. Biased opioid ligands. Molecules. 2020 Sep 16;25(18):4257

15

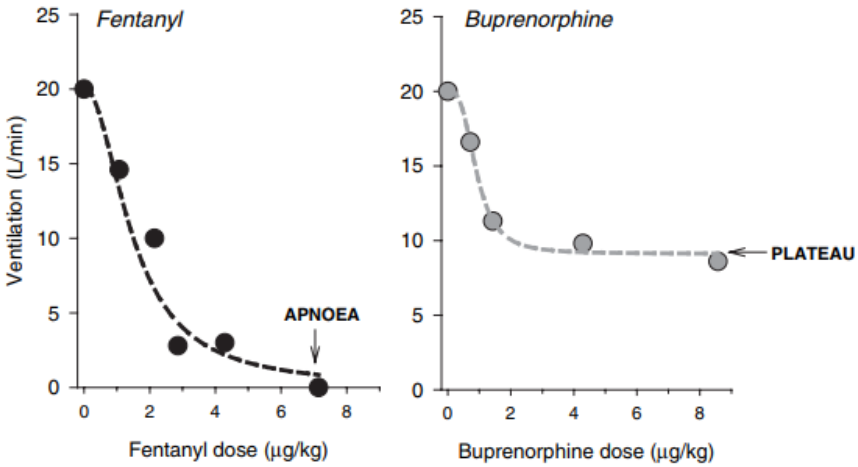
Plateau of BUP's effect in Respiratory Rate and Sedation



Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacology & Therapeutics. 1994 May 1;55(5):569-80.

16

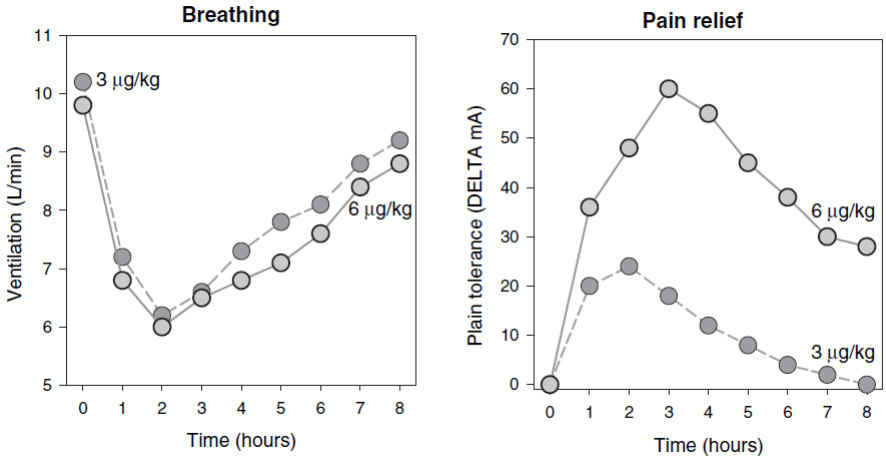
Buprenorphine – Safety



Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. Palliative medicine. 2006 Jan;20(8_suppl):3-8.

17

Buprenorphine – Safety



Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. Palliative medicine. 2006 Jan;20(8_suppl):3-8.

18

Buprenorphine

Pharmacologic characteristics and implications

- **High μ-receptor affinity = binds tightly to the receptor**
  - "Blocks" the effects of other opioids
    - Prevents OD
    - Higher full-agonist opioid doses needed (OR, acute pain)
    - *Partially reversible - can override with other opioids!*
  - Kicks out other opioids from the μ-receptor
    - can precipitate withdrawal
    - special considerations when starting BUP in those with other opioids "on board"

19

Buprenorphine

Pharmacologic characteristics and implications

- **High potency**
  - low doses
  - *no well-established conversion factors to/from other opioids*
- **Slow dissociation from the receptor**
  - long half-life

20

Buprenorphine

Pharmacologic characteristics and implications

- **Kappa receptor antagonist**
  - Antidepressant effect
  - Anti-hyperalgesic effect
- **High first-pass metabolism**
  - Poor oral bioavailability
  - Sublingual, buccal, transdermal, implants

21

Buprenorphine

Other important features of buprenorphine

- Safe in liver and kidney disease
- Less immunosuppression and hypogonadism
- Fewer drug-drug interactions
- Less monoamine reuptake inhibition
  - But still may contribute to serotonin syndrome
- May cause QTc prolongation
- Buccal forms can cause tooth decay
  - After dissolving, gently rinse with water. The water can be swallowed. Toothbrushing should be delayed at least 1 hour.

22

DOES IT WORK?

YES!!

23

Review Article | Published: 26 July 2018

Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option

Mellar P. Davis, Gavril Pasternak & Bertrand Behm

Drugs **78**, 1211–1228 (2018) | Cite this article

2710 Accesses | **66** Citations | **16** Altmetric | Metrics

September 8, 2021

Evaluation of Buprenorphine Rotation in Patients Receiving Long-term Opioids for Chronic Pain

A Systematic Review

Victoria D. Powell, MD[1,2]; Jack M. Rosenberg, MD[3,4,5,6]; Avani Yaganti, BS[7]; et al

Author Affiliations | Article Information

JAMA Netw Open. 2021;4(9):e2124152. doi:10.1001/jamanetworkopen.2021.24152

24

Current Pain and Headache Reports (2018) 22:83
https://doi.org/10.1007/s11916-018-0732-2

ANESTHETIC TECHNIQUES IN PAIN MANAGEMENT (D WANG, SECTION EDITOR)

Buprenorphine for Chronic Pain: a Systemic Review

Michael A. Fishman[1] · Phillip S. Kim[1]

Review › Pain Med. 2014 Jul;15(7):1171-8. doi: 10.1111/pme.12386. Epub 2014 Jul 4.

Sublingual buprenorphine as an analgesic in chronic pain: a systematic review

Joyce Cote [1], Lori Montgomery

Affiliations + expand

PMID: 24995716 DOI: 10.1111/pme.12386

25

Clinical studies summary

- Equivalent analgesia to other opioids
- Fewer side effects
- Safer
- Rotation from other opioids might improve pain

26

Buprenorphine

"For patients receiving daily opioids for the treatment of chronic pain, we suggest the use of buprenorphine instead of full agonist opioids due to lower risk for overdose and misuse."

CLINICAL GUIDELINE — **Annals of Internal Medicine**

The Use of Opioids in the Management of Chronic Pain: Synopsis of the 2022 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

Friedhelm Sandbrink, MD; Jennifer L. Murphy, PhD; Melanie Johansson, MD; Juli L. Olson, DC, DACM; Ellen Edens, MD, MPE; Jamie Clinton-Lont, MSN, AGPCNP-BC; James Sall, PhD; and Christopher Spevak, MD, MPH, JD; for the VA/DoD Guideline Development Group*

27

Buprenorphine

Formulations

FDA-approved for chronic pain (X-waiver was never needed):

Buccal films
- *Belbuca 75-900 mcg BID*

Transdermal patch
- *Butrans* 5-20 mcg/hr q 7 days

FDA-approved for opioid use disorder (X-waiver NO LONGER NEEDED):

Sublingual tablets/films (TID-QID for pain)
- *Suboxone, Zubsolv, Subutex*

Injectable/Implants (not used for pain)
- *Sublocade*

IV BUP

28

Buprenorphine Initiation

- Opioid naïve – transdermal 5 mcg/hr or buccal 75 mcg daily to BID
- Opioid tolerant
  - 0 – 30 MME – stop and start as in an opioid naïve patient
  - 30 – 90 MME
    - Consider weaning some, but this is a barrier
    - Stop and start: tdBUP 10 mcg/hr OR bBUP 150 mcg BID
    - Monitor for withdrawal, consider α2-agonist and/or IR opioid
    - Titrate to effect as tolerated
  - > 90 MME
    - Consider weaning some, but this is a barrier
    - Stop and start: tdBUP 15-20 mcg/hr OR bBUP 300 mcg BID
    - Monitor for withdrawal, consider α2-agonist and/or IR opioid
    - Titrate to effect as tolerated
    - **Consider Microdose induction**

(Webster et al 2020)

29

BUP microdosing

	Buprenorphine		Pain Medication (decrease dose by ~ 1/7 per day)
Day 1 (0.25mg-0.5mg total)	1/8 or 1/4 of 2mg tablet/film	Day 1	
Day 2 (1mg total)	half of 2mg tablet/film	Day 2	
Day 3 (2mg total)	one 2mg tablet/film	Day 3	
Day 4 (4mg total)	two 2mg tablets/films	Day 4	
Day 5 (8mg total)	three 2mg tablet/films	Day 5	
Day 6 (12mg total)	[xx] 2mg tablet/films	Day 6	
Day 7 (16mg total)	[xx] 2mg tablets/films	Day 7	

30

CASES:
BUP induction
& other barriers

31

Case #1

- 73 y/o male with SEVERE CHRONIC PAIN, failed multiple other Tx; no red flags for OUD; not on opioids now, but was on morphine years ago, which helped
  - BUP induction: simple
    - start BUP, patch better than buccal, at the lowest dose (5 mcg/hr patch Q 7 days)

32

Case #2

- 74 y/o female h/o anxiety/depression, severe LBP and multifocal OA pain, failed meds/injections, not a surgical candidate, transferred to PSH from retiring pain doc on OxyIR 5 mg BID and OxyER 9 mg BID = MME 45. On clonazepam. No OUD, good insight.
  - Stop oxy, start tdBUP 10 mcg/hr next AM
  - Had some w/d, diarrhea
  - Now stable on 20 mcg/hr tdBUP

33

Case #3

- 51 y/o man with severe CP, on 120 mg LA oxycodone/day (180 MME/day) x 10 yrs, doing well; no red flags for OUD; his insurance changed, and he needs to change his medications
  - **BUP induction: need to avoid precipitated withdrawal**
    1. Taper down the dose and start BUP patch or buccal
    2. Home or clinic induction: stop oxy, wait for a moderate withdrawal, then start low dose BUP, gradually increase as tolerated/needed; Rx anti-withdrawal meds
    3. *Microdosing*

Doing well on BUP 4 mg SL tab TID

34

Why is BUP underutilized?

- **Stigmatized** (as a medication for OUD)
- **Lack of adequate education** among providers
- **Fear of legal consequences** among prescribers
- **BUP prescribing waiver is NOT needed any longer, regardless of treating opioid use disorder or pain**
- **Difficulty in transitioning from higher dose COT**
  - **Is it worth it in cases of Chronic Pain w/o OUD?**
- **TRUTH BE TOLD – I HAVEN'T DONE A BUP MICROINDUCTION AND ASK FOR HELP FROM ADDICTION MEDICINE WHEN CONSIDERING**

35

Opioid withdrawal management

- **Clonidine** 0.1-0.2 mg PO BID-QID for withdrawal (also helps with sleep & anxiety) – if prescribing for more than a few days, taper off; orthostasis precautions
- **Gabapentin** 100-300 mg TID for sleep/anxiety (esp. at night)
- **Acetaminophen and/or NSAIDs** prn muscle/joint aches
- **Loperamide** 2 mg prn diarrhea
- **Dicyclomine** 100 mg TID prn abdominal cramping
- **Ondansetron** 4-8 mg SL prn nausea
- **General:** Gatorade, heating pad; do not drive

36

Acute pain management while on BUP

37

BUP in acute and peri-op pain

- Early fears: BUP would block other opioids, preventing their effects
  - NOT COMPLETELY TRUE
- WARNING: Stopping BUP perioperatively poses challenges
  - Relapse – risk of OD
  - Logistics of stopping and resuming it (re-induction is needed)
- Patients can be managed throughout the perioperative period successfully, even on BUP

38

↑↑↑ Overdose risk after stopping BUP

*"… the period following buprenorphine discontinuation is associated with rates of overdose approximately **two to three times higher** than those observed in a general sample of patients with opioid use disorder."*

39

JGIM

REVIEWS

Treating Perioperative and Acute Pain in Patients on Buprenorphine: Narrative Literature Review and Practice Recommendations

JUST STAY ON THE BUPRENORPHINE

Vitaly Gordin, MD[3], and Anika Alvanzo, MD, MS[4,5]

[1]Division of Addiction Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA; [2]Department of Family and Community Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA; [5]Pyramid Healthcare, Inc., PA, USA

Check for updates

40

LET'S KEEP IT SIMPLE

- CONTINUE BUPRENORPHINE HOME DOSE but…
  - Peri-op: take AM dose the day of (or PM dose the night before)
  - Divide into TID-QID for acute pain or when resuming it post-op
  - Can titrate up from the home dose if okay with managing provider
- USE MULTIMODAL ANALGESIA
- USE SUPPLEMENTAL OPIOIDS IF NEEDED
  - Consider IV fentanyl or hydromorphone for acute peri-op pain
- COORDINATE CARE

41

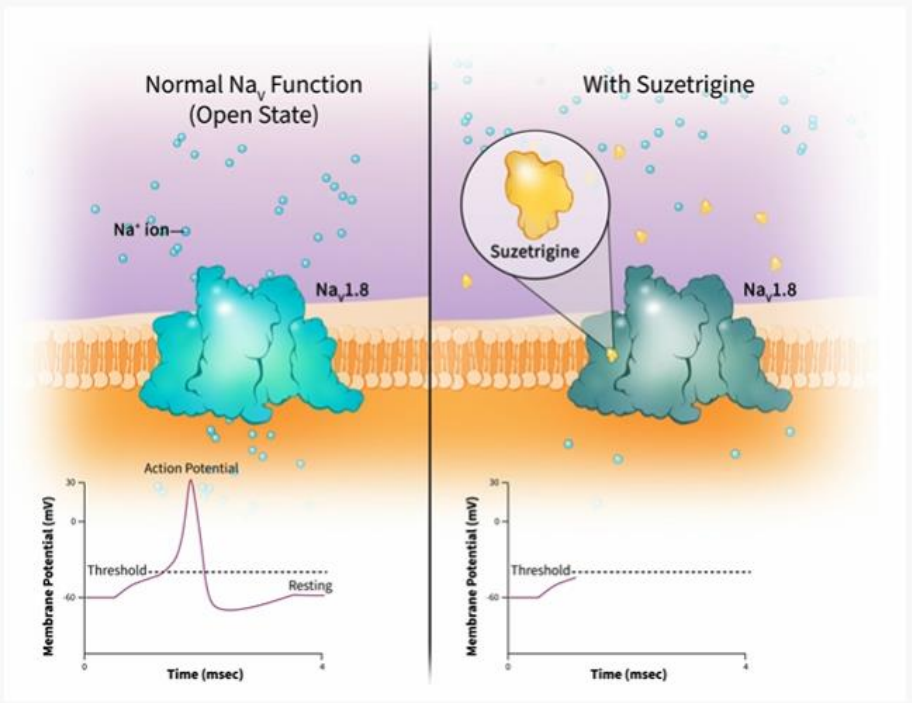
ARE THERE ANY QUESTIONS ON BUPRENORPHINE BEFORE WE MOVE ON TO SUZETRIGINE?

42

SUZETRIGINE

- Selective inhibitor of the $Na_V1.8$ voltage-gated sodium channel
- $Na_V1.8$ is predominantly located on peripheral sensory neurons, including the dorsal root ganglion (DRG)
- By inhibiting $Na_V1.8$, nociceptive transmission is limited more so than other sensory modalities and motor signaling.
  - Other sodium channel-related activity is avoided (heart and brain)
- Only FDA approved for moderate to severe acute pain

43



Suzetrigine Mechanism of Action | Vertex Pharmaceuticals

44

Voltage-Gated Sodium Channels are Crucial for Generation and Propagation of Pain Signals as Action Potentials

- There are nine voltage-gated sodium channel subtypes (NaV1.1—NaV1.9), each with a unique cell type specific expression pattern and function[2]
- NaV1.7, NaV1.8, and NaV1.9 are highly expressed in peripheral sensory neurons[2]
- These channels are essential for the initiation and propagation of pain signals in peripheral nociceptive neurons

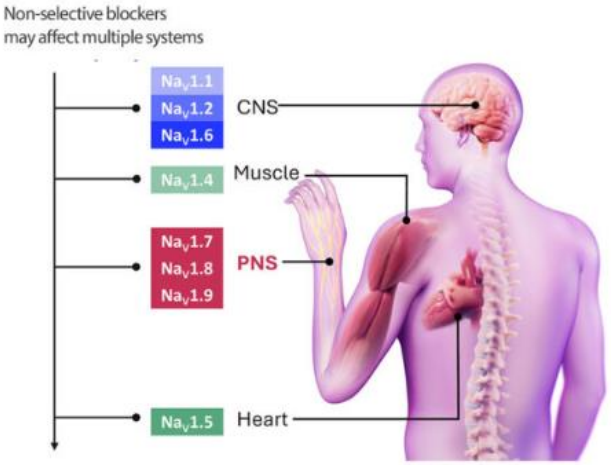


Figure 1: Voltage-gated sodium channels associated with the propagation of pain signals. Used with permission from Vertex Pharmaceuticals.

45

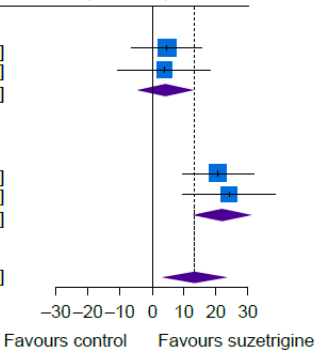
SUZETRIGINE

- 4 RCTs
  - 2768 patients in total undergoing either bunionectomy or abdominoplasty
  - Study groups = 1179 receiving suzetrigine
  - Control 1 = 1015 patients received hydrocodone with APAP
  - Control 2 = 575 received a placebo.
- Meta-analysis demonstrates a benefit in the Summed Pain Intensity Difference over 48 h (SPID48)
  - Most notable in the abdominoplasty group, and when compared to a placebo
  - Comparable to hydrocodone/APAP
- In the phase 3 trials, suzetrigine significantly reduced pain (SPID48) compared to placebo, with a 48.4% reduction in the abdominoplasty trial (P <0.001) and 29.3% in the bunionectomy trial (P =0.0002).
  - *If you look at the NPRS, this represents a 1.5-point improvement in the abdominoplasty group, and a 1-point improvement in the bunionectomy group*

46

a

Studies	Suzetrigine Mean	SD	Total	Control Mean	SD	Total	Weight	MD(h)	95% CI
Bunionectomy									
Bertoch, 2025(NCT05553366)	99.90	92.87	426	95.35	95.60	857	27.8%	4.55	[–6.35; 15.45]
Jones, 2023(NCT05034952)	112.14	91.30	155	108.36	13.64	119	22.2%	3.78	[–10.80; 18.36]
Total(95% CI)			581			976	50.0%	4.27	[–4.45; 13.00]
Heterogeneity: Tau^2=0; χ^2=0.01, df=1(*P*=0.93); I^2=0%									
Abdominoplasty									
D'Aunno, 2025(NCT05558410)	118.40	90.90	447	97.94	93.66	671	27.6%	20.46	[9.45; 31.47]
Jones, 2023(NCT04977336)	102.90	89.66	150	78.90	11.98	153	22.4%	24.00	[9.53; 38.47]
Total(95% CI)			597			824	50.0%	21.76	[12.99; 30.52]
Heterogeneity: Tau^2=0; χ^2=0.15, df=1(*P*=0.70); I^2=0%									
Total(95% CI)			1178			1800	100.0%	13.12	[2.96; 23.29]
Heterogeneity: Tau^2=65.75; χ^2=7.83, df=3(*P*=0.05); I^2=62%									
Test for overall effect: Z=2.53(*P*=0.01)									
Test for subgroup differences: Chi²=7.68, df=1(*P*<0.01)									

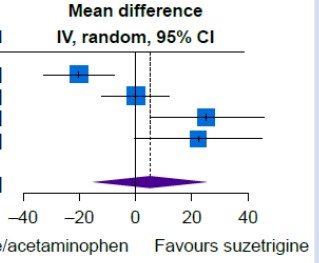


Amaral S, Marques N, Tapioca V, Pereira E, Americo A, Gadsden J. Suzetrigine for acute postoperative pain: a systematic review and meta-analysis of current evidence. British Journal of Anaesthesia. 2025 Jul 10

47

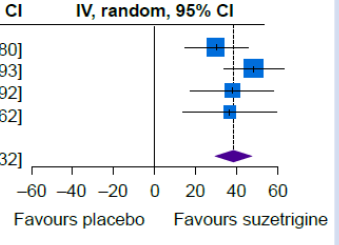
b

Studies	Suzetrigine Mean	SD	Total	Hydrocodone/acetaminophen Mean	SD	Total	Weight	MD(h)	95% CI
Bertoch, 2025(NCT05553366)	99.90	92.87	426	120.10	93.42	431	27.2%	–20.20	[–32.67; –7.73]
D'Aunno, 2025(NCT05558410)	118.40	90.90	447	118.40	90.90	448	27.5%	0.00	[–11.91; 11.91]
Jones, 2023(NCT04977336)	110.50	10.30	76	85.20	89.79	76	23.3%	25.30	[4.98; 45.62]
Jones, 2023(NCT05034952)	137.80	11.50	60	115.60	89.08	60	22.0%	22.20	[–0.53; 44.93]
Total(95% CI)			1009			1015	100.0%	5.27	[–15.03; 25.57]
Heterogeneity: Tau^2=353.45; χ^2=19.56, df=3(*P*<0.01); I^2=85%									
Test for overall effect: Z=0.51(*P*=0.61)									



c

Studies	Suzetrigine Mean	SD	Total	Placebo Mean	SD	Total	Weight	MD(h)	95% CI
Bertoch, 2025(NCT05553366)	99.90	92.87	426	70.10	91.01	216	32.8%	29.80	[14.80; 44.80]
D'Aunno, 2025(NCT05558410)	118.40	90.90	447	70.10	91.10	223	34.5%	48.30	[33.67; 62.93]
Jones, 2023(NCT04977336)	110.50	10.30	76	72.70	89.50	77	18.4%	37.80	[17.68; 57.92]
Jones, 2023(NCT05034952)	137.80	11.50	60	101.10	89.10	59	14.2%	36.70	[13.78; 59.62]
Total(95% CI)			1009			575	100.0%	38.64	[29.96; 47.32]
Heterogeneity: Tau^2=1.16; χ^2=3.04, df=3(*P*=0.39); I^2=1%									
Test for overall effect: Z=8.72(*P*<0.01)									



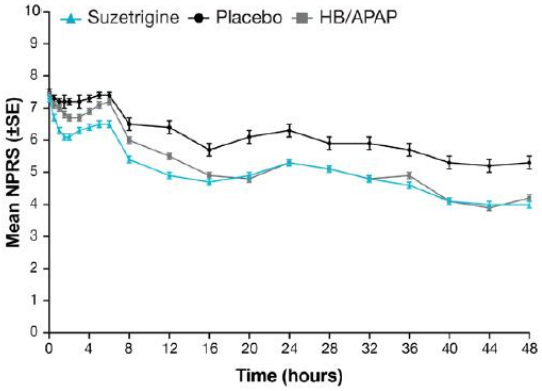
Amaral S, Marques N, Tapioca V, Pereira E, Americo A, Gadsden J. Suzetrigine for acute postoperative pain: a systematic review and meta-analysis of current evidence. British Journal of Anaesthesia. 2025 Jul 10

48

Abdominoplasty

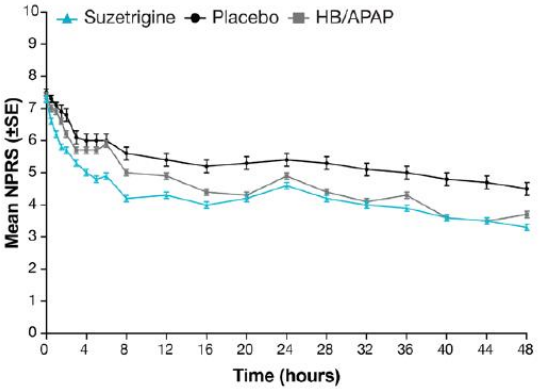
A

Prespecified analysis with rescue imputation: effect of study drug only



B

Post-hoc analysis without rescue imputation: effect of study drug plus ibuprofen (as treated)



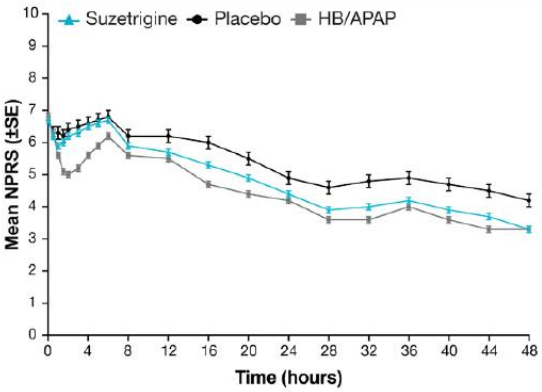
Bertoch T, D'Aunno D, McCoun J, Solanki D, Taber L, Urban J, Oswald J, Swisher MW, Tian S, Miao X, Correll DJ. Suzetrigine, a nonopioid NaV1. 8 inhibitor for treatment of moderate-to-severe acute pain: Two phase 3 randomized clinical trials. Anesthesiology. 2025 Mar 21;142(6):1085.

49

Bunionectomy

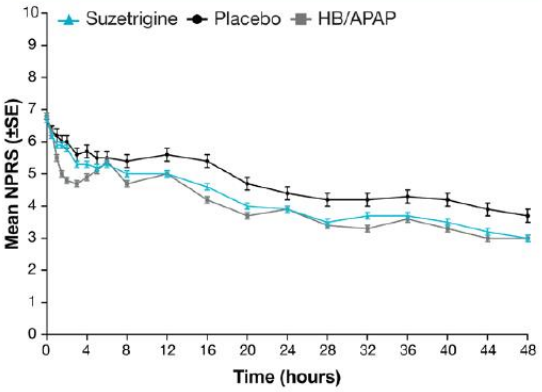
C

Prespecified analysis with rescue imputation: effect of study drug only



D

Post-hoc analysis without rescue imputation: effect of study drug plus ibuprofen (as treated)



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50

SUZETRIGINE DOSING

- 100 mg loading dose on an empty stomach, then 50 mg q 12 hrs
  - Use beyond 14 days has not been evaluated
- No dosage adjustment in renal disease aside from avoiding if eGFR ≤ 15
- Liver dz
  - Child-Pugh A: no adjustment
  - Child-Pugh B: 100 mg loading, 50 mg q 12 hrs x 4, then 50 mg q 24 hrs.
  - Child-Pugh C: avoid use

51

SUZETRIGINE WARNINGS

- Contraindications – strong CYP3A inhibitors (itraconazole, erythromycin, clarithromycin)
- Moderate CYP3A inhibitors (fluconazole) – use Child-Pugh B dosing
- Avoid grapefruit
- SIDE EFFECTS: The most common (≥1%) side events were pruritus (2.1%), muscle spasms (1.3%), elevated CPK (1.1%), and rash (1.1%).
  - No cases of respiratory depression or QTc prolongation were reported
- Low abuse with no reports of euphoria or withdrawal

52

SUZETRIGINE IN REPRODUCTION

- Suzetrigine may decrease serum concentrations of hormonal contraceptives.
  - Use a non-hormonal method
  - Use ethinyl estradiol and norethindrone or levonorgestrel
- Based on animal toxicology studies, suzetrigine may reversibly impact female fertility and cause fetal harm (no human data) at doses above the maximum recommended human dosing (MRHD)
- Long-term animal studies of carcinogenic potential have not been conducted.
  - Preliminary work did not find suzetrigine to be mutagenic or clastogenic
- Not known if it is present in breast milk – studies TBD

53

The future of SUZETRIGINE

- CHRONIC PAIN!!!
- Ongoing trials in chronic pain (12-week dosing)
  - Radiculopathy – preliminary results not promising
  - Painful Diabetic Peripheral Neuropathy – 2 ongoing trials
    - Possible dose-dependent effect on CrCl in DPN trial
- A recent phase 4 open-label study in plastic surgery
  - 100 mg loading dose can be given pre-op
  - 91% of suzetrigine patients did not receive rescue opioids
- We had a case of erythromelalgia that practically resolved with suzetrigine

54

SUMMARY

- BUP has unique pharmacology, which makes it a reasonable option and safer choice relative to other opioids for treating Chronic Pain.
- Initiating BUP is easy in patients who are not on opioids or are on low doses
- Maintain BUP therapy in the acute pain and peri-op period
- Suzetrigine is a novel non-opioid analgesic that is safe, effective, and non-addictive

55

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57

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58