



# Partial Agonist, Full Barrier: A Case-Based Discussion on Challenges with Buprenorphine in Chronic Pain Management

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## Objectives

1. Identify challenges of managing chronic pain with buprenorphine.
2. Demonstrate the role of various interdisciplinary team members in the care of patients on buprenorphine.
3. Design and modify a therapeutic regimen with buprenorphine considering dosage form, insurance coverage, and product availability.
4. Devise educational strategies for patients and healthcare providers who are unfamiliar with buprenorphine.
5. Create best practices to guide buprenorphine use within a practice or system.

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## Case #1

NR is 56 year old M with metastatic colon cancer (currently with NED for past 3 months) followed in the Palliative Care Clinic for management of cancer-related pain and chemotherapy-induced peripheral neuropathy (CIPN). At his clinic visit today, he expresses interest in coming off Xtampza due to difficulty getting medication and stigma with opioid medicines. He is willing to change to a buprenorphine product but is concerned about the transition.

### Pertinent medications:

- Xtampza 27 mg q8h
- Oxycodone IR 10 mg q4h PRN breakthrough pain
- Pregabalin 150 mg TID
- Duloxetine 60 mg daily

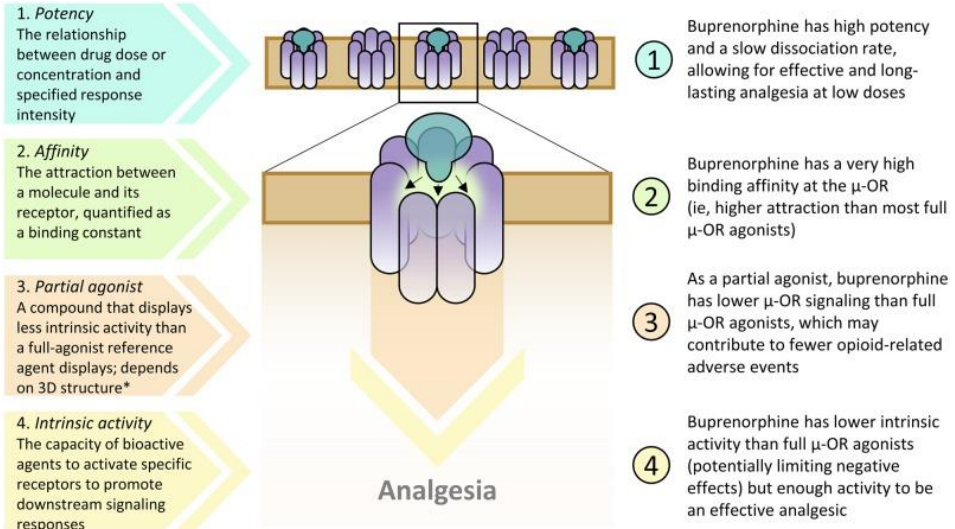
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Background

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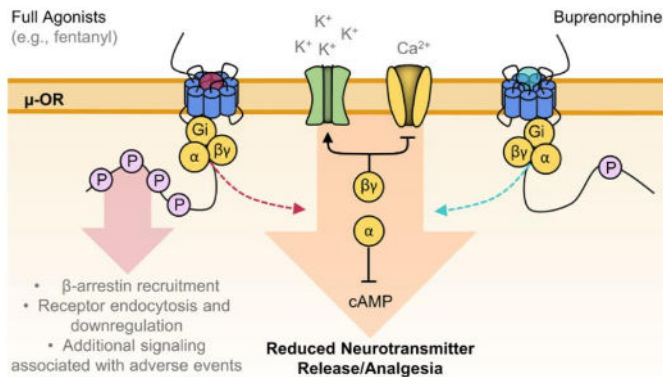
# Buprenorphine Receptor Activity



Webster L, et al. *Pain Med.* 2020 Apr 1;21(4):714-723.

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# $\mu$ -OR Downstream Effects



**Buprenorphine**  
**↓  $\beta$ -arrestin recruitment and signaling →**  
**↓ constipation, respiratory depression, tolerance, dependence**

Case AA, et al. *Curr Treat Options in Oncol.* 2021;22:116.  
 Gudini J, Fudin J. *Pain Ther.* 2020 Jun;9(1):41-54.

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## Buprenorphine Effects vs Full Agonist Opioids

Receptor Activity	Effects
<b>Mu Opioid Receptor:</b> Partial Agonist	Potent analgesia Ceiling effect (dose-related) on respiratory depression, euphoria ↓ tolerance, addiction, withdrawal ↓ constipation, immunosuppression, HPA axis suppression ↓ anxiety, depression, dysphoria, suicidal ideation

Gudin J, Fudin J. *Pain Ther.* 2020 Jun;9(1):41-54.  
U.S. Department of Veterans Affairs. Buprenorphine for Chronic Pain Clinician Guide. May 2021.

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## Buprenorphine Effects (cont.)

Receptor Activity	Effects
<b>Kappa Opioid Receptor:</b> Antagonist	↓ anxiety, depression, dysphoria, hostility, suicidal ideation ↓ tolerance, addiction ↓ sedation, hyperalgesia, immunosuppression
<b>Delta Opioid Receptor:</b> Antagonist	Anti-opioid effects Myocardial protection ↓ respiratory depression, constipation
<b>Orphan-like Receptor 1 (ORL-1):</b> Reduced Affinity	↑ spinal analgesia ↓ opioid reward effects, tolerance

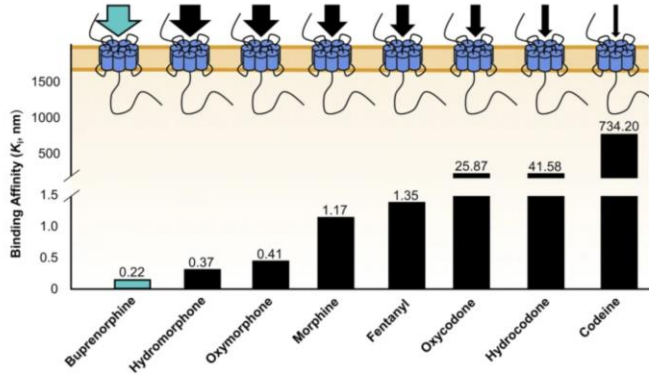
Gudin J, Fudin J. *Pain Ther.* 2020 Jun;9(1):41-54.  
U.S. Department of Veterans Affairs. Buprenorphine for Chronic Pain Clinician Guide. May 2021.

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# Binding Affinity

Fig. 1

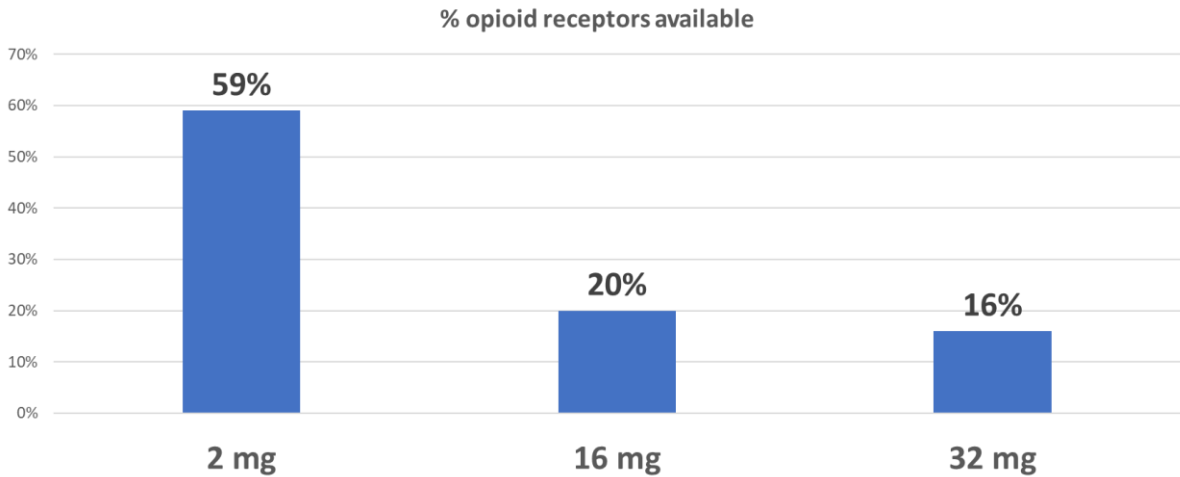


Buprenorphine exhibits a higher binding affinity at the  $\mu$ -opioid receptor than full  $\mu$ -opioid receptor agonists. A low  $K_d$  value corresponds to greater binding affinity but does not necessarily translate to greater receptor activity [18]

Gudin J, Fudin J. *Pain Ther.* 2020 Jun;9(1):41-54.

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## $\mu$ -Opioid Receptor Availability with Increasing Buprenorphine Doses



Webster L, et al. *Pain Med.* 2020 Apr 1;21(4):714-723.

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## Unique Side Effects of Buprenorphine

*Education Tip: Printed information on buprenorphine from pharmacies often has same warnings that come with full agonist opioids which may deter patients.*

- Nausea (~10%)
- **CNS:** fatigue (5%), headache (4%), dizziness, trouble sleeping
- **Dental:** tooth decay, cavities, tooth loss reported in patients using transmucosal (buccal, SL) buprenorphine with or without history of dental disease
  - Occurred any time between 5 to 77 months of therapy
  - Dose range: 2-20 mg/day
  - Proposed mechanism: acidity of product

*Education Tip: Keep up with regular dental health maintenance. After tab or film dissolved, swish a sip of water around teeth and gums and swallow.*



Lexicomp®  
Suzuki J, et al. *Prim Care Companion CNS Disord.* 2013.

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## X-Waiver Elimination

An official website of the United States government [Here's how you know](#) ▾

**SAMHSA**  
Substance Abuse and Mental Health  
Services Administration

[Find Help](#)
[Practitioner Training](#)
[Public Messages](#)
[Grants](#)
[Data](#)
[Programs](#)
[Newsroom](#)

[Home](#) » [Medications for Substance Use Disorders](#)

**Medications for Substance Use Disorders**

Medications, Counseling, and  
Related Conditions

[Find Substance Use Disorder](#)

### Waiver Elimination (MAT Act)

Section 1262 of the Consolidated Appropriations Act, 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (have a waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder (OUD). With this provision, and effective immediately, SAMHSA will no longer be accepting NOIs (waiver applications).

*Notice of Intent (NOI) was never needed for treatment of pain.*

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## Buprenorphine Products

Product	Formulation	Dosing	Indications
Butrans® (buprenorphine)	Transdermal patch	5, 7.5, 10, 15, 20 mcg/hr	Pain
Belbuca® (buprenorphine)	Buccal film	75, 150, 300, 450, 600, 750, 900 mcg	Pain
Subutex® (buprenorphine)	Sublingual tablet	2, 8 mg	OUD Off-label for pain
Suboxone® (buprenorphine/ naloxone)	Sublingual film or tablet	2/0.5, 4/1, 8/2, 12/3 mg	OUD Off-label for pain

Lexicomp®

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## Buprenorphine Bioavailability

Route of Administration	Bioavailability
Intravenous	100%
Buccal	46-65%
Sublingual	28-51%
Transdermal	15%

Gudin J, Fudin J. *Pain Ther.* 2020 Jun;9(1):41-54.

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## Transdermal Buprenorphine (Butrans®)

- For pain
- Doses: 5 mcg/h, 7.5 mcg/hr, 10 mcg/h, 15 mcg/h, 20 mcg/h
  - If opioid-naive: start 5 mcg/h every 7 days
  - If on opioids: start 10 mcg/h (or morphine-equivalent dose)
  - Max dose 20 mcg/h in U.S.
- May take 3 days to reach steady state
  - *Minimum titration interval*
- Risk of QT prolongation at higher doses (eg, 40 mcg/h) but not associated with arrhythmias

Connor R, ed. *Buprenorphine: Drug Information.* Wolters Kluwer


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**Application & Rotation Tutorial**

**Choose an application site**

1. Butrans should be applied to:



Upper outer arm    Upper chest    Upper back    Side of the chest

2. These 4 application sites (located on both sides of the body) provide a total of 8 possible Butrans application sites

3. You should change the skin site where you apply Butrans each week, making sure that at least 3 weeks (21 days) pass before you reuse the same skin site. The [Application Site Tracker](#) may be used to help you remember which sites you've already used

● ● ● ● ●

<https://butrans.com/resources/how-to-apply-patch>

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## Buccal Buprenorphine (Belbuca®)

- For pain
- Doses: 75 mcg up to 900 mcg (7 different dosage strengths)
  - BID dosing
  - <30 OME: 75 mcg once daily and then titrate to BID. Do this for at least 4 days before increasing
  - 30-89 OME per day: 150 mcg BID
  - 90-160 OME per day: 300 mcg BID
- Doses exceeding 900 mcg BID associated with QT prolongation
- May take 4 days to reach steady state
  - *Dose change no sooner than every 4 days*

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## Belbuca® Administration



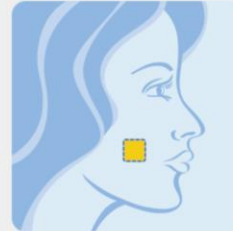
### 1 PEEL

- With clean, dry fingers, **peel** open the foil package. Fold along the dotted line at the top of the package and tear at the perforation
- You can also use scissors to carefully cut along the dotted line



### 2 PLACE

- Wet the inside of your cheek with your tongue or with water
- Carefully remove the BELBUCA film from the foil package and
- **Place** the film on your dry finger with the yellow side facing up



### 3 PRESS

- **Press** the yellow side against the inside of your cheek. Hold it in place for 5 seconds, and then take your finger away
- Leave BELBUCA on the inside of your cheek until fully dissolved, usually within 30 minutes

<https://www.belbuca.com/starting-treatment>

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## Buprenorphine (tablet)

- For OUD; off-label for chronic pain
- Sublingual
- Subutex® (brand) discontinued in 2011
- Buprenorphine 2 mg and 8 mg
- May take 7 days to reach steady state
- Pearls:
  - Bitter taste
  - Can cut tablets in half

[https://www.deadiversion.usdoj.gov/drug\\_chem\\_info/buprenorphine.pdf](https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf)  
Dong R, Wang H, Li D, et al. *Drugs R D*. 2019;19(3):255-265

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## Buprenorphine/Naloxone (Suboxone®)

- Sublingual tablet or film
- For OUD; off-label for chronic pain
  - Dosed **daily** for OUD
  - Dosed **2-3 times daily** for pain
- Products: 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg
- May take 7 days to reach steady state
- Can also be administered buccally (for maintenance)
  - Exposure to naloxone is higher after buccal than after sublingual administration
- Avoid in patients with moderate to severe hepatic impairment (due to reduced naloxone clearance) – FDA warning

Dong R, Wang H, Li D, et al. *Drugs R D*. 2019;19(3):255-265

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### To take SUBOXONE sublingual film under your tongue (sublingual administration):

- Hold the film between two fingers by the outside edges.
- Place the SUBOXONE sublingual film under your tongue, close to the base either to the left or right of the center (see Figure 3).



Figure 3

- If your healthcare provider tells you to take 2 films at a time, place the second film under your tongue on the opposite side. Avoid letting the films touch.
- Keep the films in place until they have completely dissolved.
- If your healthcare provider tells you to take a third film, place it under your tongue on either side after the first 2 films have dissolved.

Suboxone® Medication Guide

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## Naloxone in Combination Buprenorphine Products

- Mechanism of action: competitive opioid antagonist
- Component of buprenorphine SL tablet and film (Suboxone) to **discourage misuse by injection**
  - If product is crushed and injected, naloxone will block mu-opioid receptors
- Low oral bioavailability (2%) → minimal activity when taken SL
  - Does not induce withdrawal (unless combo product is injected via abuse)
- Extensive hepatic metabolism
  - Decreased clearance in moderate to severe liver impairment → increased exposure to drug → increased risk of precipitated withdrawal

Tylleskar I, et al. *Eur J Clin Pharmacol.* 2021;77(12):1901-1908.  
Buprenorphine StatPearls. National Library of Medicine. Updated 8 Jun 2024.

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## Other Buprenorphine Products

### Buprenorphine/naloxone (Bunavail®)

- For OUD
- Buccal film
- 2.1 mg/0.3 mg, 4.2 mg/0.7 mg, 6.3 mg/1 mg
- Daily dosing

### Buprenorphine/naloxone (Zubsolv®)

- For OUD; off-label for pain
- Sublingual tablet
- 0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg
- Daily dosing
- May take 7 days to reach steady state

Connor R, ed. *Buprenorphine and naloxone: Drug Information.* Wolters Kluwer.

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# Dosing Principles

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## Buprenorphine Conversions

	Oral Morphine Equivalent (OME)/24 Hours								
	7	15	30	48	60	80	100	120	300
<b>Butrans q7 days</b>	5 mcg/hr		10 mcg/hr	20 mcg/hr					
<b>Belbuca</b>	75 mcg daily	150 mcg q12h	300 mcg q12h	450 mcg q12h	600 mcg q12h	750 mcg q12h		900 mcg q12h	
<b>Suboxone or Subutex</b>						1 mg BID (split tabs or cut film)		1 mg TID	2 mg TID

Adapted from Case AA, et al. *Curr Treat Options in Oncol.* 2021;22:116.

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## General Conversion Rule

**30:1**

**30 OME = 1 mg SL buprenorphine**

*Potential use: Patient with low OME but insurance will only cover Subutex or Suboxone OR patient has to pay out of pocket and Subutex or Suboxone are cheapest. Could start with ½ of a 2 mg film (1 mg) qday to start. This is about 30 OME. If reducing for cross tolerance, could start with ¼ of a 2 mg film (0.5 mg qday) to start.*

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## Traditional Induction (Stop/Start)

1. Stop full agonist opioids.
2. Wait for withdrawal (COWS >8-12).
  - a. Resting heart rate, sweating, restlessness, pupil size, bone/joint aches, runny nose or tearing, GI upset, tremor, yawning, anxiety/irritability, gooseflesh skin
3. Give 1st dose (2-4 mg buprenorphine per dose) and repeat in 1-2 hours.
4. Uptitrate to effective dose over next 1-3 days.

*Potential problems:*

- *Withdrawal symptoms*
- *May require hospitalization*
- *Uncontrolled pain*

Wesson DR, Ling W... *J Psychoactive Drugs*. 2003;35(2):253-259.

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## Microinduction

- **Concept:** Administer small and gradually increasing doses of buprenorphine while continuing a full agonist opioid (including long-acting forms)
  - Buprenorphine is like a sneaky bully on the playground!
  - Gradually “sneaks” onto receptors and kicks other agonists off
  - Gradually increase dose to slowly overtake full agonists to not induce withdrawal
- **Benefits:** lower risk of withdrawal symptoms, worsened pain

Case AA, et al. *Curr Treat Options in Oncol.* 2021;22:116.

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## Buprenorphine Microinduction

Day	Buprenorphine Dose	Full Agonist Opioid
1	0.5 mg SL daily	Full dose
2	0.5 mg SL BID	Full dose
3	1 mg SL BID	Full dose
4	2 mg BID	Full dose
5	4 mg BID	Full dose
6	8 mg AM, 4 mg PM	Full dose
7	12 mg	Stop

Case AA, et al. *Curr Treat Options in Oncol.* 2021;22:116.

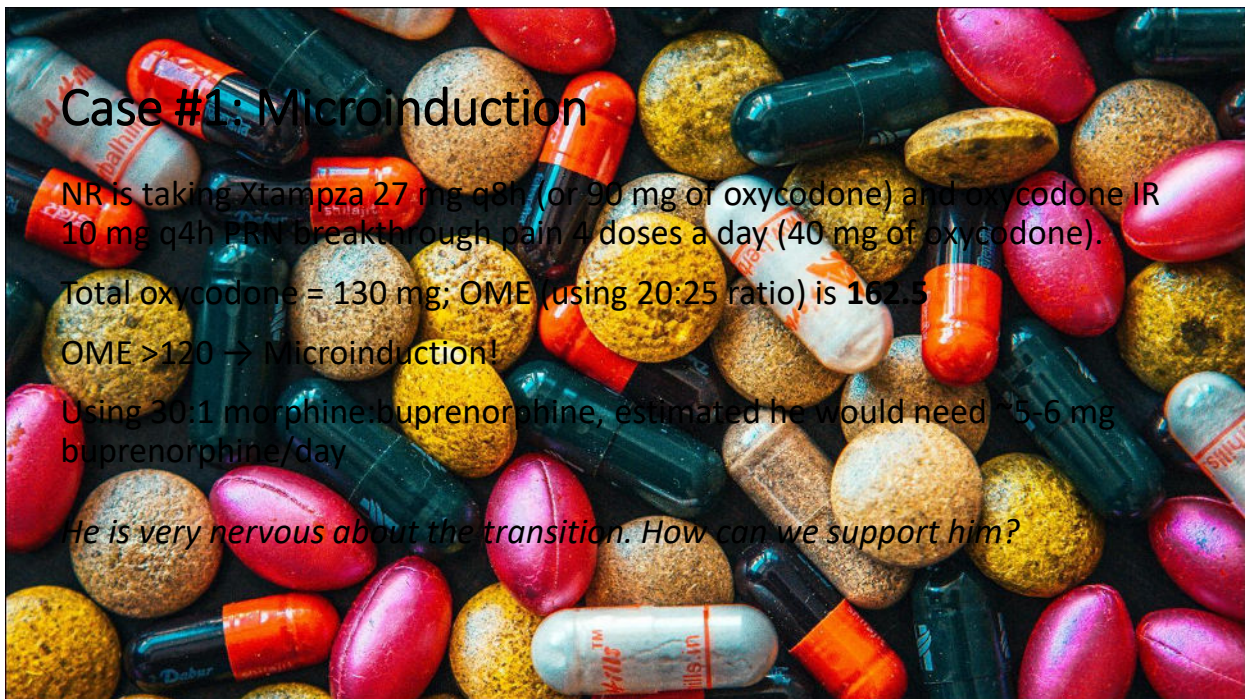
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## Low-Dose Buprenorphine Initiation

Day	SL Tablet or Film	Full Agonist
1	0.5 mg SL daily	Continue
2	0.5 mg SL q12h	
3	1 mg SL q12h	
4	2 mg SL q12h	
5	3 mg SL q12h	
6	4 mg SL q12h	Discontinue or start tapering off
7	6 mg SL q12h	

Fast Facts #457: Buprenorphine Initiation – Low Dose Methods.

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**Case #1: Microinduction**

NR is taking Xtampza 27 mg q8h (or 90 mg of oxycodone) and oxycodone IR 10 mg q4h PRN breakthrough pain 4 doses a day (40 mg of oxycodone).

Total oxycodone = 130 mg; OME (using 20:25 ratio) is 162.5

OME >120 → Microinduction!

Using 30:1 morphine:buprenorphine, estimated he would need ~5-6 mg buprenorphine/day

*He is very nervous about the transition. How can we support him?*

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Day	Buprenorphine Dose	Full Agonist Opioid	Notes
1	0.5 mg SL daily (1/4 film)	Full dose	
2	0.5 mg SL BID (1/4 film)	Full dose	
3	1 mg SL BID (1/2 film)	Full dose	
4	1 mg SL TID (1/2 film)	Full dose	
5	<b>1 mg SL TID (1/2 film)</b>	<b>Stop Xtampza Continue oxycodone IR for breakthrough pain</b>	<b>Close to OME</b>

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## *What happened?*

- Called patient on days 3, 5, 7 for close follow up for his comfort
- No withdrawal symptoms
- On day 7, pain manageable but not as well controlled as before.
  - Increased buprenorphine to 2 mg AM, 1 mg afternoon, 2 mg PM (5 mg/day)

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# Patient to Product

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## Low OME or Opioid-naïve

**Butrans:** 5 mcg/hr patch

**Belbuca:** 75 mcg film 1x daily, increased to q12h if needed

*Could also use ¼ (0.5 mg) or ½ (1 mg) of a Suboxone film for OME 15 or 30, respectively*

	Oral Morphine Equivalent (OME)/24 Hours									
	7	15	30	48	60	80	100	120	300	
<b>Butrans q7 days</b>	5 mcg/hr		10 mcg/hr	20 mcg/hr						
<b>Belbuca</b>	75 mcg daily	150 mcg q12h	300 mcg q12h	450 mcg q12h	600 mcg q12h	750 mcg q12h		900 mcg q12h		
<b>Suboxone or Subutex</b>						1 mg BID (split tabs or cut film)		1 mg TID	2 mg TID	

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## High OME

### Suboxone or Subutex preferred

Lower doses usually needed for pain; higher doses for OUD for receptor blockade, suppression of cravings

	Oral Morphine Equivalent (OME)/24 Hours									
	7	15	30	48	60	80	100	120	300	
<b>Butrans q7 days</b>	5 mcg/hr		10 mcg/hr	20 mcg/hr						
<b>Belbuca</b>	75 mcg daily	150 mcg q12h	300 mcg q12h	450 mcg q12h	600 mcg q12h	750 mcg q12h		900 mcg q12h		
<b>Suboxone or Subutex</b>					1 mg BID (split tabs or cut film)		1 mg TID	2 mg TID		

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## When to Consider Buprenorphine

- **Nonadherence** (Butrans: once-weekly patch change)
- **Intolerance to full agonist opioids (side effects)**
- **Complex persistent opioid dependence (CPOD)**
- **PO access difficulty or poor GI absorption**
  - Difficulty swallowing
- **Cancer pain with no evidence of disease**
  - Young patient with cancer in remission and longer life expectancy
- **Renal or liver impairment\***
- **Risk reduction**



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## Case #1

NR (56 year old M with metastatic colon cancer with NED for past 3 months) who is interested in rotating from Xtampza to a buprenorphine product. He notes that he has had some sexual dysfunction and depressed mood that he can attribute to nothing else except the opioids. He wonders if buprenorphine can cause these same problems.

What would you tell him?

*Lower risk of both of these side effects. Buprenorphine may be a good option for these reasons.*

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## Case #2

JB is a 68 year old F with squamous cell carcinoma of the tongue s/p glossectomy and extensive oral surgery and radiation who has now been disease-free for 4 months. She is on transdermal fentanyl 25 mcg/hr and oxycodone IR 5-10 mg q4h PRN moderate to severe breakthrough pain (takes 5 mg once a day and 10 mg three times a day). She has tried to taper her opioids but has had a difficult time doing so.

You would like to rotate her to control.

When you meet with her to discuss her concerns about the dental side effects of the opioids, she asks you for advice.

What do you tell her?

*A transmucosal product would likely not be ideal for her.*

*Her OME is too high for a Butrans patch at her current doses.*

*She may need to try methadone instead, unless she is able to wean down her opioids in the future.*

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## Cautionary Use of Buprenorphine

- **Dental concerns**
  - May need to consider transdermal product
- **Severe liver impairment**
  - AVOID combo product (buprenorphine/naloxone) in moderate to severe liver impairment
  - Use buprenorphine alone; 50% reduction of starting dose
- Rare risk of anaphylactic reaction



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## Practical Tips: Application and Administration

- **Transmucosal products**
  - Moisten inside of cheek with tongue or water
  - Dissolve times
    - SL tab: up to 10 minutes
    - Buccal film: up to 30 minutes
  - Bitter taste
    - Suboxone: nasty orange taste
    - Zubsolv: cool mint taste
- **Transdermal product**
  - Patch irritation → fluticasone nasal spray
  - Patch adhesion
    - Tegaderm or first aid tape around edges

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## Barriers: Access

- **Cost or insurance coverage**
  - Cost may not be affordable
  - Other agents may be preferred

### Mitigation Strategies

Coupons: GoodRx, Belbuca copay card

Cheaper out-of-pocket: Suboxone (tabs are cheaper than films) or Subutex

Include appropriate diagnosis code and a note to pharmacy in e-Rx

Review insurance formulary proactively to determine options

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## Barriers: Prescribers

- May think X-waiver is required
- Lack of education or understanding on how and when to use

### Resources

Buprenorphine CE (this presentation!)

CAPC Buprenorphine Blog

FastFacts: Buprenorphine Initiation

American Society of Addiction Medicine (ASAM)

American Academy of Hospice and Palliative Medicine (AAHPM) Substance Use Disorder Special Interest Group

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## Barriers: Patients

- **Patient buy-in**
  - Google “buprenorphine” or Suboxone → OUD
  - Patients may think you think they are an addict.
- **Use IDT members to help with education.**
  - Refer patients to pharmacist for education and answering questions.

### Strategies

Be up front with patients. (“If you look up ‘Suboxone’ you may find...”)

“Look up ‘buprenorphine and chronic pain’ for good information.”

Reinforce educational points frequently.

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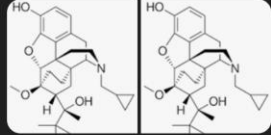
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**Buprenorphine is a synthetic opioid developed in the late 1960s and is used to treat pain and opioid use disorders (OUDs). This drug is a synthetic analog of thebaine—an alkaloid compound derived from the poppy flower.** Nov 30, 2023

National Institutes of Health (NIH) (.gov)  
<https://www.ncbi.nlm.nih.gov/books/NBK459126>

**Buprenorphine - StatPearls - NCBI Bookshelf**



About featured snippets Feedback


**People also ask**

- What is the main use of buprenorphine?
- Is Suboxone the same as buprenorphine?
- Is buprenorphine the same as tramadol?
- What is the 3 day rule for Suboxone?

Feedback

SAMHSA - Substance Abuse and Mental Health Services Administration (.gov)  
<https://www.samhsa.gov/buprenorphine>

**What is Buprenorphine? Side Effects, Uses, Dose & Risk**  
 Mar 28, 2024 — Buprenorphine is the first medication to treat opioid use disorder



**Buprenorphine**  
 Common brands: Belbuca, Probuphine, Buprenex

**Narcotic**  
 It can treat pain as well as addiction to narcotic pain relievers.

**Controlled substance**  
 High risk for addiction and dependence. Can cause respiratory distress and death when taken in high doses or when combined with other substances, especially alcohol or other illicit drugs such as heroin or cocaine.

Learn more on drugfree.org

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Google

AI Overview Learn more

Suboxone is a prescription medication used to treat opioid use disorder in adults and children over 15 years of age. It's a combination of two drugs, buprenorphine and naloxone, that work together to reduce cravings and withdrawal symptoms, and help patients become less dependent on opioids over time. Suboxone is usually part of a complete treatment program that also includes counseling and behavioral therapy.

suboxone.com Patient information for  
 European Medicines Agency Suboxone / European Medicines  
 American Addiction Suboxone Users Act

Show more

Suboxone  
<https://www.suboxone.com>

**Patient Information for SUBOXONE® (buprenorphine and ...**  
 SUBOXONE Sublingual Film contains an opioid medicine called buprenorphine that can cause serious and life-threatening breathing problems, especially if you take ...

**People also ask**

- What does Suboxone do exactly?
- Is Suboxone considered a narcotic?
- Why is Suboxone being discontinued?

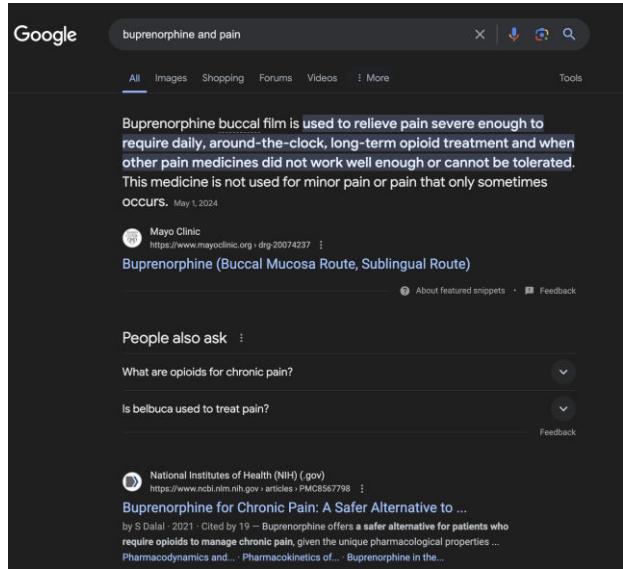
**Buprenorphine / Naloxone**  
 Brand name: Suboxone

**Narcotic**  
 It can treat narcotic dependence.

**Brands:** Zubsolv, Suboxone, and Bunavail  
**Availability:** Prescription needed  
**Pregnancy:** Consult a doctor  
**Alcohol:** Avoid. Very serious interactions can occur  
**Drug class:** Opioid

Q side effects Q interactions Q war

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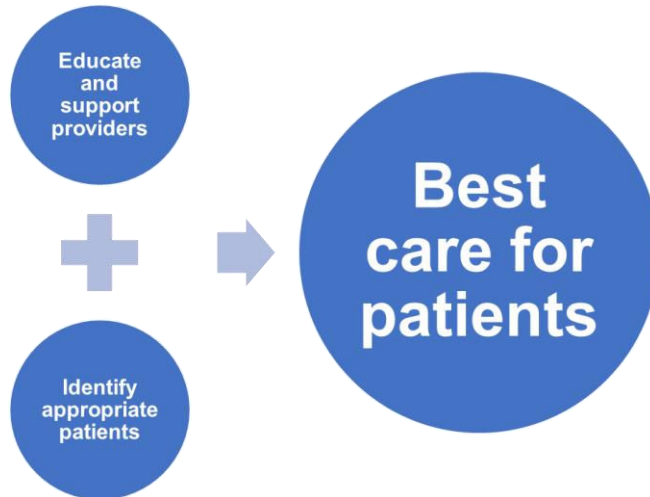


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## Why is this important?



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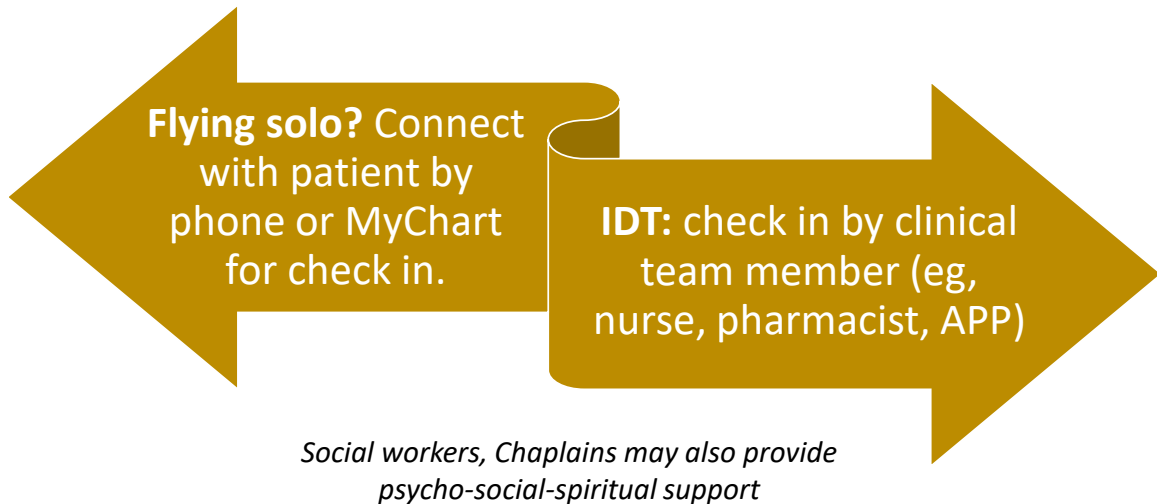
## Components of a Protocol

- Criteria for identifying patients
- Dosing guidance
  - Conversion factors
  - Opioid-naïve or opioid-tolerant
  - Microinduction
  - Titration
- Product selection
- Breakthrough medication use
- Patient education
- Monitoring/follow up
  - When?
  - Who? Role of interdisciplinary team members



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## Role of the Interdisciplinary Team



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## Take-home Points

- Consider buprenorphine for patients who have pain, especially if they are intolerant of full agonist opioids or there are concerns about their use of other opioids.
- Provide education on buprenorphine to patients, pharmacies, and other healthcare providers to minimize stigma associated with its use.
- Consider a microinduction for patients who are hesitant to transition to buprenorphine or who have OME >120.

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## References

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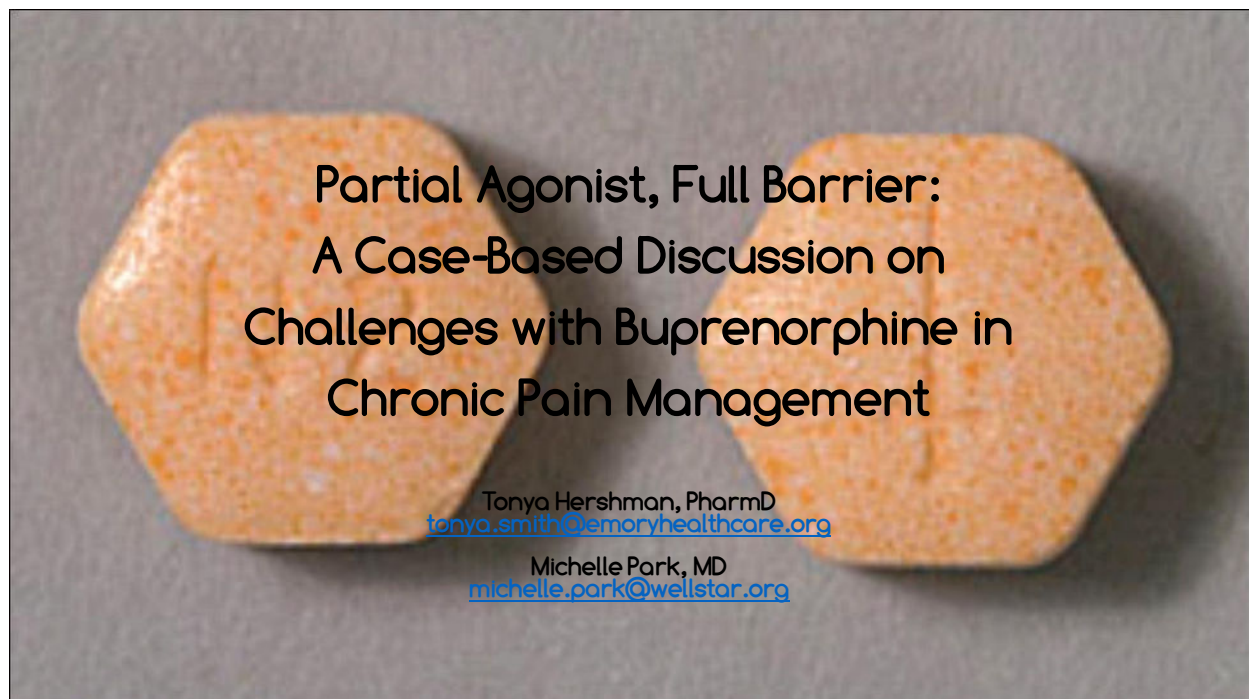
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