Buprenorphine for Pain:
An Evidence-based, Practical Approach

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Disclosure Information

Buprenorphine for Pain

April, 2023

Lee Radosh, MD, FAAFP, FASAM

- No Disclosures

Disclaimer

- I will be discussing off-label uses of certain buprenorphine formulations

Learning Objectives

- By the end of the presentation, attendees will be able to:
  - List available published evidence supporting buprenorphine's use in acute and chronic pain
  - Identify patients with pain whom providers should consider for buprenorphine
  - Safely and comfortably initiate and manage buprenorphine for pain

"I believe that practicing addiction medicine includes proactive care of patients with pain management issues. I push buprenorphine for the treatment of chronic pain."

LikeMindedDocs List-Serve, February 2023

Other Disclaimers

- Limited research
- OUD vs. dependence?
- Acute vs. chronic pain?
- Pain in patients with OUD vs. without OUD?
- Trade names (especially when only one product)
- Conclusions about one formulation may be based on research on other formulations
- Some slides included as reference/information → I may gloss over

- SUMMARY: recommendations based on INFERRING FROM ALL TYPES OF STUDIES . . .
  - May not be fully delineated

Roadmap

- Buprenorphine pharmacology
- Efficacy
- Safety and the “ceiling”
- OUD vs. dependence
- Dosing
- Cases
- References

What Affects “Pain”?

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

“Pain is inevitable; suffering is optional.”

Buddhist proverb

Pain Treatment Goals ("Metrics")

- Improve physical function
- Improve functional status
- Increase self-management of pain
- Reduce pain level (very subjective!)
- Improve vocational ability and status
- Reduce health care utilization
- Eliminate, minimize or even stabilize the use of opioids

Ablin, 2015
Sanders, 2005

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Ablin, 2015
Sanders, 2005

One Stop Shopping (For Reference): Simple LBP Guidelines

- VA/DoD Clinical Practice Guideline: Diagnosis and Treatment of Low Back Pain
  - https://www.healthquality.va.gov/guidelines/pain/lbp/index.asp
  - "Pocket card": https://www.healthquality.va.gov/guidelines/Pain/lbp/VADoDLBPCPGPocketCard092917.pdf
- Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians
  - https://www.acpjournals.org/doi/full/10.7326/M16-2367?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

VA/DoD, 2022
Qaseem, 2017

Opioids For CNCP?

- "Don't prescribe opioid analgesics as long-term therapy to treat chronic non-cancer pain until the risks are considered and discussed with the patient"

American Society of Anesthesiologists – Pain Medicine, 2014

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

A-Z Index

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Opioids

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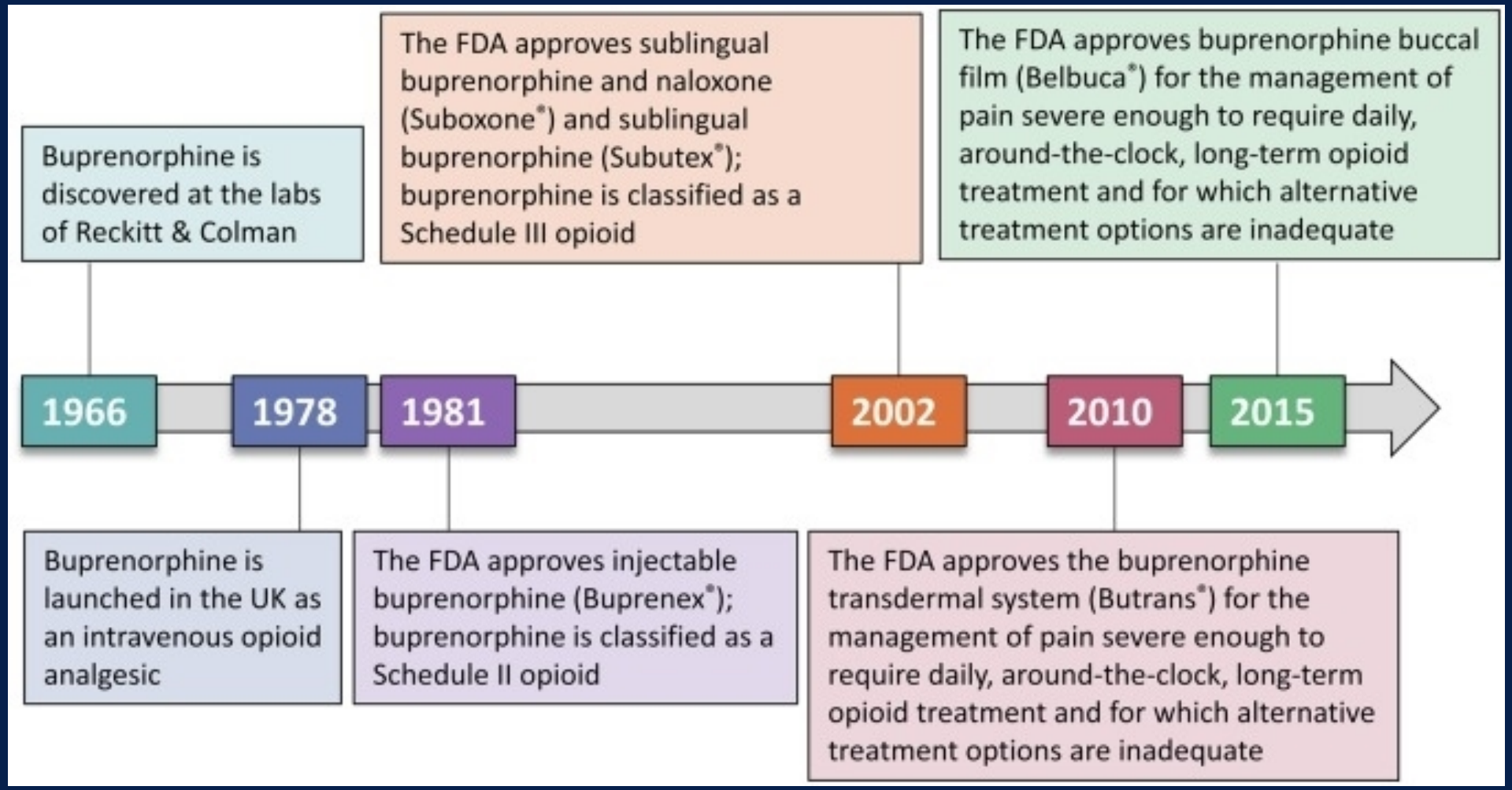
Opioid Prescribing Guideline Resources

- Guideline Overview
- Clinical Tools
- Training for Providers
- Mobile App for Providers
- Videos on Prescription Opioids
- Posters for Providers and Patients
- Providers' FAQs

Safer Prescribing Saves Lives: Opioid Prescribing Guideline

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2022

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. FDA=Food and Drug Administration; OUD=opioid use disorder."

Webster, 2020

No More X-Waiver

- "All practitioners who have a current DEA registration that includes Schedule III authority, may now prescribe buprenorphine for Opioid Use Disorder in their practice if permitted by applicable state law and SAMHSA encourages them to do so."

SAMHSA, 2023

Brief Review:
Opioid Receptors and Pharmacology

Agonists

- Bind to the receptor
- Fully activates receptor
- Highly reinforcing
- Most likely to develop tolerance

Antagonists

- Bind to the receptor
- No biological response
- Blocks opiates
- Least likely to develop tolerance

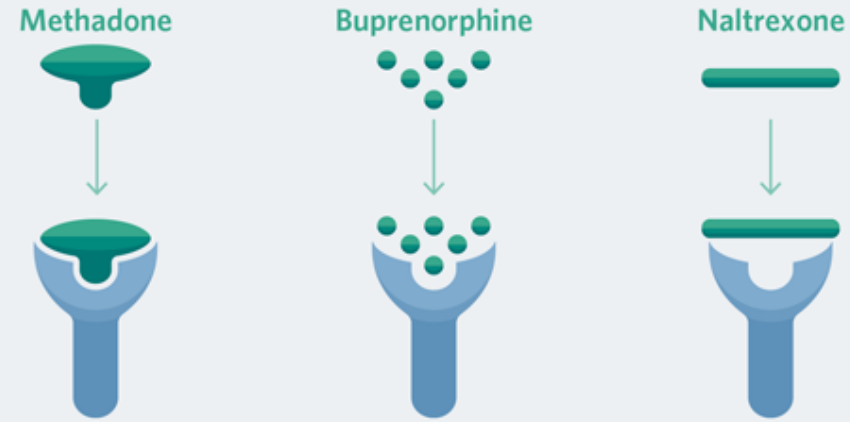
Partial Agonists

- Bind to the receptor
- Activates at a lower level
- Less reinforcing
- Less likely to develop tolerance

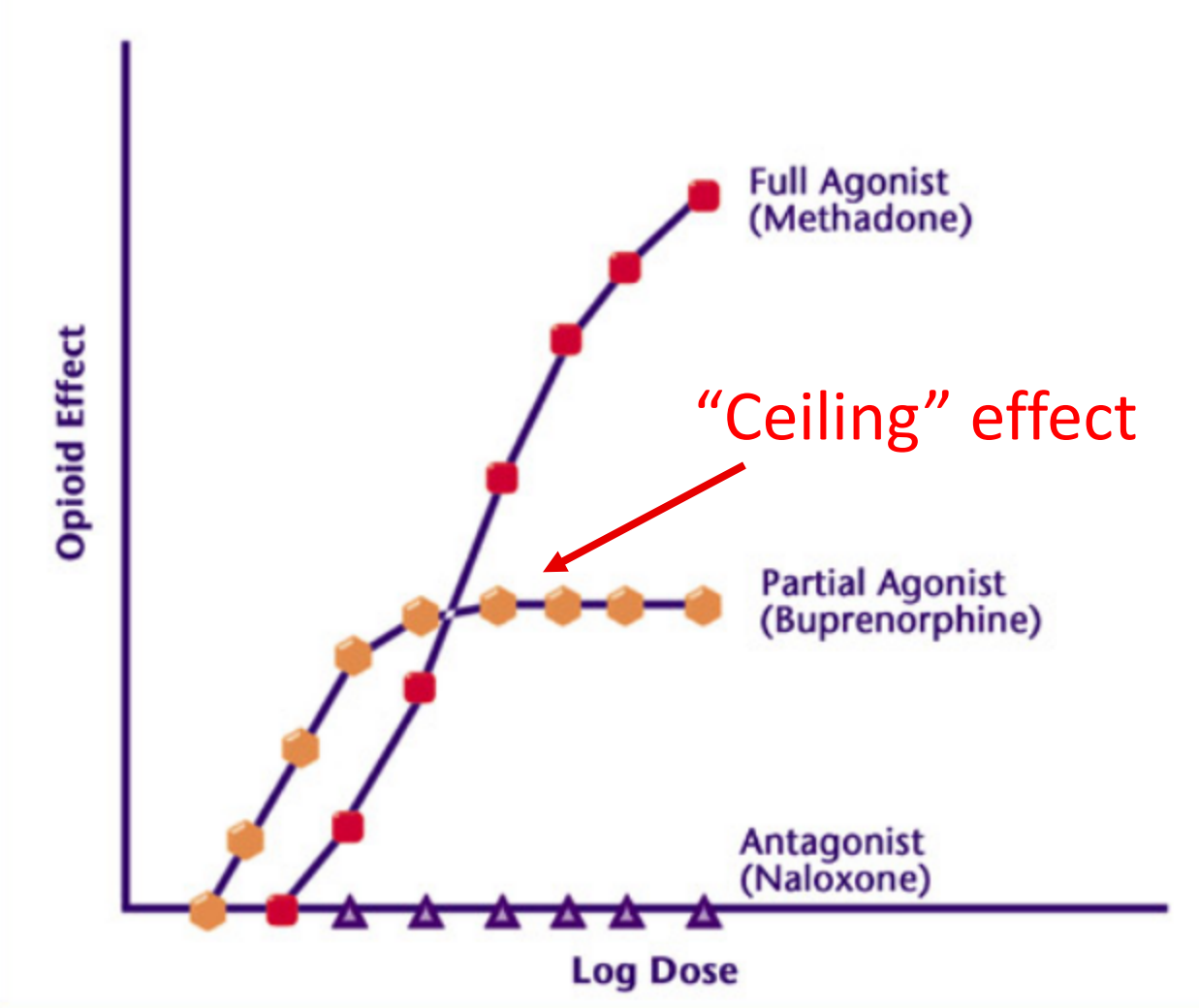
Figure 1

How OUD Medications Work in the Brain

Empty opioid receptor



Pew Charitable Trust, 2016


Full Agonist
(Methadone)
"Ceiling" effect
Partial Agonist
(Buprenorphine)
Antagonist
(Naloxone)
Opioid Effect
Log Dose

VA Guidelines

BUPRENORPHINE FORMULATIONS FOR CHRONIC PAIN MANAGEMENT IN PATIENTS WITH OPIOID USE DISORDER OR ON LONG-TERM OPIOID THERAPY WITH PHYSIOLOGIC TOLERANCE

Buprenorphine Inj, Buprenorphine TDS, Buprenorphine SL Film, Buprenorphine/Naloxone SL tabs Recommendations for Use

October 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives; National Mental Health Office – Substance Use Disorders; National Pain Management Strategy Coordinating Committee

VA Pharmacy Benefits Management Services, 2022

Buprenorphine products for Pain Management

Generic Name	Brand Name	Formulation	FDA-Approved Indications	Bioavailability	Elimination Half-Life
Buprenorphine	Butrans® (VANF)	Transdermal delivery system Available in 5, 7.5, 10, 15 and 20 mcg/hr	Management of pain severe enough to require around-the-clock, long-term opioid treatment	~15%	~26 hours
Buprenorphine	Belbuca® (VANF)	Buccal film Available in 75, 150, 300, 450, 600, 750, 900 mcg films Max dose: 900 mcg every 12 hours	Management of pain severe enough to require around-the-clock, long-term opioid treatment	46 to 65%	11.2 to 27.6 hours
Buprenorphine and naloxone	Suboxone® (VANF)	Sublingual tablet and film Available in 2-0.5 and 8-2 mg SL tabs and 2-0.5, 4-1, 8-2, and 12-3 mg film Target maintenance dose for OUD is 16 – 24mg/day	**Used off-label for pain management.** FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab) ~36% (film)*	24 to 42 hours
Buprenorphine	Subutex® (VANF)	Sublingual tablet Available in 2mg and 8 mg SL tablets Target maintenance dose for OUD is 16 – 24mg/day	**Used off-label for pain management.** FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab)	24 to 42 hours
Buprenorphine	Buprenex® (NF)	IM, IV Available in 0.3 mg/ml ampules Dosing: 0.3 mg every 6-8 hours as needed	Indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.	100%	1.2-7.2 hours (mean 2.2 hours)

VA Pharmacy Benefits Management Services, 2022

Generic Name	Brand Name	Formulation	FDA-Approved Indications
Buprenorphine	Butrans	Transdermal patch	Management of pain severe enough to require around-the-clock, long-term opioid treatment
Buprenorphine	Belbuca	Buccal film	Management of pain severe enough to require around-the-clock, long-term opioid treatment
Buprenorphine and naloxone	Suboxone	Sublingual tablet and film	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD)
Buprenorphine	Subutex	Sublingual tablet	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD)
Buprenorphine	Sublocade	Subcutaneous extended-release	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD)
Buprenorphine	Buprenex	IM, IV	Indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate

Example Costs

Drug	30-day supply	Brand vs. Generic	Price
Belbuca 75 mcg	bid (60 films)	Brand only	$434
Belbuca 600 mcg	bid (60 films)	Brand only	$977
Buprenorphine 10 mcg/hour transdermal film, extended release	Weekly (4 films)	Generic	$135
Buprenorphine/naloxone 8/2 mg	Daily (30 films)	Generic	$93

Drugs.com, 2023

Pharmacokinetic Parameters

- “Cmax is the highest concentration of a drug in the blood, cerebrospinal fluid, or target organ after a dose is given”

Sample Pharmacokinetic Parameters (For Reference Only)

Table VI. Pharmacokinetic parameters of buprenorphine and norbuprenorphine in healthy volunteers treated with multiple (escalating) buccal doses of buprenorphine.

Parameter	Buccal Buprenorphine Dose (Study Day) 60 µg (Day 1)	60 µg (Day 3)	120 µg (Day 6)	180 µg (Day 9)	240 µg (Day 12)
Buprenorphine*					
$AUC_{0-\tau}$, mean (SD), h · ng/mL	NA	0.490 (0.140)	0.966 (0.247)	1.358 (0.595)	2.343 (0.742)
C_{max}, mean (SD), ng/mL	0.080 (0.018)	0.077 (0.020)	0.156 (0.044)	0.216 (0.106)	0.364 (0.125)
T_{max}, h					
Median	1.75	3.0	2.5	2.0	2.0
Range	1.0–3.0	2.0–4.0	2.0–4.0	0–3.0	2.0–3.0
Norbuprenorphine*					
$AUC_{0-\tau}$, mean (SD), h · ng/mL	NA	0.320 (0.153)	0.596 (0.254)	1.159 (0.532)	1.784 (1.031)
C_{max}, mean (SD), ng/mL	0.014 (0.003)	0.033 (0.017)	0.067 (0.027)	0.122 (0.056)	0.179 (0.100)
T_{max}, h					
Median	3.0	2.0	3.0	2.0	2.0
Range	1.5–6.15	1.0–4.0	2.0–4.0	1.0–4.0	0–3.0

NA = not applicable.
*Plasma concentrations below the limit of quantitation were excluded from the pharmacokinetic analysis.

Purdue Pharma, 2014

Indivior, 2018

Bai, 2016

Indivior, 2021

Table 4 Pharmacokinetic parameters (Mean ± SD) of buprenorphine, norbuprenorphine and naloxone following SUBOXONE sublingual tablet administration

PK Parameter	SUBOXONE Sublingual Tablet Dose (mg) 2/0.5	8/2
Buprenorphine		
C_{max} (ng/mL)	0.780 ± 0.323	2.58 ± 1.10
T_{max} (hr)*	1.50 (0.75-3.00)	1.50 (0.50-3.03)
AUC_{inf} (ng.hr/mL)	7.651 ± 2.650	25.31 ± 9.500
$t_{1/2}$ (hr)	30.75 ± 15.04	31.94 ± 15.27

Dose	Timing	Level
SL 12 mg	Steady state	1.71 ng/mL
SL 16 mg	Steady state	2.31 ng/mL
SL 24 mg	Steady state	2.91 ng/mL
300 mg	1st injection	2.19 ng/mL
100 mg	Steady state*	3.12 ng/mL
300 mg	Steady state**	6.54 ng/mL

Sublocade Monthly dose (mg) regimen:
*300-300-100-100-100-100
**300-300-300-300-300-300

Single 7-day Application	AUC_{inf} (pg.h/mL)	C_{max} (pg/mL)
BUTRANS 5 mcg/hour	12087 (37)	176 (67)
BUTRANS 10 mcg/hour	27035 (29)	191 (34)
BUTRANS 20 mcg/hour	54294 (36)	471 (49)
Multiple 7-day Applications	**$AUC_{tau,ss}$ (pg.h/mL)**	**$C_{max,ss}$ (pg/mL)**
BUTRANS 10 mcg/hour, steady-state	27543 (33)	224 (35)

Summary: Sample *Approximate* Levels

Medication	Dose (steady-state)	Level (ng/mL)
Transdermal (Butrans)	10 mcg/hour	0.224
Buccal (Belbuca)	240 mcg bid	0.364
Sublingual (Suboxone)	16 mg daily	2.31
SQ (Sublocade)	100 mg monthly	3.12
SQ (Sublocade)	300 mg monthly	6.54

Suboxone & Sublocade →10 X blood levels of the others!

But do levels predict clinical response?

Potency

- No head-to-head, double-blind placebo-controlled trials
- Given the buprenorphine blood levels, at least *in theory*:
  - 300 mg extended-release SQ buprenorphine >
  - 8/2 mg SL buprenorphine/naloxone >
  - 10 mcg/hour transdermal >
  - 60 mcg bid buccal

Which of the following is NOT FDA-approved for pain?

A. Buccal buprenorphine (Belbuca)
B. Intravenous buprenorphine (Buprenex)
C. Subcutaneous extended-release buprenorphine (Sublocade)
D. Transdermal buprenorphine (Butrans)

Which of the following is NOT FDA-approved for pain?

A. Buccal buprenorphine (Belbuca)
B. Intravenous buprenorphine (Buprenex)
C. Subcutaneous extended-release buprenorphine (Sublocade)
D. Transdermal buprenorphine (Butrans)

Efficacy

"Twelve Reasons for Considering Buprenorphine as a Frontline Analgesic in the Management of Pain"

(1) Effective in cancer pain

(2) Effective in neuropathic pain

(3) Treats broader array of pain phenotypes than certain potent mu agonists, associated with less analgesic tolerance, and can be combined with other mu agonists

(4) Produces less constipation than certain other potent mu agonists ???; does not affect sphincter of Oddi

(5) Ceiling effect on respiratory depression but not analgesia ???

(6) Less cognitive impairment certain other opioids

(7) Not immunosuppressive like morphine and fentanyl

(8) Does not adversely affect hypothalamic-pituitary-adrenal axis or cause hypogonadism ???

(9) Does not significantly prolong QTc interval; less sudden death than is methadone

(10) Safe and effective analgesic for the elderly

(11) One of the safest opioids to use in patients in renal failure and those on dialysis

(12) Withdrawal symptoms are milder, drug dependence is less with buprenorphine ???

Davis, 2012

3/2019 Expert Panel: Buprenorphine for Pain

- Classification as *partial* m-opioid receptor agonist not be clinically translated to mean *partial* analgesic efficacy
- Buprenorphine be considered before some Schedule II, III, or IV opioids in patients with a favorable risk/benefit profile based on metabolic factors, abuse potential, and tolerability

Webster, 2020

Selected Studies of Buprenorphine

- Produced equivalent or superior peri-operative analgesia c/w traditional opioids (23/24 controlled trials)
- Reduced chronic pain without precipitating opioid withdrawal or serious adverse effects in patients with chronic pain who used LTOT (systematic lit review, low quality studies)
- Anti-hyperalgesic effect differentiates buprenorphine from other opioids
- Beneficial effect (varied formulations) on pain intensity overall → bigger effect in those with*out* OUD

Raffa, 2014; Richardson, 2018; Powell, 2021; Infantino, 2021; Lazaridou, 2020

"Treating Chronic Pain with Buprenorphine - The Practical Guide"

- "Buprenorphine has unique and favorable pharmacological properties that make it useful in a variety of clinical scenarios"
- "It has been recommended to consider buprenorphine first-line opioid for chronic pain, especially in the elderly as it may be associated with less cognitive impairment, falls, sexual dysfunction, and sarcopenia when compared with schedule II opioids."
- "It may be useful in patients with comorbid substance use disorder or non-medical opioid use, as there is less risk of misuse and euphoria"
- "For many reasons outlined in this article, the popularity of using buprenorphine for analgesia continues to grow and a practitioner should consider this as an excellent and safe option for chronic pain."

Case, 2021

MedPage February 13, 2023

- “Buprenorphine, rather than a full agonist opioid, should be used for patients taking daily opioids for chronic pain, given its lower risk for overdose or misuse, new guidelines from the Department of Veterans Affairs (VA) and Department of Defense (DoD) recommended.”

George, 2023

February 2023

Annals of Internal Medicine

CLINICAL GUIDELINE

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*

Description: In May 2022, leadership within the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) approved a joint clinical practice guideline for the use of opioids when managing chronic pain. This synopsis summarizes the recommendations that the authors believe are the most important to highlight.

Methods: In December 2020, the VA/DoD Evidence-Based Practice Work Group assembled a team to update the 2017 VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. The guideline development team included clinical stakeholders and conformed to the National Academy of Medicine's tenets for trustworthy clinical practice guidelines. The guideline team developed key questions to guide a systematic evidence review that was done by an independent third party and distilled 20 recommendations for care using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. The guideline team also created 3 one-page algorithms to help guide clinical decision making. This synopsis presents the recommendations and highlights selected recommendations on the basis of clinical relevance.

Recommendations: This guideline is intended for clinicians who may be considering opioid therapy to manage patients with chronic pain. This synopsis reviews updated recommendations for the initiation and continuation of opioid therapy; dose, duration, and taper of opioids; screening, assessment, and evaluation; and risk mitigation. New additions are highlighted, including recommendations about the use of buprenorphine instead of full agonist opioids; assessing for behavioral health conditions and factors associated with higher risk for harm, such as pain catastrophizing; and the use of pain and opioid education to reduce the risk for prolonged opioid use for postsurgical pain.

Ann Intern Med. doi:10.7326/M22-2917 **Annals.org**

For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 14 February 2023.

* For members of the VA/DoD Guideline Development Group, see the **Appendix** (available at Annals.org).

Sandbrink, 2023

Table. Recommendations and Evidence Table

Recommendation	2017 Strength of Recommendation	2022 Strength of Recommendation	Recommendation Category	Evidence
1. We recommend against the initiation of opioid therapy for the management of chronic noncancer pain (for nonopioid treatments of chronic pain, see the VA/DoD CPGs for Low Back Pain, Headache, and Hip and Knee Osteoarthritis*).	Strong against	Strong against	Reviewed, new replaced	(21-30, 32-37, 117)
2. We recommend against long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk for opioid use disorder and overdose.	Strong against	Strong against	Reviewed, new replaced	(27-30, 32-34, 36, 38-46) Additional references: (19, 47-51)
3. We recommend against long-term opioid therapy, particularly for patients with chronic pain who have a substance use disorder (refer to the VA/DoD CPG for the Management of Substance Use Disorders†).	Strong against	Strong against	Reviewed, new replaced	(27, 29, 30, 33, 38, 39, 41, 42, 52-57) Additional reference: (19)
4. For patients receiving medication for opioid use disorder, there is insufficient evidence to recommend for or against the selection of any one of the following medications over the other for the management of their co-occurring chronic pain: methadone, buprenorphine, or extended-release naltrexone injection. Treat the opioid use disorder according to the VA/DoD CPG for the Management of Substance Use Disorders†.	Strong for	Neither for nor against	Reviewed, new replaced	(58-60) Additional references: (57, 61)
5. 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.	Not applicable	Weak for	Reviewed, new added	(21, 22, 25, 31, 62) Additional references: (61, 63-73)
6. We recommend against the concurrent use of benzodiazepines and opioids for chronic pain (refer to recommendation 10 in the VA/DoD CPG for the Management of Substance Use Disorders† for further guidance related to tapering 1 or both agents).	Strong against	Strong against	Reviewed, amended	(29, 52) Additional references: (19, 74)
7. If prescribing opioids, we recommend using the lowest dose of opioids as indicated by patient-specific risks and benefits.	Strong for	Strong for	Reviewed, amended	(27-30, 32, 33, 34, 39, 52, 75, 76, 118) Additional reference: (19)
8. If considering an increase in opioid dosage, we recommend reevaluation of patient-specific risks and benefits and monitoring for adverse events, including opioid use disorder and risk for overdose with increasing dosage.	Strong for	Strong for	Reviewed, new replaced	(27-30, 32-34, 39, 52, 75, 76) Additional reference: (19)
9. When prescribing opioids, we recommend the shortest duration as indicated.	Strong for	Strong for	Reviewed, new replaced	(28, 30, 38-40) Additional references: (19, 77)
10. After initiating opioid therapy, we recommend reevaluation at 30 d or fewer and frequent follow-up visits if opioids are to be continued.	Strong for	Strong for	Reviewed, new replaced	(28, 30, 38-40) Additional references: (19, 77)
11. We recommend against prescribing long-acting opioids: For acute pain As an as-needed medication When initiating long-term opioid therapy	Strong against	Strong against	Reviewed, amended	(28, 30, 31, 42, 62, 78-84) Additional references: (19, 85)
12. We suggest a collaborative, patient-centered approach to opioid tapering.	Strong for	Weak for	Reviewed, new replaced	(86, 87)
13. There is insufficient evidence to recommend for or against any specific tapering strategies.	Strong for	Neither for nor against	Reviewed, new replaced	(86, 87)

Continued on following page

2022 VA/DoD Updated Guidelines

Recommendations	2017 Strength of Recommendation	2022 Strength of Recommendation	Recommendation Category
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.	Not applicable	Weak for	Reviewed, new added

Sandbrink, 2023

Which of the following did NOT recommend considering buprenorphine for pain?

A. An expert consensus panel in 2019
B. CDC Guidelines (2022 revision) for opioid management
C. VA/DoD guidelines (2022) for the use of opioids in chronic pain
D. Several published articles including systematic reviews and meta-analyses

Which of the following did NOT recommend considering buprenorphine for pain?

A. An expert consensus panel in 2019
B. CDC Guidelines (2022 revision) for opioid management
C. VA/DoD guidelines (2022) for the use of opioids in chronic pain
D. Several published articles including systematic reviews and meta-analyses

Which of the following is most accurate about buprenorphine's efficacy in pain?

A. Evidence suggests it can be helpful for pain, but not even close to traditional opioids
B. The little available evidence has explored only pharmacokinetics; nothing has assessed clinical outcomes such as pain relief
C. There is strong evidence proving a very significant clinical response
D. There is some evidence proving a mild/moderate clinical response

Which of the following is most accurate about buprenorphine's efficacy in pain?

A. Evidence suggests it can be helpful for pain, but not even close to traditional opioids
B. The little available evidence has explored only pharmacokinetics; nothing has assessed clinical outcomes such as pain relief
C. There is strong evidence proving a very significant clinical response
D. There is some evidence proving a mild/moderate clinical response

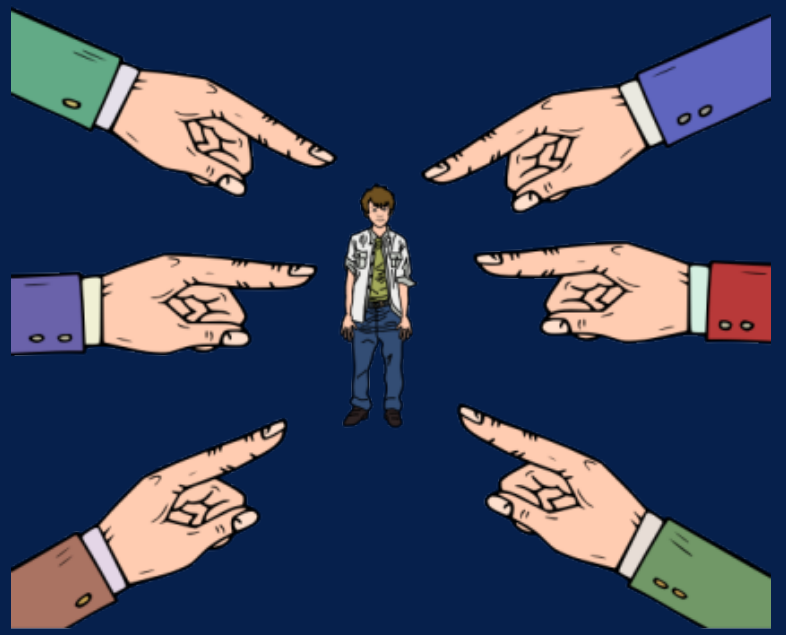
Not So Fast . . .

- "Few studies have compared buprenorphine to other opioids for the treatment of chronic pain. Even fewer data are available to guide clinicians on how pharmacologic, clinical, and patient characteristics may affect buprenorphine's effectiveness in treating chronic pain . . . Clearly, more research about formulation, dosing, and clinical characteristics will be crucial to guide buprenorphine treatment for chronic pain . . . this recommendation is exciting, but underdeveloped, and many questions about implementation remain."

Cunningham, 2023

Elephant in the Room: Stigma

- Could be deciding factor AGAINST using buprenorphine for pain
- How do nurses, providers and others react when “buprenorphine/naloxone” is on medication list?
- Sad . . . But reality



Safety and the “Ceiling”

Ceiling

- “A ‘ceiling effect’ is observed in respiratory depression . . . For this characteristic, buprenorphine has drawn attention as a more manageable drug among other full opioids, although respiratory depression can occur”

Infantino, 2021

2008 Consensus Group of Experts

- Behaves as full μ-opioid agonist for analgesia with no ceiling effect, but there is a ceiling effect for respiratory depression, reducing the likelihood of this potentially fatal adverse event
- The effects of buprenorphine can be reversed by naloxone
- Pronounced anti-hyperalgesic effect → potential advantages in the neuropathic pain?
- Buprenorphine can be considered a safe and effective option for treating chronic cancer and noncancer pain

Pergolizzi, 2010

Narcan: Does It Work?

- Buprenorphine is relatively *resistant* to reversal by naloxone
  - "We tested the effect of naloxone on buprenorphine induced respiratory depression and compared with naloxone-reversal of morphine and alfentanil-induced respiratory depression"
- Increasing doses of naloxone caused a bell-shaped reversal curve of buprenorphine with maximal reversal at naloxone doses between 2 and 4 mg
  - Reversal was short-lived

Sarton, 2008

Effective, BUT Respiratory Depression

- No significant difference in the incidence of respiratory depression with morphine c/w buprenorphine
  - *"Theoretical* ceiling effect may exist for respiratory depression, in clinical application there is still a profound effect on the respiratory drive that can lead to significant adverse outcomes"
- Our study confirms no ceiling effect for analgesia → no difference in analgesia provided by buprenorphine compared with morphine
- Buprenorphine administered in the ED was reported in four studies → equivalent to morphine for acute pain

White, 2018

Concomitant Benzodiazepines and/or Misuse

- "In France where high-dose buprenorphine has been marketed since 1996, several cases of asphyxic deaths were reported among addicts treated with buprenorphine"
- Death resulted from buprenorphine intravenous misuse or concomitant sedative drug ingestion, such as benzodiazepines

Megarbane, 2006

Safety in Special Populations

TABLE 5. Summary of recommendations for buprenorphine use in special populations.

Special Population	Recommendations
Hepatic Impairment	• Buprenorphine is primarily glucuronidated; metabolism less affected in hepatic impairment • Interaction studies indicate that buprenorphine can be used safely in mild and moderate hepatic impairment • Recommend hepatic function monitoring
Renal Impairment	• Buprenorphine can be used safely in renal dysfunction • No evidence of accumulation leading to opioid-related adverse effects
Elderly	• Buprenorphine can be used with caution in the elderly • Transdermal buprenorphine shown to be safe and effective in the elderly and can improve adherence
Pregnancy & Lactation	• Buprenorphine is a first-line agent for the treatment of OUD in pregnancy • Avoid buprenorphine (and all opioids) in pregnancy for pain management • Recommend continuing buprenorphine for OUD during lactation if no contraindications to breastfeeding

Brandt, 2022

Safety in Children

- "An increasing number of children are being exposed to buprenorphine as more adults in US households receive take-home prescriptions. The ceiling effect seen in adults does **not** seem to apply to young children, and intoxication with severe symptoms including fatalities can occur."
- "Oral absorption less potent than sublingual absorption, the tendency of children to lick or suck candy-like substances rather than swallow them actually increases the risk of harm
  - Toddlers in particular are likely to suck on tablets rather than swallow them."

Lo Re, 2019

Which of the following is most accurate about buprenorphine as a partial agonist?

A. As a partial agonist, it can help pain only a teeny-weeny bit
B. Research shows that, as a partial agonist, there is *no* risk of respiratory depression
C. Different formulations and dosing can cause vastly different buprenorphine levels in the blood
D. A higher serum buprenorphine *always* means more pain relief than lower levels

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OUD vs. Dependence

Use Disorder Diagnostic Criteria

- Using larger amounts/for longer time than intended
- Desire/unable to ↓/control use
- Lot of time spent to obtain/use/recover
- Craving
- Failure to fulfill major life roles
- Use despite social problems
- Giving up important activities/isolation
- Use in hazardous situations

- Use despite causing/exacerbating physical or psychological problem(s)
- Tolerance
- Withdrawal

2-3 criteria → mild
4-5 criteria → moderate
>=6 criteria→ severe

American Psychiatric Association 2013

DSM-5 Criteria of Tolerance and Withdrawal

- Do NOT count as OUD criteria in patients who are only taking opioids under appropriate medical supervision
  - Committee wanted to avoid OUD diagnosis for *physiologic* tolerance and withdrawal from taking opioids as prescribed
  - Thus, they eliminated these two criteria for taking as prescribed

Opioid Dependence ICD-10

- This has created DSM-5 “diagnostic orphans” → manifest tolerance, withdrawal, and one other symptom of opioid-related behavioral problems
- “They do not meet DSM-5 opioid use disorder criteria; however, by ICD-10 definition, such patients have ICD-10 opioid dependence . . This ambiguity creates an opportunity for clinical judgement and shared decision-making between the patient and provider . .”

VA Pharmacy Benefits Management Services, 2022

OUD vs. Pain Diagnosis

- “One critical issue regarding the buprenorphine recommendation is the need for clinicians to be clear about which conditions they are treating - chronic pain, OUD, or both - and treatment goals.”

Cunningham, 2023

Buprenorphine for Pain in Opioid Dependence

- While legal to prescribe buprenorphine/naloxone “off-label” for pain, in practice patients on high-risk opioid pain regimens often meet the ICD-10 definition of opioid dependence and have this diagnosis on encounter forms in their record
  - And I thought this was my idea ☺
- Good for insurance coverage

VA Pharmacy Benefits Management Services, 2022

Dosing

Consider Buprenorphine (vs. Traditional Opioids) for Pain if:

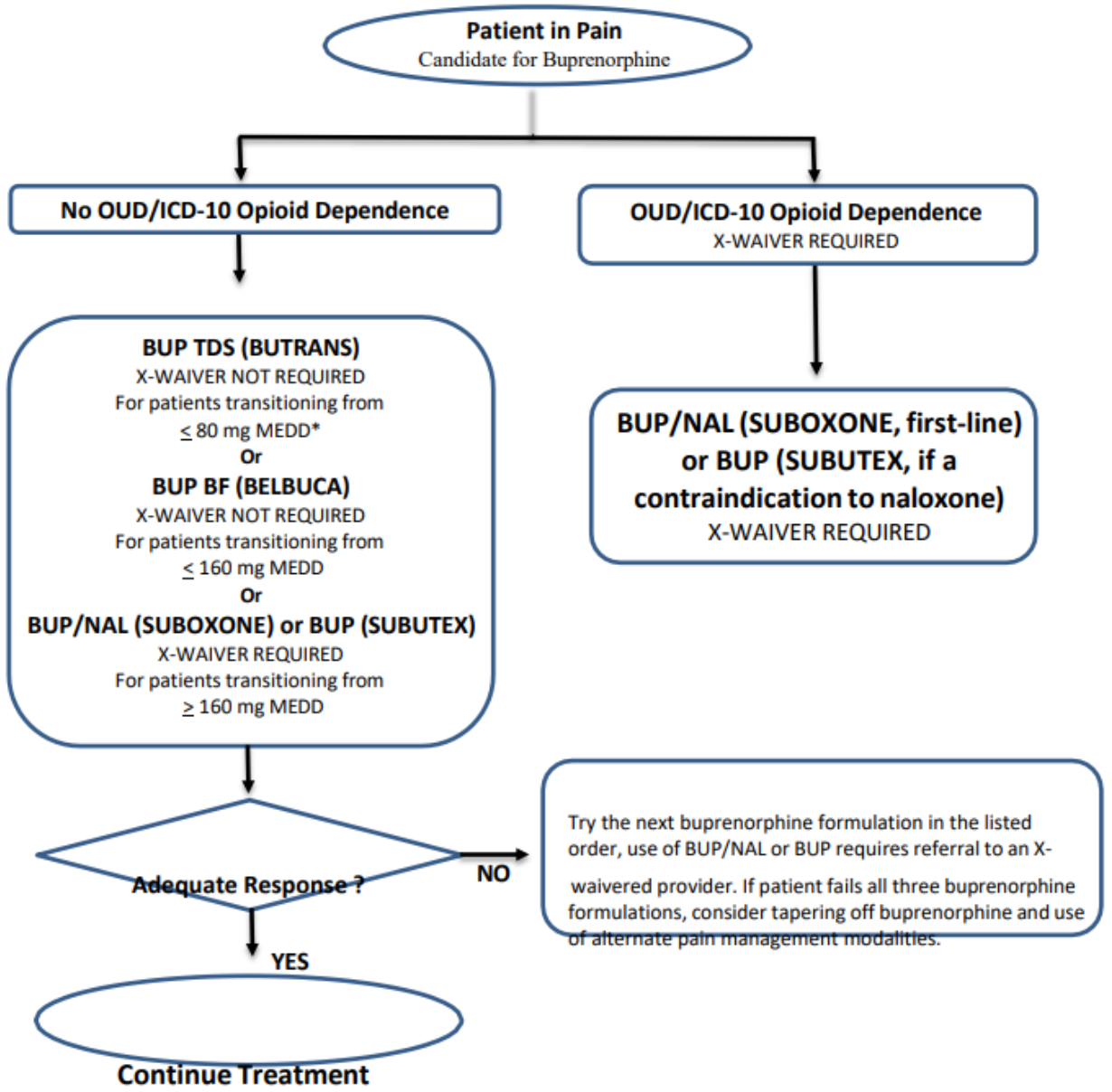
- History of problems with drugs/alcohol
- Co-morbidities and risks from opioids?
  - Concurrent benzodiazepines
  - Sleep apnea / other pulmonary risks
  - Renal disease
- Risks of diversion and/or stealing medications
- Adverse reactions and/or poorer QOL from traditional opioids

When to Consider Which Formulation

- Transdermal & buccal?
  - No h/o OUD
  - Insurance coverage?
  - Not on (or on low-dose) traditional opioids
- Sublingual
  - Above ineffective
  - OUD history
  - Want/need to come off traditional opioids (“opioid dependence”)
- Extended-release monthly subcutaneous
  - Already on sublingual, but pain persists and/or only short relief
  - Logistics → difficulty remembering medications, keeping them secure, etc.
  - Insurance coverage?

Same Thing, Visually

NOTE: outdated already (X-waiver no longer required)



*Abbreviations: MEDD = Morphine Equivalent Daily Dose, BUP = Buprenorphine, BUP/NAL = Buprenorphine/Naloxone, BUP TDS = Buprenorphine Transdermal System, BUP BF = Buprenorphine Buccal Film, OUD = Opioid Use Disorder, ICD = International Classification of Diseases.

VA Pharmacy Benefits Management Services, 2022

Tip: FDA-Labeled vs. Sublingual Formulation for Patients NOT on Traditional Opioids - Insurance Coverage

- Maybe start with buccal or transdermal even if you think sublingual would be better
  - Start with the standard (FDA-approved)
- Then if it doesn't work, you can appeal to insurance → you tried standard already

Suggested Conversation with Insurance Reviewer for SL Buprenorphine for patients NOT already on opioids

- You:
  - "We attempted buccal and/or transdermal, it didn't work, so we want the patient to be on sublingual"
- Peer reviewer:
  - "I get that, but sublingual is not FDA-approved for pain."
- You:
  - "Yes, I know, but it's got a much better safety profile than traditional opioids. Given the opioid crisis, and the patient's co-morbidities [list some – OSA, etc.], I think the patient would be better on sublingual buprenorphine rather than traditional opioids. I'm sure you don't want them on traditional opioids, stop breathing and die, correct? By the way, how do you spell your name, so I can document our conversation in the medical record?"

Initiation (Systematic Review)

- "Overall, 95.6% of patients in the traditional initiation group and 96% of patients in the microdosing group successfully rotated to sublingual buprenorphine. Initiation regimens can vary widely depending on patient-specific factors and buprenorphine formulation. A variety of buprenorphine transition strategies are published in the literature, many of which were effective for patients with OUD, pain, or both"

Spreen, 2022

Induction Options

- If not already on opioids → just start buprenorphine?
- If already on opioids → prevent precipitated withdrawal
- Three options
  - Slow opioid wean (months); when off, start buprenorphine
  - "Traditional" induction → d/c opioids, comfort meds, start buprenorphine when in w/d
  - "Low-dose" induction → continue opioids, start buprenorphine at very low dose, increase (over a week?), then d/c opioids

- See other sessions at ASAM for detailed regimens and suggestions

Split Dosing

- "To optimize analgesic efficacy, the drug should be given three times a day when pain reduction is a goal" (SAMHSA, 2011)
- " . . Split dosing strategy better aligns the dosing with buprenorphine's analgesic properties. The analgesic effects of buprenorphine last for approximately 6–8 hours while the withdrawal and craving suppressing properties last for approximately 24 hours. When moving to split dosing the clinician should ensure that the patient has not missed their last non-split dose. Increasing the daily dose of buprenorphine by 20–25% and splitting it into 3–4 doses can often adequately address acute pain." (ASAM, 2020)
- "Split dosing of buprenorphine (with dosing every 6–8 hours) may be adequate for chronic pain management in many patients with opioid use disorder and chronic pain." (ASAM, 2020)
- "For concurrent chronic pain, consider dividing [Buprenorphine/Naloxone or Buprenorphine] total daily dose into twice or thrice daily administration" (VA/DoD, 2021)

SAMHSA, 2011
ASAM, 2020
VA/DOD, 2021

Dose buprenorphine tid (or qid), NOT qd or bid, for pain

Dose to Start?

- Buccal, transdermal → follow instructions (ePocrates, etc.)
- Sublingual dose? Factors:
  - High tolerance d/t chronic opioids?
  - Multiple other medications that cause CNS depression?
  - "Sensitive" to medications?
- Reminder: cutting strips (commonly done!) → off-label

- I usually start 4/4/4 in most situations
- Can easily go up or down for some or all the doses
- Usually, I Rx half of 8/2 mg strips
  - Flexibility in dosing (can cut to 2, 4, or keep at 8)
  - Usually in stock at pharmacies (4 mg strips, not so much)
- Sometimes Rx'd as 1.5 strips per day
  - But tell patient, do 0.5 tid

Review with ALL Patients: How to Take Buprenorphine

- No eating, drinking, smoking 20 minutes before
- But, sip water (moisten mouth)
- Place under tongue
- Lean forward → NO swallowing saliva
  - Drooling ok
- Do not chew or swallow the film, or talk
- After dissolved (10 minutes), spit out
- Wait for at least one hour before brushing teeth

Indivior, 2022

Monitoring

- Even if no OUD . . . It's still a controlled substance!
- Periodic UDS, medication/wrapper counts, etc.
- Watch for SE
  - Constipation? Bowel regimen

Cases

- We may not get to all . . . That's ok!

Luke (background)

- 38 y.o., seizures, neuropathic pain, obesity
- Previous addiction to pain pills
- Sober since 4/2019, AND in “good recovery”
- On SQ extended-release buprenorphine monthly
- S/p root canal → dentist (who communicated with you) offered hydrocodone → pt declined initially, didn’t want → but now has pain and calls

Which of the following is NOT a reasonable next step for Luke?

A. Rx hydrocodone/acetaminophen 5/300 mg, 1-2 every 8 hours PRN pain, #10, call if persists (or needs higher dose to overcome buprenorphine blockade)
B. Rx SL buprenorphine/naloxone 8/2 mg, ½ - 1 strip every 8 hours PRN pain, #9, call if persists
C. Review ideas with patient but have them call the dentist
D. Tell them because they are in good recovery and you don't want to "ruin" it, he *absolutely* should not have ANY opioids

Which of the following is NOT a reasonable next step for Luke?

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C. Review ideas with patient but have them call the dentist
D. Tell them because they are in good recovery and you don't want to "ruin" it, he *absolutely* should not have ANY opioids

Roy (background)

- 70 y.o.
- No h/o opioids until 15 years ago → work back injury
- Pain management (on about 50 MEDD)
  - Hydrocodone/acetaminophen 10/325 bid
  - Morphine sulfate ER 15 mg bid
- Remote h/o cocaine and alcohol use, sober X decades
- Patient: “It’s time to get off of these things“
  - Has tried, but significant w/d
  - "I’ve had it with them, and the pain doctor does not want me on them”
- Referred by pain management → buprenorphine?

Roy → Next Steps?

Roy (next steps)

- Daughter present → nurse at a detox center
- Options:
  - Slow (months) wean
  - "Traditional" induction (but cardiac disease, co-morbidities)
  - "Low-dose" induction
- Chose low-dose induction
  - Daughter was paranoid about it . . .
- Doing GREAT!
- Last visit 3/2023, on 4 mg/4 mg/8 mg based on his symptoms (actually, 4/4/4/4)

Jason

- 28 y.o., L knee injury (high school football)
- Developed chronic pain
- Now oxycodone 10 mg qid PRN
- No h/o drug use/misuse; work & home life are fine
- Past 2-3 months → more “cravings” due to pain
  - Needs more pills to get same relief (no street drugs through)
- Referred by PCP for consideration of buprenorphine

Of the following, which is the best next step for Jason?

A. Given cravings/tolerance, he certainly DOES qualify for (at least mild) OUD per DSM-5 and should start bid 8/2 mg SL buprenorphine/naloxone
B. He certainly does NOT meet criteria for OUD; start transdermal buprenorphine 5 mcg/hour
C. Great candidate to get test dose of 8/2 mg SL buprenorphine/naloxone in the office now, and see if it helps pain
D. Diagnosing OUD vs. dependence here is a gray zone → have informed discussion about pros/cons and FDA-labeling/off-labeling of buprenorphine products for shared decision-making

Of the following, which is the best next step for Jason?

A. Given cravings/tolerance, he certainly DOES qualify for (at least mild) OUD per DSM-5 and should start bid 8/2 mg SL buprenorphine/naloxone
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Alexa (background)

- 37 y.o. chronic pain → non-specific muscle disorder and fibromyalgia
- Co-morbid anxiety
- “Sensitive to meds” → wants to avoid traditional opioids
- In your office

Alexa → Next Steps?

Alexa (next possible steps)

- Non-opioid treatments (SNRI, aqua-therapy, etc.)
- Transdermal buprenorphine patch
  - Start 5mcg/hour patch weekly
  - Increase over 2 months (slowly) to 10 mcg/hour patch
  - She tried → minimal difference
- Wants to try sublingual
  - Start 2/0.05 mg buprenorphine/naloxone SL tid
  - Prior authorization needed→ successful (d/t transdermal failure); otherwise, could (sort of) diagnose “opioid dependence” given the patch?
- 2 weeks later, NO change

What is the BEST immediate next step?

A. Confirm proper technique (how to take SL buprenorphine) → re-assess if she hadn't been doing
B. Watchful waiting; re-assess Alexa in 6 weeks
C. Adjust the dose now to 8/2 mg SL tid
D. Stop buprenorphine and start tramadol 50 mg qid

What is the BEST immediate next step?

A. Confirm proper technique (how to take SL buprenorphine) → re-assess if she hadn't been doing
B. Watchful waiting; re-assess Alexa in 6 weeks
C. Adjust the dose now to 8/2 mg SL tid
D. Stop buprenorphine and start tramadol 50 mg qid

Charlie (background)

- 72 y.o.
- Chronic back pain → helicopter accident in Vietnam
- Escalating doses of opioids over years
- On 160 MEDD → fatigue, depression, constipation, isolation from family and events
- Decided to stop . . . suddenly . . . on his own
- Admitted for delirium and agitation

Charlie → Next steps?

Charlie (next steps)

- Safety first
  - Low-dose anti-psychotics, benzodiazepines
- “Comfort” medications
- Started 8/2 mg SL buprenorphine/naloxone
  - Chosen d/t high MEDD, significant withdrawal and pain
- Felt better, dose adjusted over time to half of 8/2 mg (total 4 mg) SL tid

You see him 2 weeks later; which of the following is the BEST way to gauge efficacy?

A. On pain scale administered by the MA, scores 4 frowny faces
B. Serum buprenorphine level = 3.47 (if obtained for some reason)
C. Can now walk up the hill to watch grand-daughter play field hockey
D. Charlie's insurance company sends you fruit basket because his medication is cheaper than many previous opioids & ED visits

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Charlie (conclusion)

- Eventually, 8/4/4 (8 mg in AM, 4 mg afternoon, 4 mg evening)
- Three months later, struts into office:
- “I wish I did this years ago!”

Learning Objectives: Met?

- By the end of the presentation, attendees will be able to:
  - List available published evidence supporting buprenorphine's use in acute and chronic pain
  - Identify patients with pain whom providers should consider for buprenorphine
  - Safely and comfortably initiate and manage buprenorphine for pain

Final Takeaways/Summary

- Consider buprenorphine for acute and chronic pain, especially in those with OUD and/or physiologic opioid dependence
- Evidence is limited . . . But growing and promising
- Many advantages over traditional opioids
- Formulations vary
  - FDA-labeling, costs, administration routes, potential buprenorphine levels
  - Sublingual buprenorphine tends to get higher levels
  - Dose tid (not qd or bid) for pain

References

- Ablin JN, Buskila D. "Real-life" treatment of chronic pain: Targets and goals. Best Pract Res Clin Rheumatol. 2015;29(1):111-119.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM–5). 2013.
- American Society of Anesthesiologists – Pain Medicine. Don’t prescribe opioid analgesics as long-term therapy to treat chronic non-cancer pain until the risks are considered and discussed with the patient. 2014 January 21. Available at https://www.choosingwisely.org/clinician-lists/american-society-anesthesiologists-opioid-analgesics-as-long-term-therapy-for-non-cancer-pain/.
- ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. J Addict Med. 2020 Mar/Apr;14(2S Suppl 1):1-91. doi: 10.1097/ADM.0000000000000633. Erratum in: J Addict Med. 2020 May/Jun;14(3):267. PMID: 32511106.
- Bai SA, Xiang Q, Finn A. Evaluation of the Pharmacokinetics of Single- and Multiple-dose Buprenorphine Buccal Film in Healthy Volunteers. Clin Ther. 2016 Feb;38(2):358-69. doi: 10.1016/j.clinthera.2015.12.016. Epub 2016 Jan 21. PMID: 26804639.
- Brandt C, Atkinson TJ. A review of the safety of buprenorphine in special populations. Am J Med Sci. 2022 Dec;364(6):675-684. doi: 10.1016/j.amjms.2022.06.025. Epub 2022 Jul 16. PMID: 35843298.

References

- Case AA, Kullgren J, Anwar S, Pedraza S, Davis MP. Treating Chronic Pain with Buprenorphine-The Practical Guide. Curr Treat Options Oncol. 2021 Nov 18;22(12):116. doi: 10.1007/s11864-021-00910-8. PMID: 34791564.
- Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Opioid Prescribing Resources. 2022 November 3. Accessed February 9, 2023 from https://www.cdc.gov/opioids/healthcare-professionals/prescribing/index.html.
- Cunningham CO, Starrels JL. Guideline Promoting Buprenorphine for Treatment of Chronic Pain: Transformative Yet Underdeveloped. Ann Intern Med. 2023 Feb 14. doi: 10.7326/M23-0229. Epub ahead of print. PMID: 36780656.
- Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012 Nov-Dec;10(6):209-19. doi: 10.1016/j.suponc.2012.05.002. Epub 2012 Jul 17. PMID: 22809652.
- Drugs.com. Price Guide. Accessed February 22, 2023 athttps://www.drugs.com/price-guide/ .
- George, J. (2023, February 13). Buprenorphine for Chronic Pain, Not Full Agonist Opioids, New VA Guidance Says. MedPage Today. https://www.medpagetoday.com/neurology/painmanagement/103090.
- Hale M, Gimbel J, Richard R. Buprenorphine Buccal Film for Chronic Pain Management. Pain Manag. (2020) 10(4), 213–223.

References

- Indivior. Annual Report 2017: ATRIGEL Delivery System. https://www.indivior.com/resources/dam/id/755/211013%20INDIVIOR-2017%20annual%20report.pdf. Accessed 9/21/2021.
- Indivior. Sublocade Prescribing Information. https://www.sublocade.com/Content/pdf/prescribing-information.pdf. Accessed 9/21/2021.
- Indivior. Suboxone (buprenorphine/naloxone) [package insert].US Food and Drug Administration website. February 2018. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020733s022lbl.pdf
- Infantino R, Mattia C, Locarini P, Pastore AL, Maione S, Luongo L. Buprenorphine: Far Beyond the "Ceiling". Biomolecules. 2021 May 31;11(6):816. doi: 10.3390/biom11060816. PMID: 34072706; PMCID: PMC8230089.
- Lazaridou A, Paschali M, Edwards RR, Gilligan C. Is Buprenorphine Effective for Chronic Pain? A Systematic Review and Meta-analysis. Pain Med. 2020 Dec 25;21(12):3691-3699. doi: 10.1093/pm/pnaa089. PMID: 32330264.
- Lo Re M, Chaplin M, Aronow B, Modesto-Lowe V. Buprenorphine Overdose in Young Children: An Underappreciated Risk. Clin Pediatr (Phila). 2019 Jun;58(6):613-617. doi: 10.1177/0009922819829038. Epub 2019 Feb 10. PMID: 30740990.

References

- Mégarbane B, Hreiche R, Pirnay S, Marie N, Baud FJ. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. Toxicol Rev. 2006;25(2):79-85. doi: 10.2165/00139709-200625020-00002. PMID: 16958555.
- National Alliance of Advocates for Buprenorphine Treatment. Accessed February 23, 2023 at https://www.naabt.org/education/technical_explanation_buprenorphine.cfm.
- Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R, Mercadante S, Morlion B, Raffa RB, Sabatowski R, Sacerdote P, Torres LM, Weinbroum AA. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010 Sep-Oct;10(5):428-50. doi: 10.1111/j.1533-2500.2010.00378.x. PMID: 20492579.
- Pew Charitable Trust. Medication-Assisted Treatment Improves Outcomes for Patients With Opioid Use Disorder. 2016 November 22. Available at: https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2016/11/medication-assisted-treatment-improves-outcomes-for-patients-with-opioid-use-disorder.
- Powell VD, Rosenberg JM, Yaganti A, et al. Evaluation of Buprenorphine Rotation in Patients Receiving Long-term Opioids for Chronic Pain: A Systematic Review. JAMA Netw Open. 2021;4(9):e2124152. doi:10.1001/jamanetworkopen.2021.24152.

References

- Purdue Pharma L.P. BUTRANS® (buprenorphine) Transdermal System for transdermal Administration [package insert].US Food and Drug Administration website. June 2014. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021306s015s019lbl.pdf.
- Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166(7):514-530.
- Raffa RB, Haidery M, Huang HM, Kalladeen K, Lockstein DE, Ono H, Shope MJ, Sowunmi OA, Tran JK, Pergolizzi JV Jr. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther. 2014 Dec;39(6):577-83. doi: 10.1111/jcpt.12196. Epub 2014 Jul 29. PMID: 25070601.
- Richardson MG, Raymond BL. Lack of Evidence for Ceiling Effect for Buprenorphine Analgesia in Humans. Anesth Analg. 2018 Jul;127(1):310-311. doi: 10.1213/ANE.0000000000003368. PMID: 29624528.
- Sandbrink F, Murphy JL, Johansson M, Olson JL, Edens E, Clinton-Lont J, Sall J, Spevak C; VA/DoD Guideline Development Group. 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. Ann Intern Med. 2023 Feb 14. doi: 10.7326/M22-2917. Epub ahead of print. PMID: 36780654.

References

- Sanders SH, Harden RN, Vicente PJ. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. Pain Pract. 2005;5(4):303-315.
- Sarton E, Teppema L, Dahan A. Naloxone reversal of opioid-induced respiratory depression with special emphasis on the partial agonist/antagonist buprenorphine. Adv Exp Med Biol. 2008;605:486-91. doi: 10.1007/978-0-387-73693-8_85. PMID: 18085322.
- Spreen, LA, Dittmar, EN, Quirk, KC, Smith, MA. Buprenorphine initiation strategies for opioid use disorder and pain management: A systematic review. Pharmacotherapy. 2022; 42: 411– 427. doi:10.1002/phar.2676
- Substance Abuse and Mental Health Services Administration. Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders. Treatment Improvement Protocol (TIP) Series 54. HHS Publication No. (SMA) 12-4671. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011.
- Substance Abuse and Mental Health Services Administration. Removal of DATA waiver (X-waiver) requirement. 2023 Jan 25. Accessed at www.samhsa.gov/medications-substance-use-disorders/removal-data-waiver-requirement.

References

- VA/DoD Clinical Practice Guideline for the Diagnosis and Treatment of Low Back Pain. Version 3.0, 2022. https://www.healthquality.va.gov/guidelines/Pain/lbp/VADoDLBPCPGFinal508.pdf. Accessed February 22, 2023.
- VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Version 4.0,2021. https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Accessed February 22, 2023.
- VA Pharmacy Benefits Management Services. Buprenorphine Formulations for Chronic Pain Management in Patients with Opioid Use Disorder or on Long-Term Opioid Therapy with Physiologic Tolerance. October 2022. Accessed at https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Buprenorphine_Formulations_for_Pain_Management_RFU_Rev_Oct_2022.pdf.
- Webster L, Gudin J, Raffa RB, Kuchera J, Rauck R, Fudin J, Adler J, Mallick-Searle T. Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. Pain Med. 2020 Apr 1;21(4):714-723. doi: 10.1093/pm/pnz356. PMID: 31917418; PMCID: PMC7139205.
- White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM. Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2018 Apr;120(4):668-678. doi: 10.1016/j.bja.2017.11.086. Epub 2017 Dec 2. PMID: 29576108.