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Clinical Support
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Initiating Buprenorphine for Patients Using Fentanyl

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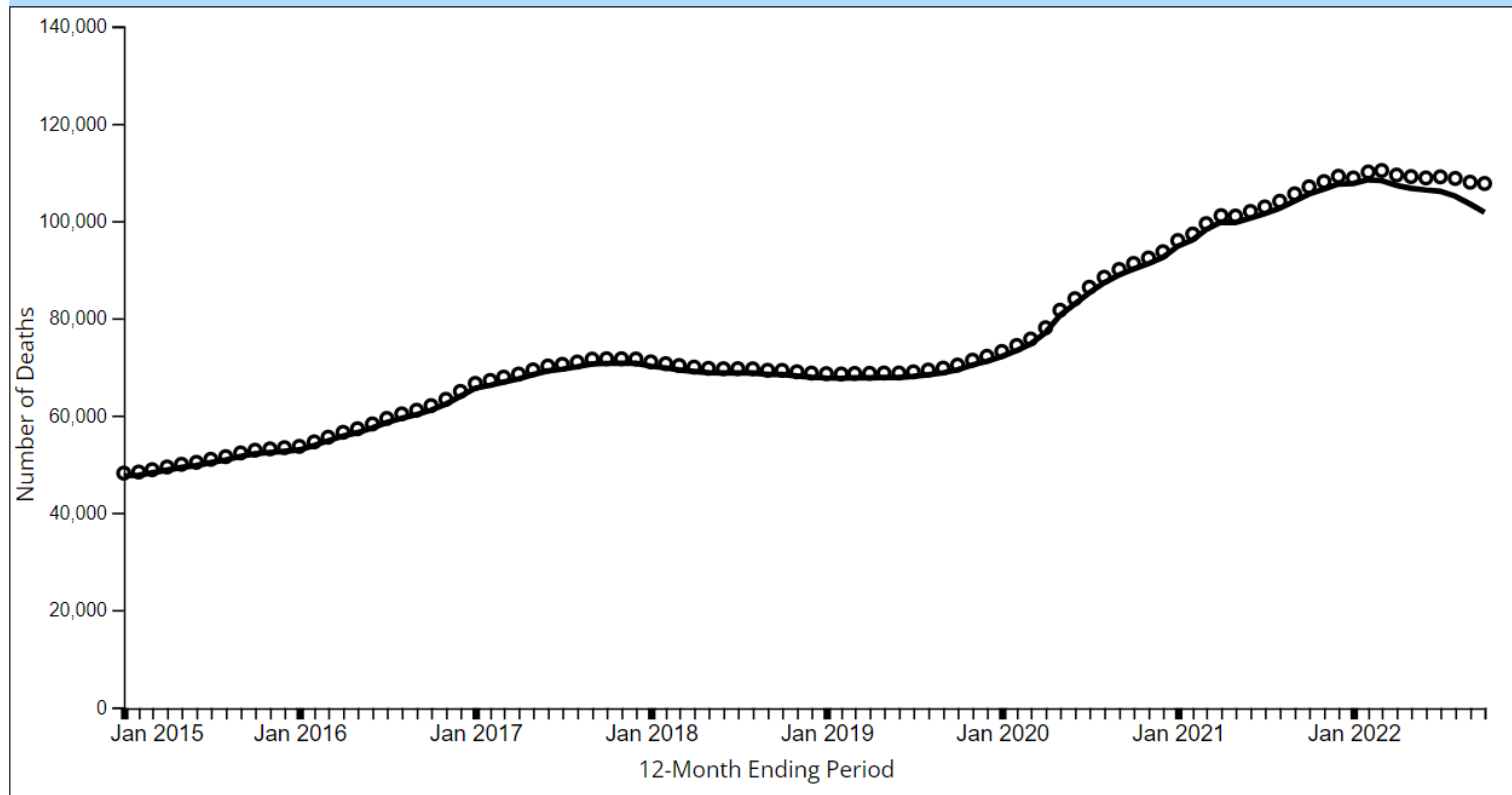
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Disclosures

- **Brian Hurley, M.D., M.B.A., DFASAM, FAPA**
- **No financial conflicts of interests**

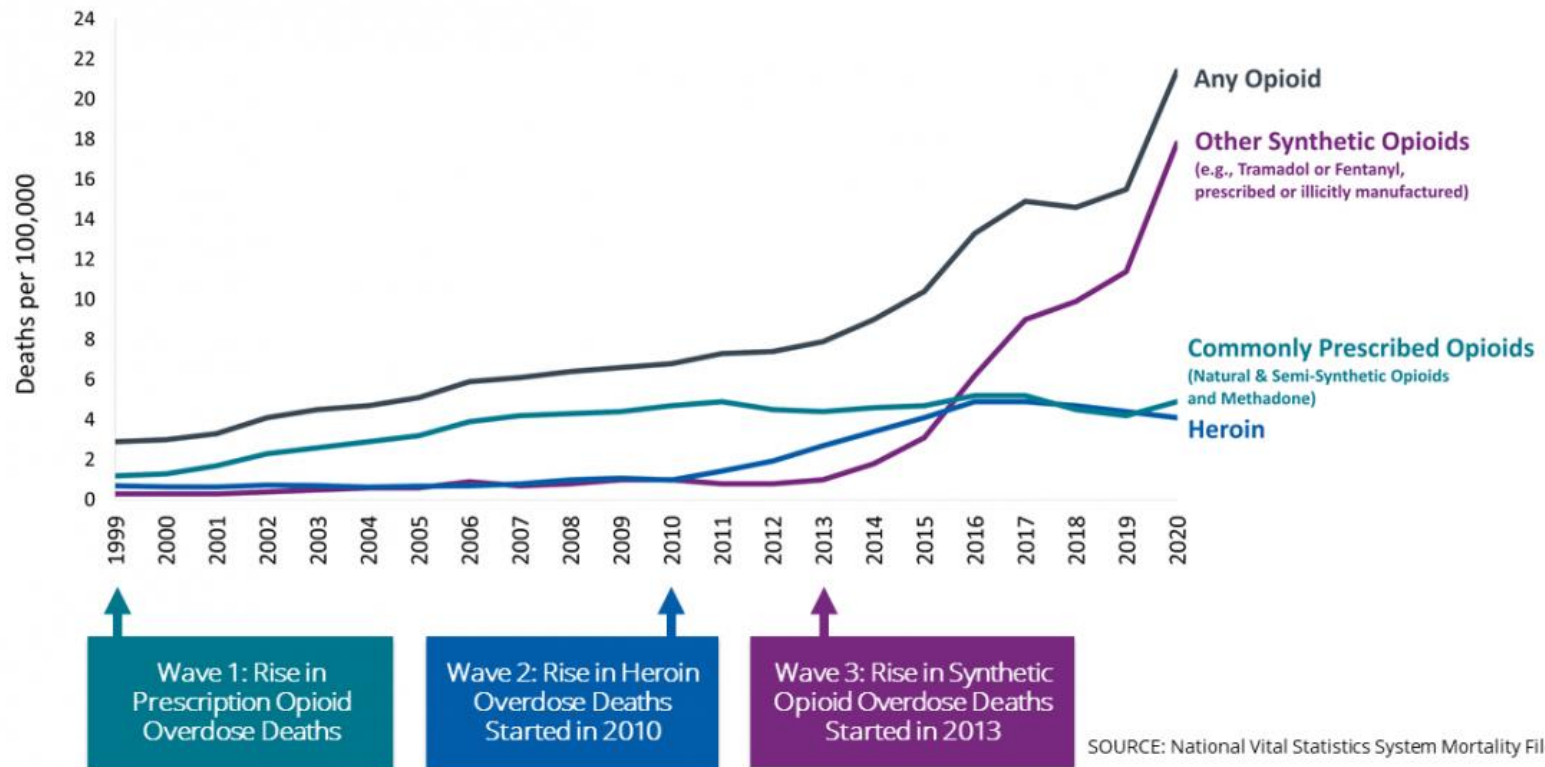
*The content of this activity may include discussion of off label or investigative drug uses.
The faculty is aware that is their responsibility to disclose this information.*

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



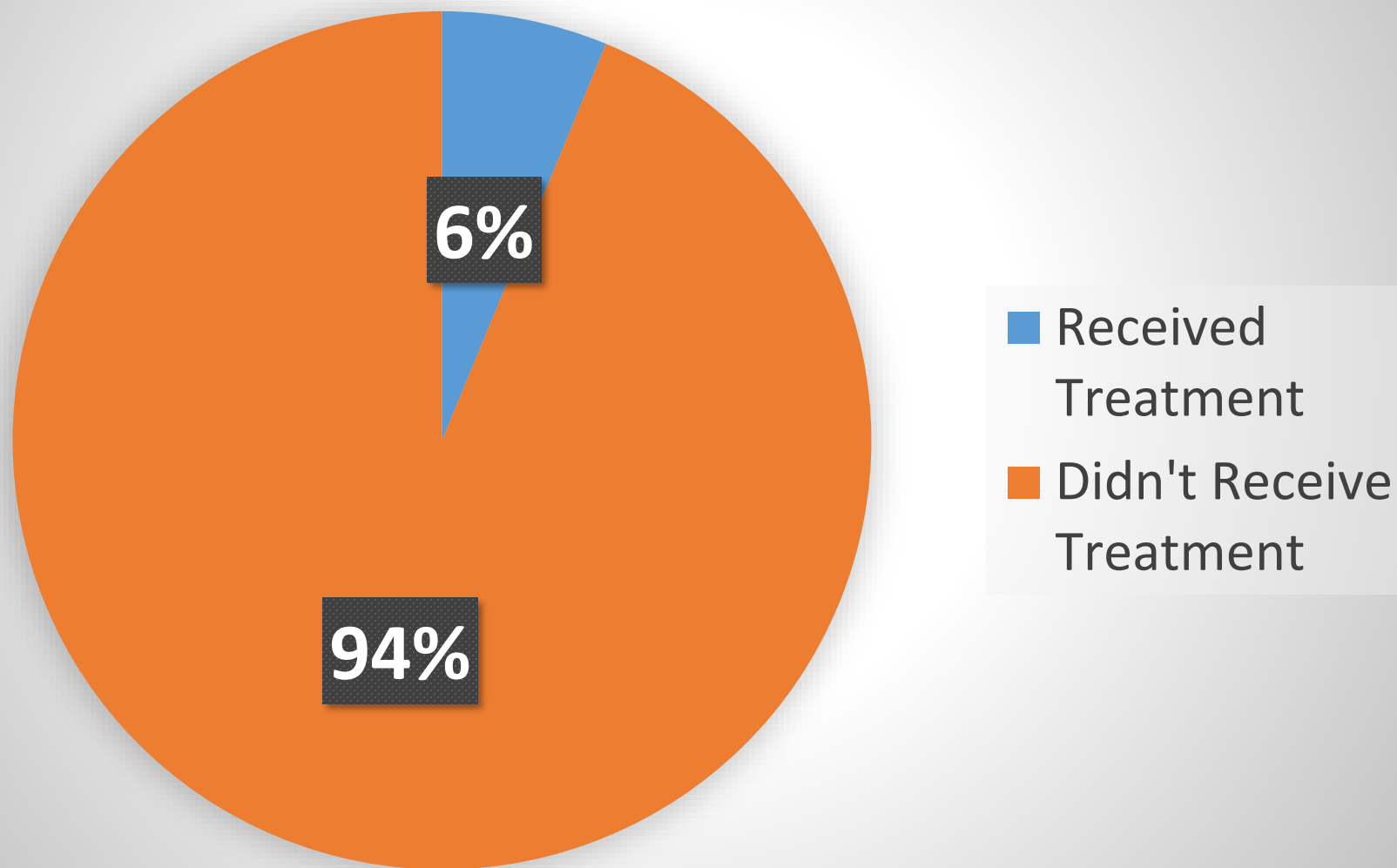
Centers for Disease Control. 12 Month-ending Provisional Number of Drug Overdose Deaths. Based upon Data available as of 3/4/2023. Retrieved from <http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

Three Waves of Opioid Overdose Deaths

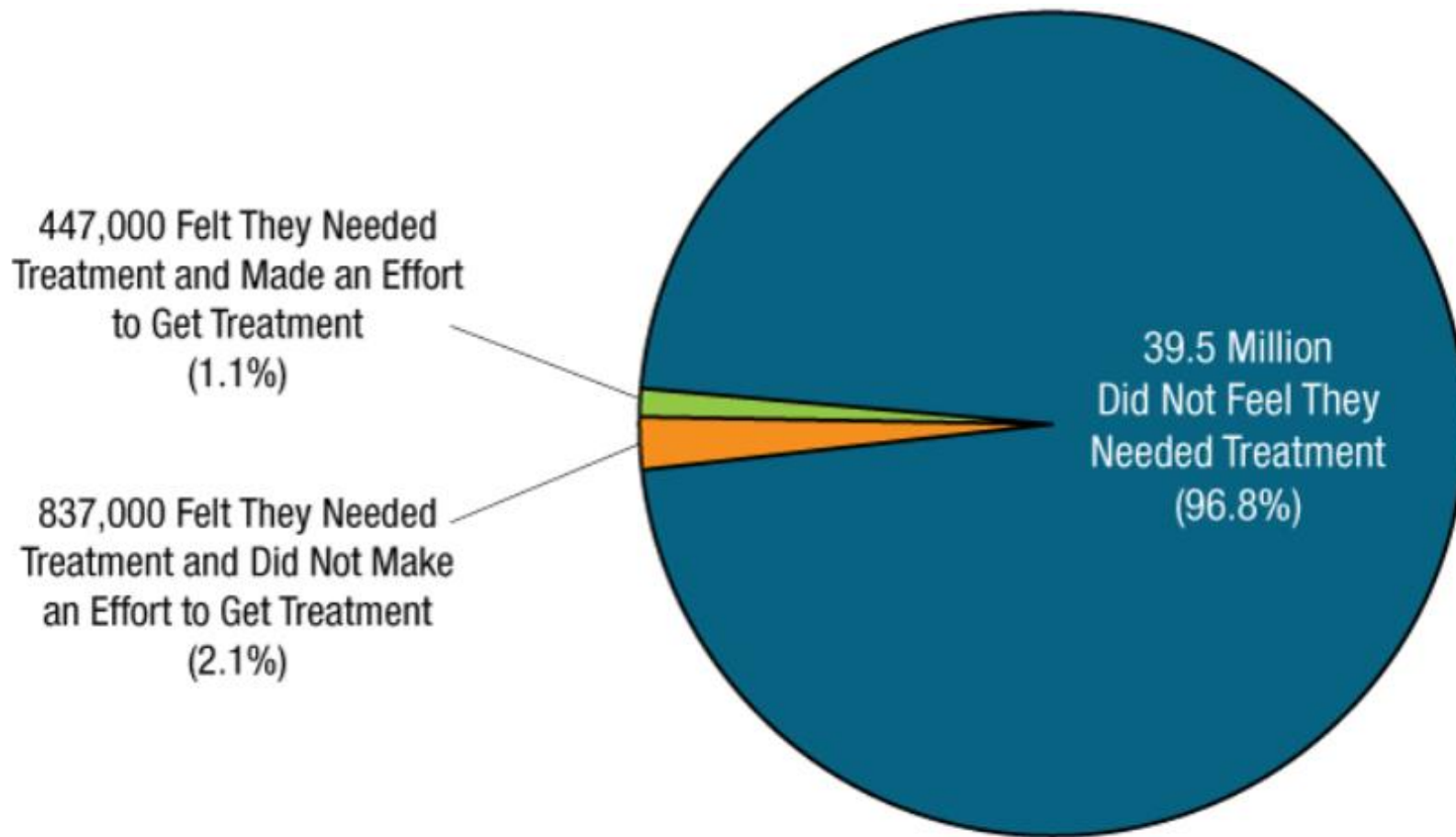


<http://www.cdc.gov/opioids/basics/epidemic.html>

Receipt of Any Substance Use Treatment among People with a Past Year SUD



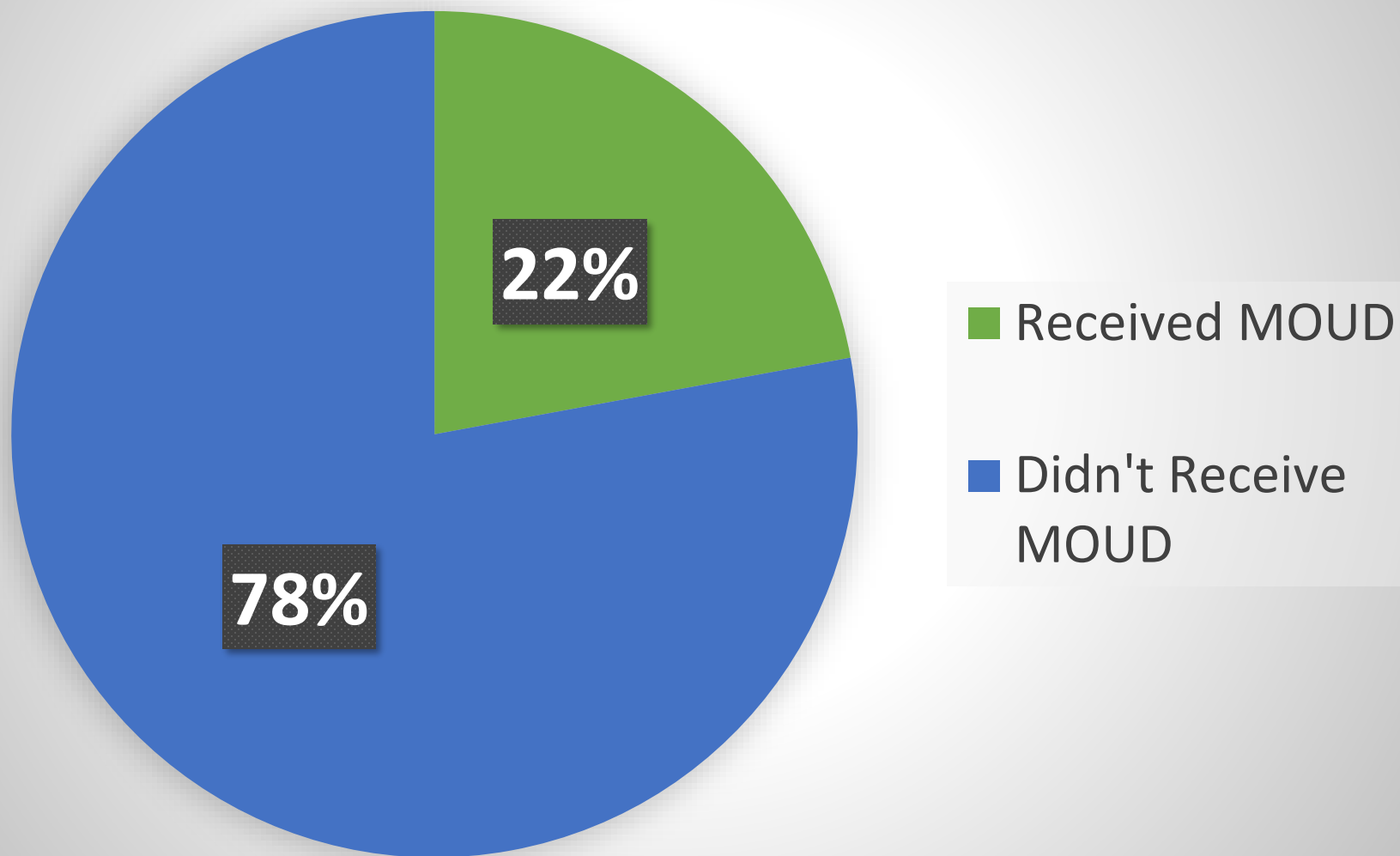
Substance Abuse and Mental Health Services Administration. (2022). *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health* (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report>



40.7 Million People with an Illicit Drug or Alcohol Use Disorder Who Did Not Receive Substance Use Treatment at a Specialty Facility

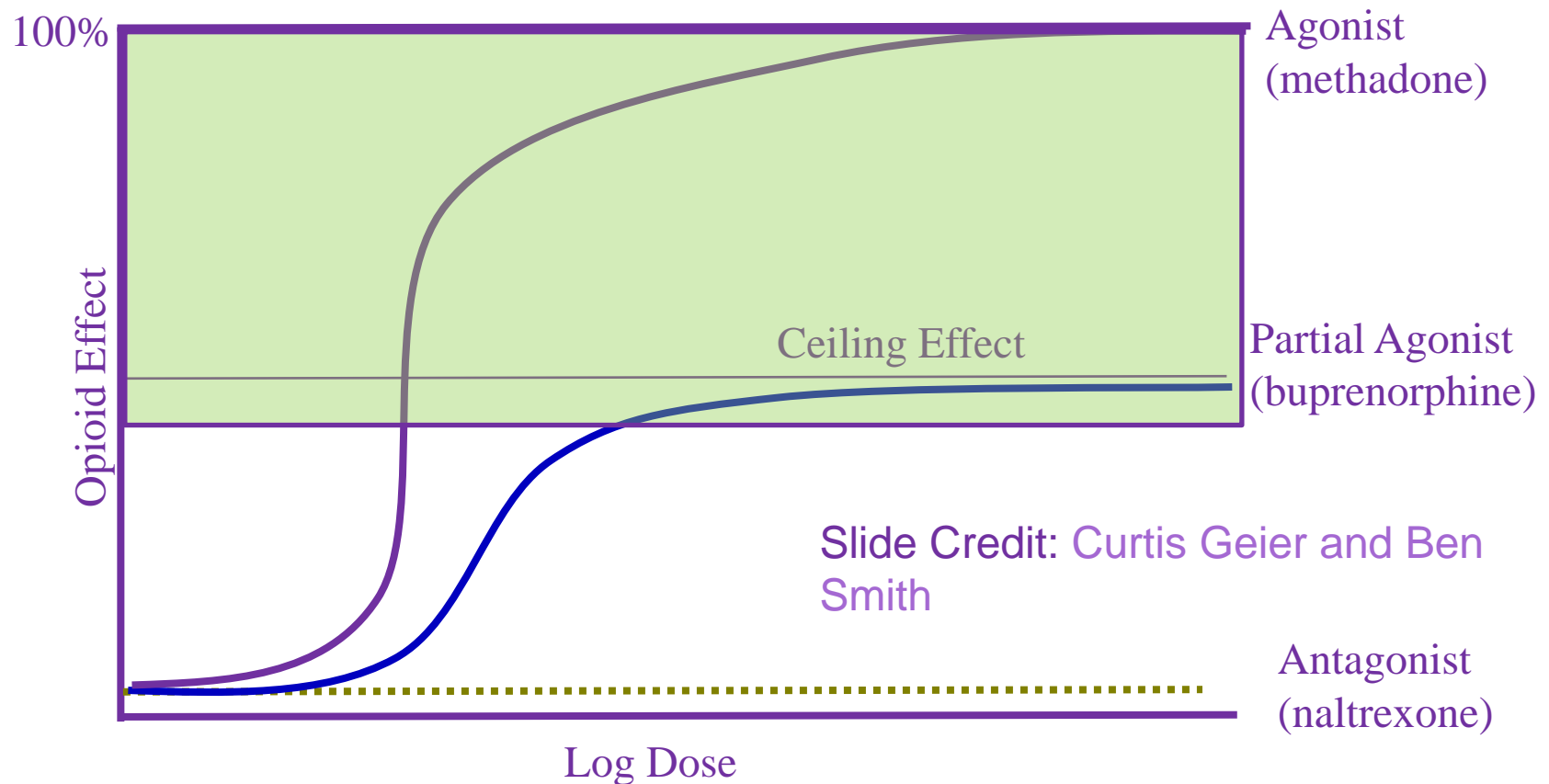
Substance Abuse and Mental Health Services Administration. (2022). *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health* (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report>

Receipt of Medication for Opioid Use Disorder among People with a Past Year OUD



Substance Abuse and Mental Health Services Administration. (2022). *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health* (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report>

Buprenorphine & Methadone Pharmacokinetics

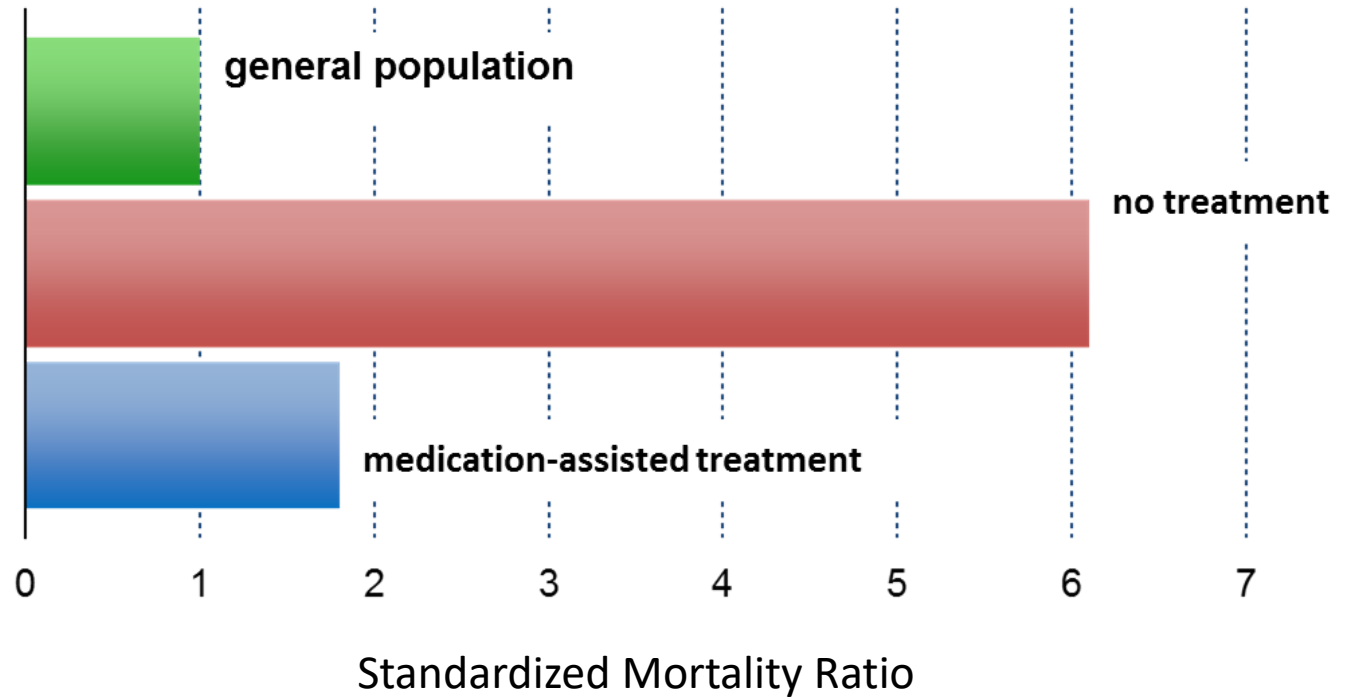


Buprenorphine Formulations for Opioid Use Disorder

Content	Route	Product	Available Doses	Equivalent Dose
Combo Product (with Naloxone)	Sublingual	Film - Generic, Suboxone	2 mg Bup/0.5mg Nx	
			4 mg Bup/1mg Nx	
			8 mg Bup/2mg Nx	8mg
			12mg Bup/3mg Nx	
	Sublingual	Tablet-Generic	2 mg Bup/0.5mg Nx	
			8 mg Bup/2mg Nx	8mg
	Sublingual	Tablet-Zubsolv	0.7mg Bup/0.18mg Nx	
			1.4mg Bup/0.36mg Nx	
			2.9mg Bup/0.7mg Nx	
			5.7mg Bup/1.4mg Nx	5.7mg
			8.6mg Bup/2.6mg Nx	
			11.4mg Bup/4mg Nx	
	Sublingual	Film - Cassipa	16mg Bup/4mg Nx	2 x 8mg
Mono Product	Sublingual	Tablet-Generic	2mg Bup	
			8mg Bup	8 mg
	Subcutaneous	Sublocade	100mg	approx 12 mg
			300mg	approx 24 mg
Pending Mono Product	Injectable	"Brixadi"	Weekly and Monthly	

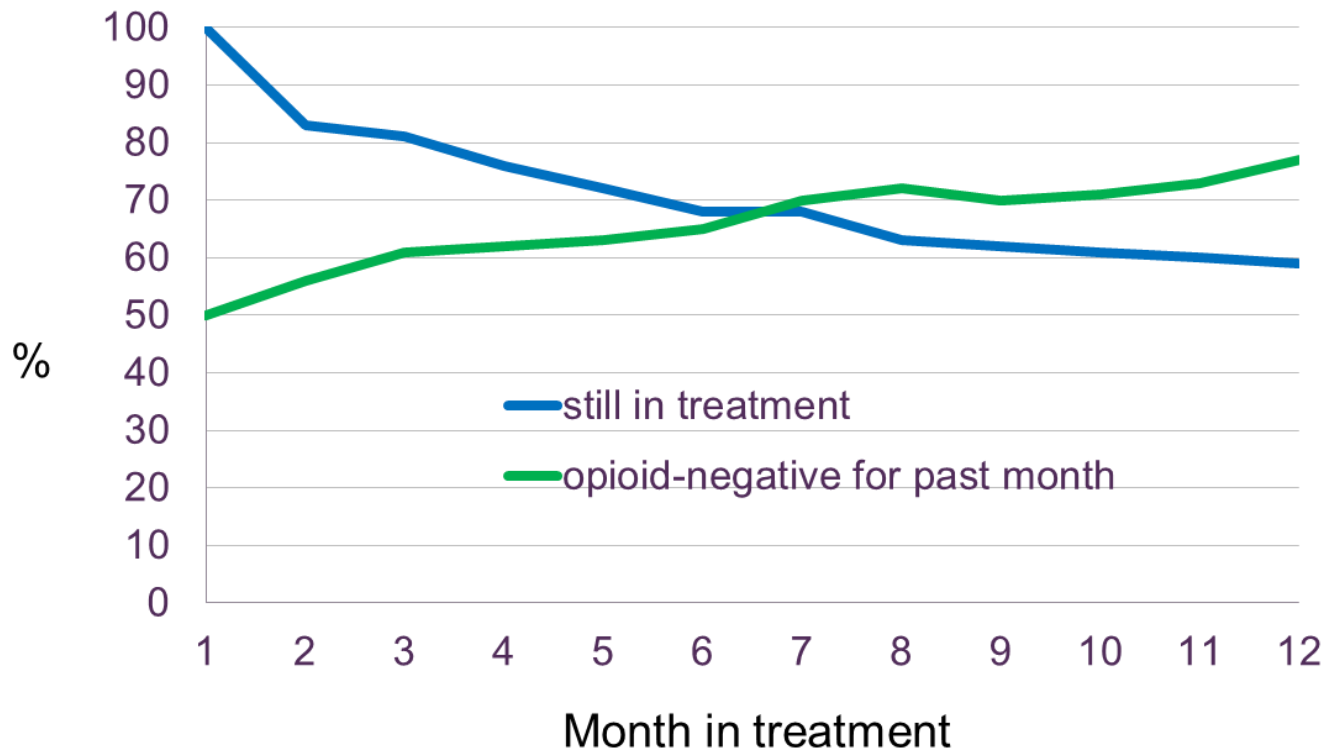
Benefits of MAT: Decreased Mortality

Death rates:



Treatment Retention and Decreased Illicit Opioid Use on MAT

- Buprenorphine promotes retention, and those who remain in treatment become more likely over time to abstain from other opioids



Major Features of Buprenorphine

Partial agonist at mu receptor

- Comparatively minimal respiratory suppression and no respiratory arrest when used as prescribed

Long acting

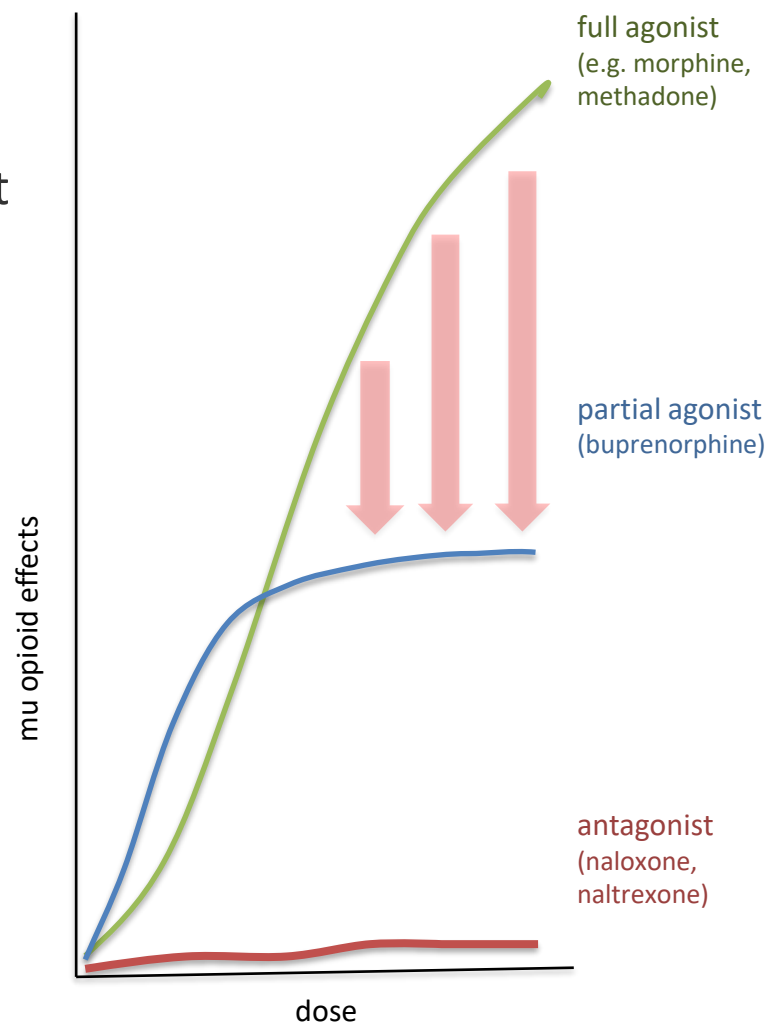
- Half-life ~ 24-36 Hours

High affinity for mu receptor

- *Blocks* other opioids
- *Displaces* other opioids
 - Can precipitate withdrawal

Slow dissociation from mu receptor

- *Stays on receptor for a long time*



Classic Buprenorphine Initiation

- Instruct the patient to abstain from any opioid use for a minimum of:
 - 12-16 hours for short-acting opioids
 - 24 hours for sustained-release opioid medications
 - 36 hours for methadone
- Observe and document Mild vs. Moderate withdrawal:
 - **NOTE:** Be aware of **Fentanyl**; do not induce unless moderate withdrawal (COWS 13 to 15) is observed

Classic Buprenorphine Initiation

- First dose: 2-4 mg SL buprenorphine/naloxone
- Relief of opioid withdrawal symptoms should begin within 30-45 minutes after the first dose
- Re-dose every 2-4 hours, if opioid withdrawal subsides then reappears
- Stabilize at dose that eliminates craving; typical dose range from 8 mg to 16 mg
- Gradually increase dose after establishment of a steady state over as needed for continued craving.
 - Note: This can be increased more rapidly if the patient has a lot of craving.

Classic Buprenorphine Initiation

- Day #2: Continue dose established on Day #1
 - Encourage patient to preferably take Day #1 dose on the morning of Day #2
 - Encourage office staff to contact patient on Day #2 to assess dose response
 - After contact with patient there may be reason for additional dose adjustments:
 - If patient feels well, instruct patient to continue Day #1 dosing
 - If patient is experiencing cravings or discomfort consider increasing dose by 2-4 mg
- OR**
 - discuss relapse prevention and assure patient that discomfort will stabilize over time
- Avoid rapid dose adjustments

Classic Buprenorphine Initiation

- Stabilization will occur for most patients between 8 to 16mg per day:
 - Most individuals do not need more than 16mg per day but occasionally higher doses may be needed for persistent symptoms/ongoing opioid use
 - Most insurance companies limit daily doses to 24 mg
 - Though there is approval for a maximum dose of 32mg, doses above 24mg may increase risk of diversion
 - Note – If there are concerns for diversion:
 - Consider more intensive monitoring [E.g. more frequent urine testing, shorter prescription durations, supervised dosing]



Research Paper

“Everything is not right anymore”: Buprenorphine experiences in an era of illicit fentanyl

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ARTICLE INFO

Keywords:

Buprenorphine

Fentanyl

Illicit fentanyl

Non-pharmaceutical fentanyl

Non-prescribed buprenorphine

Qualitative analysis

Self-treatment

ABSTRACT

Background: Conducted in the Dayton Metropolitan area of Southwestern Ohio, this qualitative study explores the self-treatment practices of people who use illicit opioids (PWUIO) amidst the new risk environment produced by illicit, non-pharmaceutical fentanyl (NPF). We explore local perceptions of the presence of NPF in the Dayton area, and how this has both positively and negatively impacted practices of non-prescribed buprenorphine use among PWUIO.

Methods: This study analyzes qualitative data from 63 interviews conducted between October 2018 and June 2019. Participants were selected from a larger longitudinal study on non-prescribed buprenorphine use among individuals with opioid use disorder. Qualitative interviews were transcribed in their entirety, and their transcripts were analyzed using NVivo software, drawing on a mix of thematic and inductive coding.

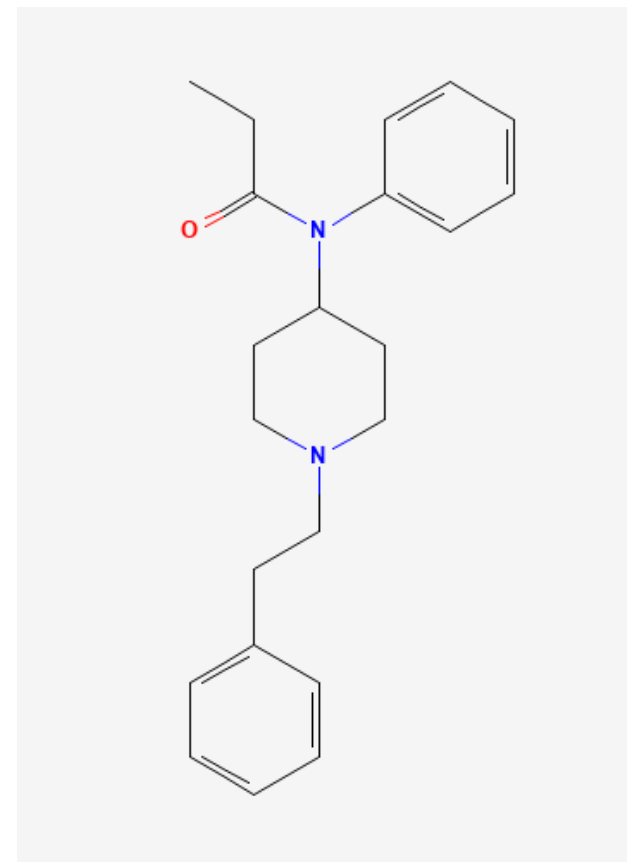
Results: Interview respondents ranged from 19 to 70 years old, with a mean age of 38.9 years. 54% of them were male, and 85.7% identified as non-Hispanic White. 98.4% of the sample had used heroin, and 93.7% of the sample reported use of NPF. Participants agreed NPF dominated the illicit opioids market in the area, and was



Image: <http://www.justice.gov/usao-ndia/pr/using-opioids-leads-three-deaths-eastern-iowa>

Fentanyl Pharmacokinetics

- $t_{1/2}$ of 2–4 h
- Rapidly decline → redistribution to other tissues
- Rapid sequestration in adipose
- Case series of 12 patients:
 - Mean time for utox clearance
Fentanyl – 7.3 days
Norfentanyl – 13.3 days



Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend.* 2020 Sep 1;214:108147. doi: 10.1016/j.drugalcdep.2020.108147. Epub 2020 Jul 2. PMID: 32650192; PMCID: PMC7594258.

Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57. doi: 10.1016/j.neubiorev.2018.12.005. Epub 2018 Dec 5. PMID: 30528374; PMCID: PMC7233332.

Buprenorphine Initiation Options

High Dose Starts

Low Dose Starts

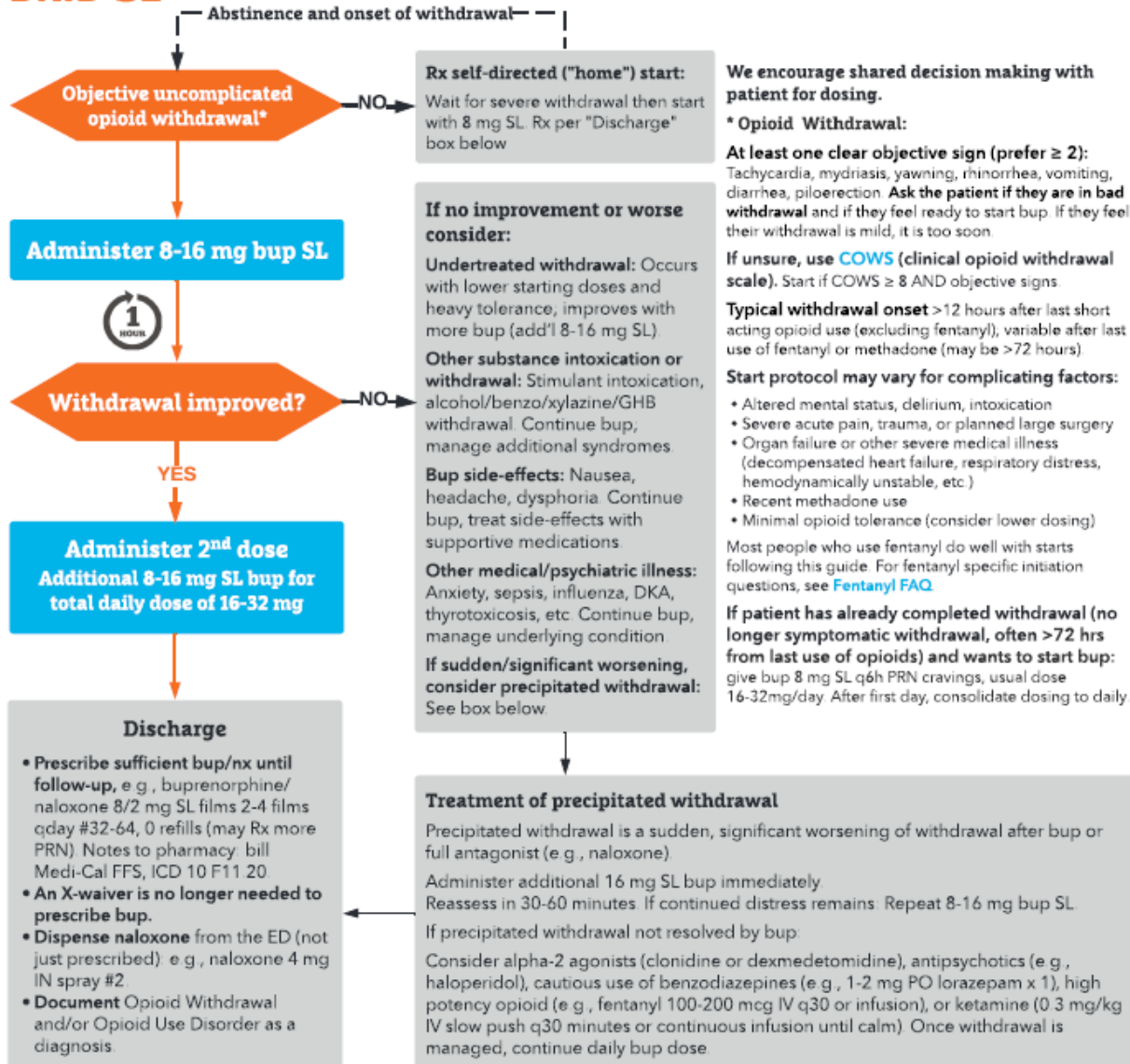
Controlled
Environment
Starts

Pain
Management /
Analgesic Dosing

High Dose Starts



Buprenorphine (Bup) Emergency Department Quick Start

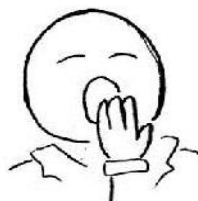


High Dose Buprenorphine Outcomes: Hospital Settings

- 492 patients administered buprenorphine, 44 (9.5%) used fentanyl
- 439 patients (89.3%) initiated high-dose buprenorphine (8-32 mg)
 - Follow-up at 30 days among patients administered buprenorphine was similar for those who did and did not report fentanyl use: 36 patients [41.4%] vs 301 patients [37.2%]
- Precipitated withdrawal was documented for 8 patients overall (1.6%).
 - For patients who reported fentanyl use, 2 cases (4.5%) of precipitated withdrawal.
 - No precipitated withdrawal required hospital admission
 - 4 patients (50.0%) had documentation of follow-up at 30 days.
- Adjusted odds ratios for patients who reported fentanyl use compared with patients who reported other opioid use:
 - 0.60 (95% CI, 0.32-1.07) for administered or prescribed buprenorphine in the ED encounter
 - 1.09 (95% CI, 0.62-1.92) for follow-up at 7 days
 - 1.33 (95% CI, 0.73-2.41) for follow-up at 30 days.
- No differences in follow-up engagement by patients with self-reported fentanyl use (adjusted odds ratio, 1.09), and precipitated withdrawal was rare (8 patients [1.6%]).

High Dose Buprenorphine: Ambulatory

You need at least 3 of the following feelings before taking your first buprenorphine dose*:



Yawning

Enlarged pupils

Joint and bone aches

Shaking or twitches

Watery eyes/Runny Nose

Nausea, vomiting or Diarrhea

Sweating or chills

Restless/Can't sit still

Anxiety, irritable, fast heart beat

Bumpy skin (Gooseflesh)

Lost Appetite, Stomach cramps

- Dosing: Take ½ to 1 strip or tab every 1 hour until withdrawal / cravings are gone
- Can go up to a recommended max dose of 32mg, but not every patient needs this dose



2. Put the tablet / film under your tongue and let it dissolve [don't swallow, don't chew]



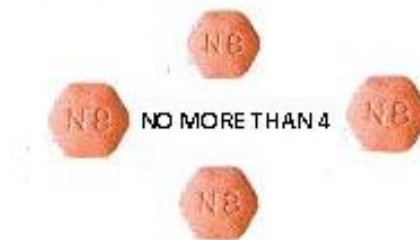
3. After 1 hour, how are you feeling?
- o IF GOOD: nothing more to do
 - o IF still having the withdrawal symptoms or feeling worse:
put another tablet under your tongue





Day 2:

- IF you feel good the next day, take the same number of total pills you took the day before
- during the day: if you feel withdrawal symptoms or feel cravings you can take another tablet under your tongue

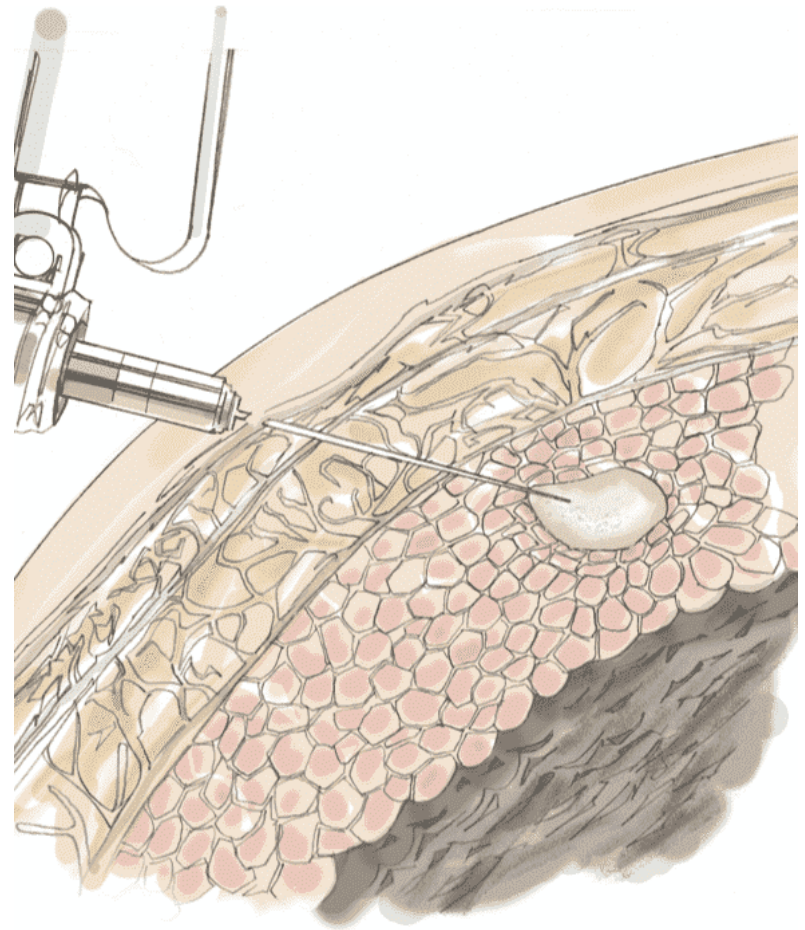
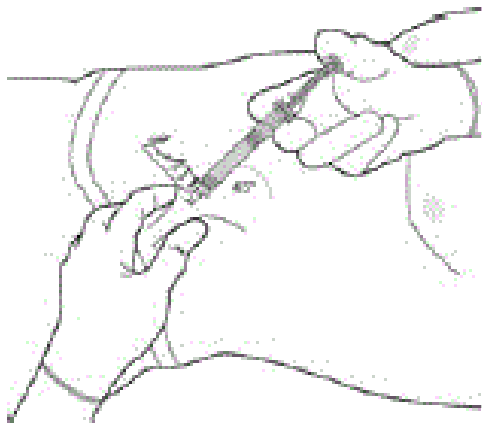
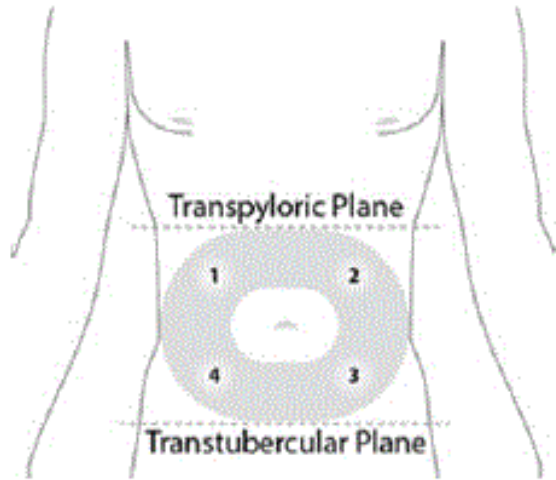
Day 3:

- IF you feel good, you can take the same number of pills you took the day before or split it however you want throughout the day.
- If you are taking LESS than 4 tablets AND you have cravings later in the day, you can take yourself the 4th tablet whatever time of the day you want.



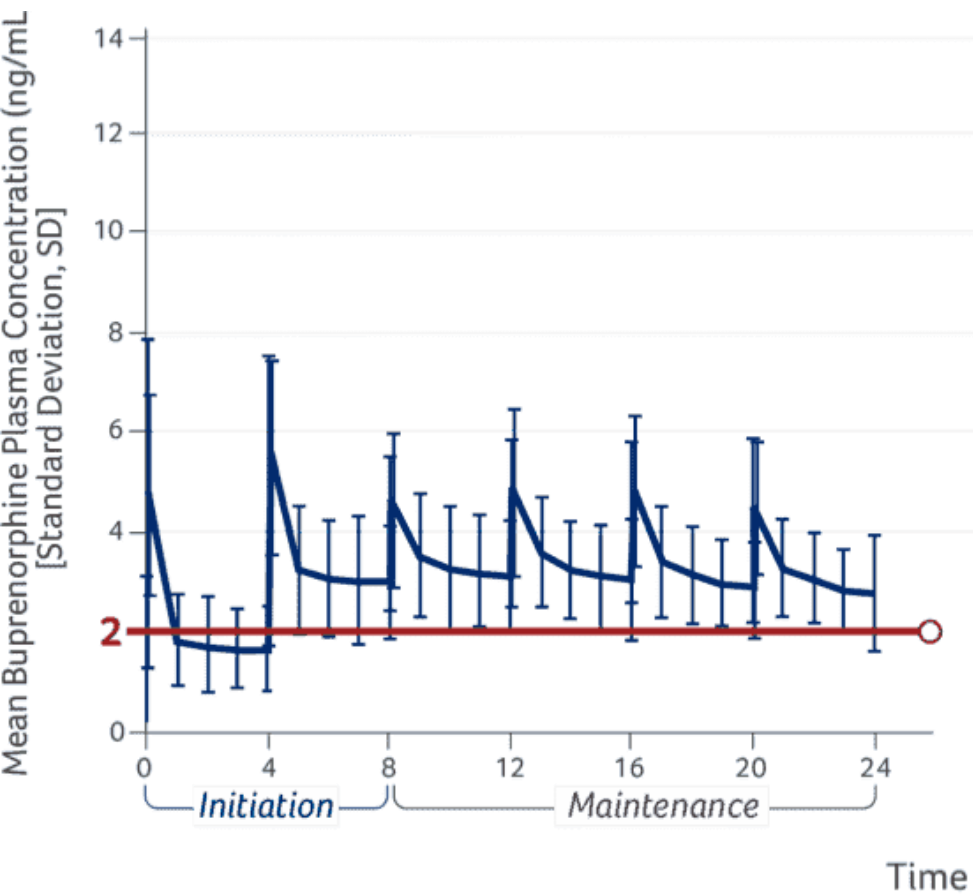
			
8 mgs.	4 mgs.	2 mgs	

ER Buprenorphine Injection

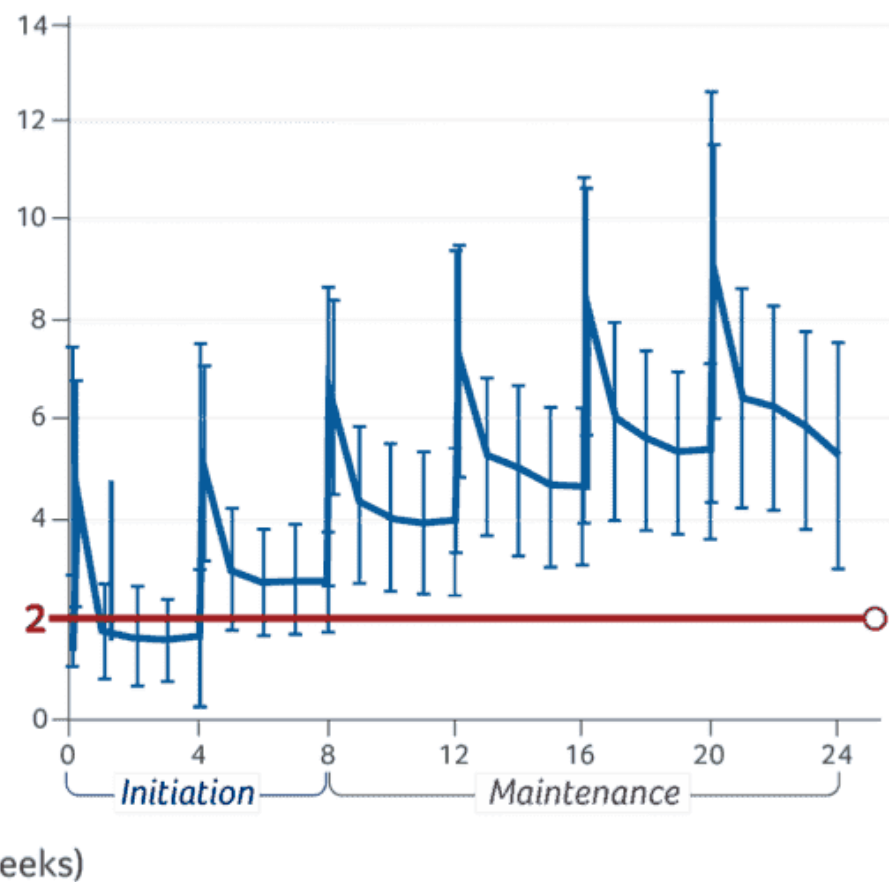


ER Buprenorphine Injection

ER Bup 300mg/300mg, then 100mg qMonth



ER Bup 300mg qMonth



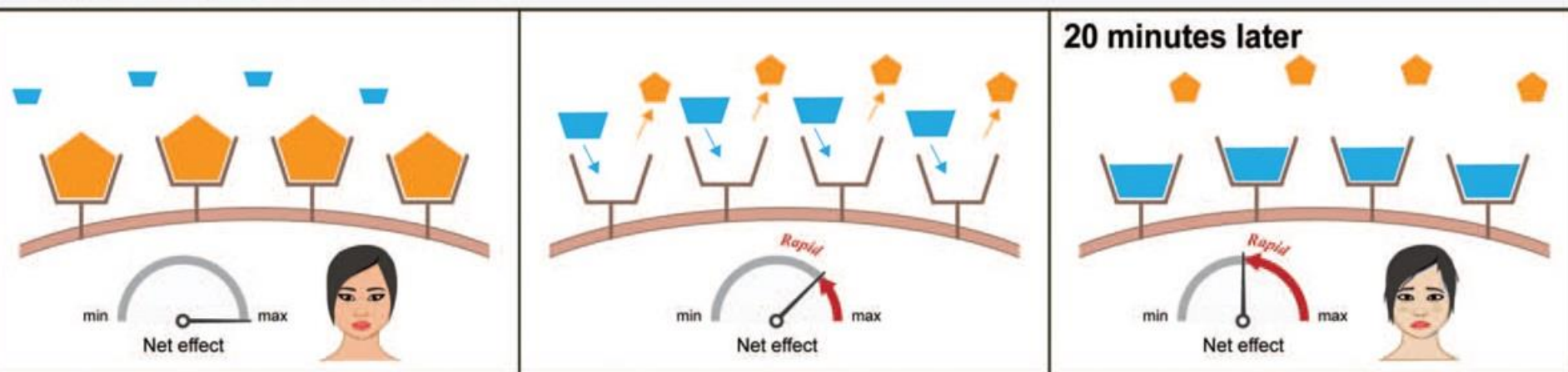
Single Day ER Bup Inj Protocol

- Five patients, open label protocol, 12 week study
- ER Bup Inj 300 mg after patient tolerated > 24 mg of SL buprenorphine in a single day
 - In clinic-setting
 - Hourly SL buprenorphine dosing schedule was 2 mg-6 mg-8 mg-8 mg
 - One hour after last buprenorphine dose → ER Bup Inj 300 mg
- Three total monthly injections of BXR (300 mg-300 mg-100 mg), patients monitored 4 weeks following third injection
- 5 (100%) retained all 12-weeks & received all three injections
- Acceptability of the single-day start on ER Bup inj was high
- Longest period of illicit opioid use during study period: 5 days

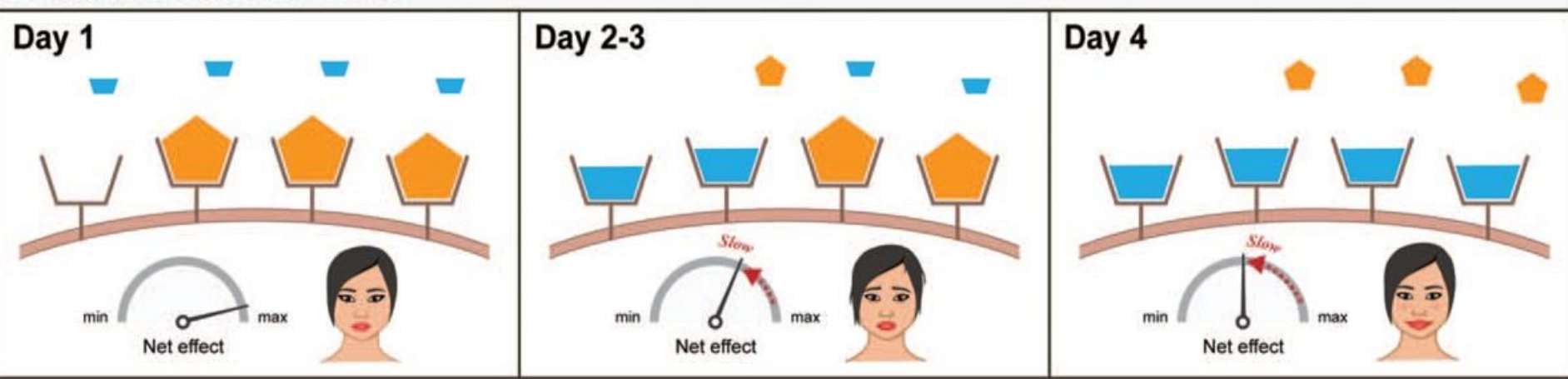
Mariani JJ, Mahony AL, Podell SC, Brooks DJ, Brezing C, Luo SX, Naqvi NH, Levin FR. Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl. Am J Addict. 2021 Sep;30(5):470-476. doi: 10.1111/ajad.13193. Epub 2021 Jul 5. PMID: 34223681; PMCID: PMC8459386. <http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34223681>

Low Dose Starts

Precipitated Withdrawal Mechanism



Bridging at Molecular Level



Orange pentagon: Full agonist opioid
Blue trapezoid: Buprenorphine

Ghosh, S. M., Klaire, S., Tanguay, R., Manek, M., & Azar, P. (2019). A review of novel methods to support the transition from methadone and other full agonist opioids to buprenorphine/naloxone sublingual in both community and acute care settings. *Canadian Journal of Addiction*, 10(4), 41-50. <http://doi.org/10.1097/CXA.0000000000000072>

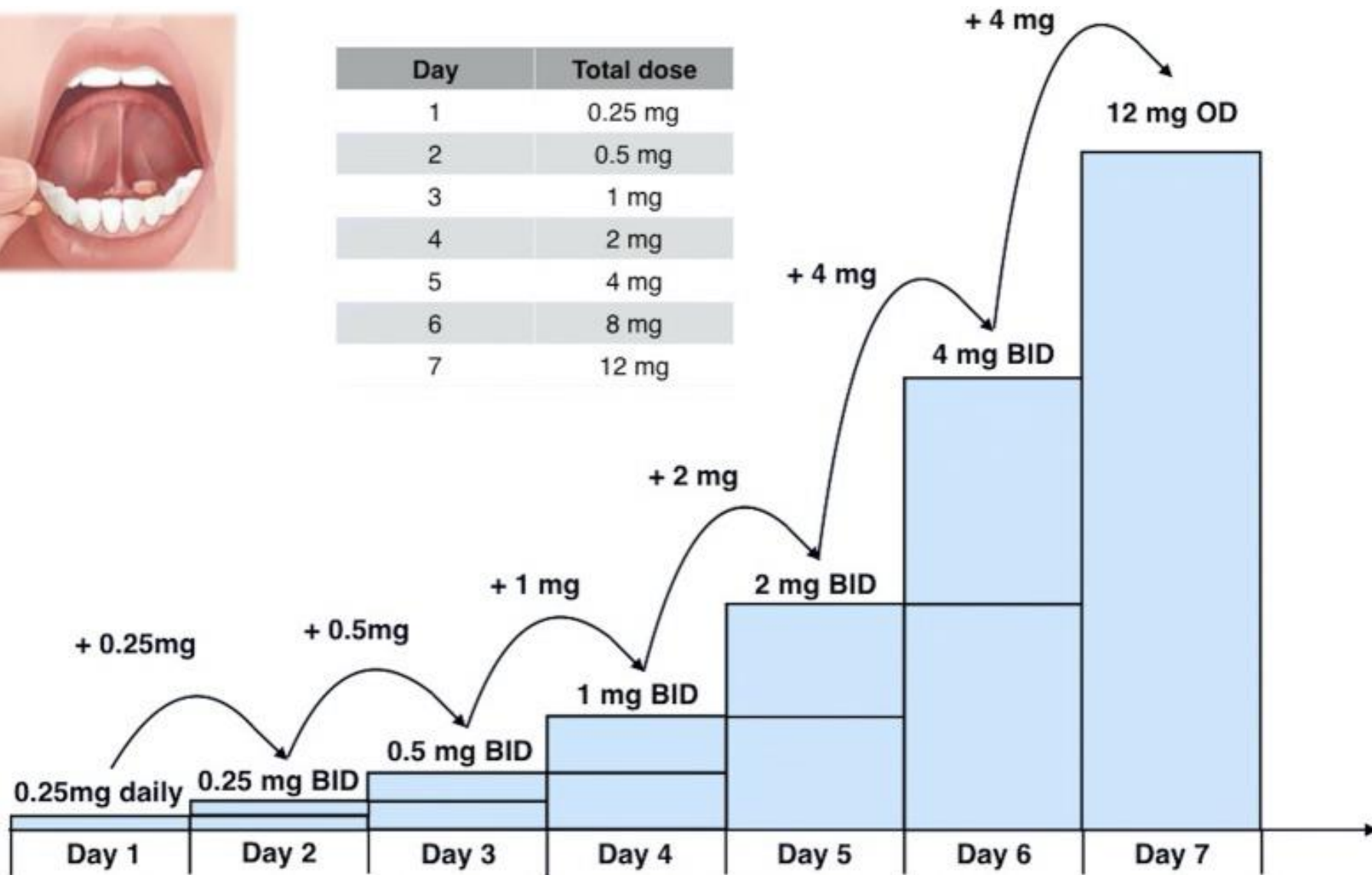
Table 2. Outpatient Microinduction Protocol Using Sublingual 2 mg Buprenorphine/Naloxone Tablets or Films

Day	Bup/Nlx Dose and Frequency	Full Agonist Opioid
1	0.5 mg daily (1/4 tablet or film)	No change
2	0.5 mg BID	No change
3	1 mg BID (half-tablet or film)	No change
4	2 mg BID	No change
5	2 mg TID	No change
6	4 mg TID	No change
7 and beyond	Per provider discretion	Taper by 25% weekly

Robbins JL, Englander H, Gregg J. Buprenorphine Microdose Induction for the Management of Prescription Opioid Dependence. J Am Board Fam Med. 2021 Feb;34(Suppl):S141-S146. doi: 10.3122/jabfm.2021.S1.200236. PMID: 33622829. <http://pubmed.ncbi.nlm.nih.gov/33622829>



Day	Total dose
1	0.25 mg
2	0.5 mg
3	1 mg
4	2 mg
5	4 mg
6	8 mg
7	12 mg



Rozylo J, Mitchell K, Nikoo M, Durante SE, Barbic SP, Lin D, Mathias S, Azar P. Case report: Successful induction of buprenorphine/naloxone using a microdosing schedule and assertive outreach. *Addict Sci Clin Pract.* 2020 Jan 15;15(1):2. doi: 10.1186/s13722-020-0177-x. PMID: 31941547; PMCID: PMC6964069.

<http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31941547>

BUPRENORPHINE-NALOXONE DOSAGES				ADJUNCTIVE THERAPIES FOR MANAGING WITHDRAWAL SYMPTOMS
DAY	OPTION 1	OPTION 2	OPTION 3	
1	0.5 mg and 0.125 mg SL daily	0.5 mg and 0.125 mg SL once daily	0.25 mg and 0.0625 mg SL once daily	<ul style="list-style-type: none">• 0.1 mg of clonidine twice daily as needed for agitation• 400-600 mg of ibuprofen 4 times daily as needed and 650-1000 mg acetaminophen every 6 h as needed for myalgia• 50 mg of dimenhydrinate every 6 h as needed for nausea or vomiting• 2 mg of loperamide after loose bowel movement as needed for diarrhea• Can consider providing 2 doses of 2 mg and 0.5 mg of SL buprenorphine-naloxone every h as needed for withdrawal
2	0.5 mg and 0.125 mg SL daily	0.5 mg and 0.125 mg SL twice daily	0.25 mg and 0.0625 mg SL twice daily	
3	1 mg and 0.25 mg SL daily	1 mg and 0.25 mg SL twice daily	0.5 mg and 0.125 mg SL twice daily	
4	1.5 mg and 0.375 mg SL daily	2 mg and 0.5 mg SL twice daily (can stop short-acting or begin tapering long-acting opioids)	1 mg and 0.25 mg SL twice daily	
5	2 mg and 0.5 mg SL daily	3 mg and 0.75 mg SL twice daily	2 mg and 0.5 mg SL twice daily (can stop short-acting or begin tapering long-acting opioids)	
6	3 mg and 0.75 mg SL daily	4 mg and 1 mg SL twice daily	4 mg and 1 mg SL twice daily	
7	4 mg and 1 mg SL daily (can stop short-acting or begin tapering long-acting opioids)	12 mg and 4 mg SL once daily (stop all opioids)	12 mg and 4 mg SL once daily (stop all opioids)	
8	5 mg and 1.25 mg SL daily	Adjust further dosing based on patient symptoms	Adjust further dosing based on patient symptoms	
9	6 mg and 1.5 mg SL daily			
10	7 mg and 1.75 mg SL daily			
11	8 mg and 2 mg SL daily			
12	10 mg and 3 mg SL daily			
13	12 mg and 4 mg SL daily (stop all opioids)			
14	Adjust further dosing based on patient symptoms			

SL—sublingual.
Data from Patel et al,⁴ Lee,⁵ Crawley et al,⁶ Sandhu et al,⁷ and Cho and Lu.⁸

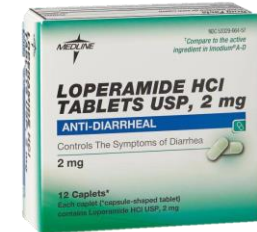
Marwah R, Coons C, Myers J, Dumont Z. Buprenorphine-naloxone microdosing: Tool for opioid agonist therapy induction. Can Fam Physician. 2020 Dec;66(12):891-

894. doi: 10.46747/cfp.6612891. PMID: 33334955; PMCID: PMC7745932. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7745932>

Slide Credit: Joshua Bloom, MD

Supportive medications

- Clonidine 0.1-0.2 every 4-6h
 - Sweating, goosebumps
- Ondansetron 8 mg every 8h
 - Nausea, vomiting
- Hydroxyzine 50 mg every 6h
 - Anxiety, insomnia
- Ibuprofen 600 mg every 6h
 - Myalgias, arthralgias
- Loperamide 1-2 at onset of diarrhea



Pain Management / Analgesic Dosing

How to Switch to Buprenorphine from Opioids

like oxycodone, hydrocodone, morphine or methadone

Goal: Start buprenorphine without period of withdrawal

Apply Butrans Patch.

Remove bedtime on 5th day

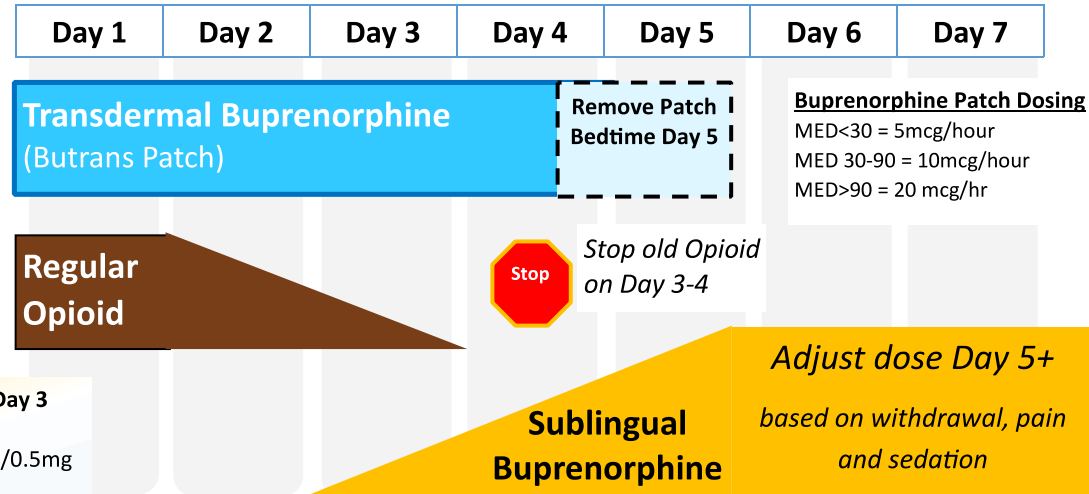
- Rarely covered by insurance.
- Cheap via 340B and only need a single patch

Taper Opioid as tolerated

- Use clonidine as needed
- Reduce by ~50% Day 2
- Stop on Day 3 or 4

Start Sublingual Buprenorphine on Day 3 and gradually increase.

Prescribe buprenorphine/naloxone 2/0.5mg film #30 and a single Butrans patch



	Butrans Patch*	Oxycodone etc	SL Buprenorphine*
Day 1	Apply Patch	Continue same dose	
Day 2	Continue	Reduce 50% dose	
Day 3	Continue	Stop at Bedtime	1mg TID (1/2 film)
Day 4	Continue		2mg TID
Day 5	Remove at Bedtime		2-4mg TID
Day 6			2-4mg TID or more

*Adjust per patient needs/MED.

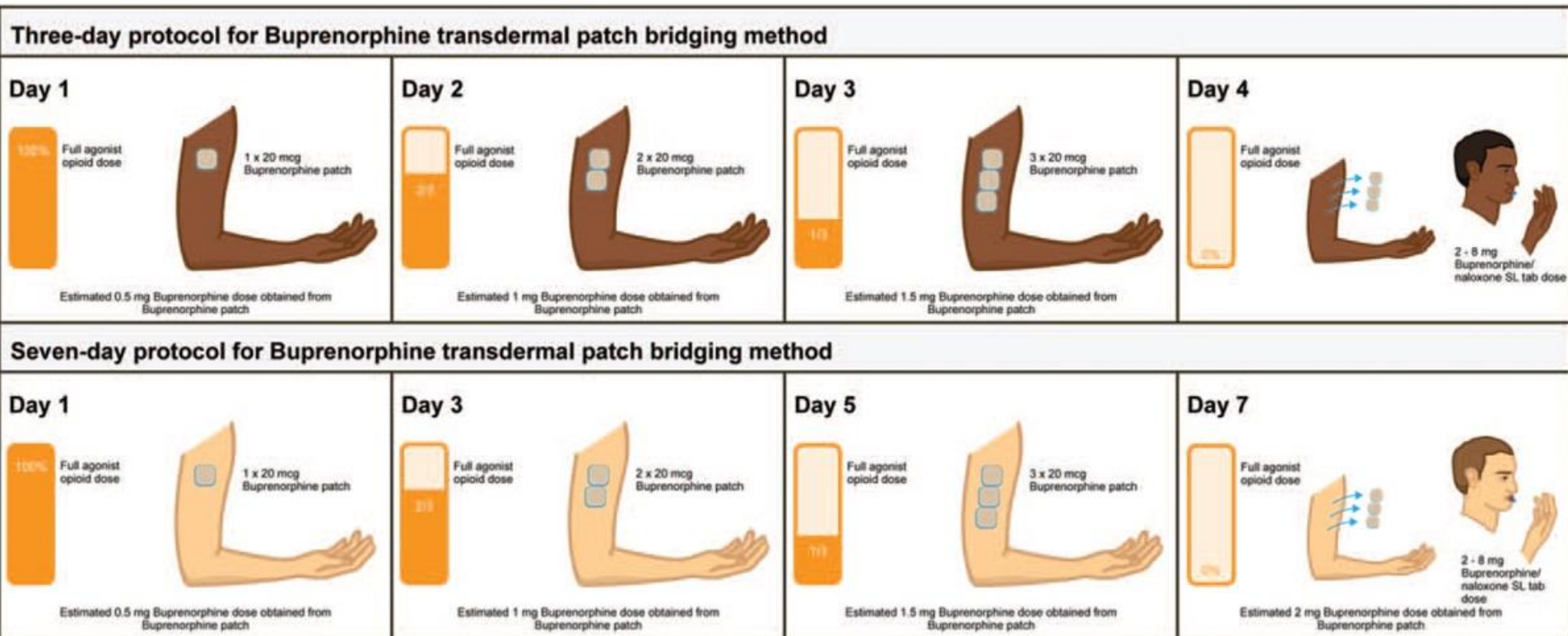
Consult expert for MED <15 or >90, methadone or questions

Adapted from

1. Amer Raheemullah, MD; Anna Lembke, MD, JAMA internal medicine. January 2019. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting A Teachable Moment
2. Saal D, Lee F. Rapid induction therapy for opioid use disorder using buprenorphine transdermal patch: A case series. Perm J 2020;24:19.124. DOI: <https://doi.org/10.7812/TPP/19.124>
3. Webster et al., Understanding Buprenorphine for use in Chronic pain: Expert Opinion. Pain Medicine, 0(0), 2020, 1–10 doi: 10.1093/pm/pnz356

Slide Credit: Joshua Bloom, MD

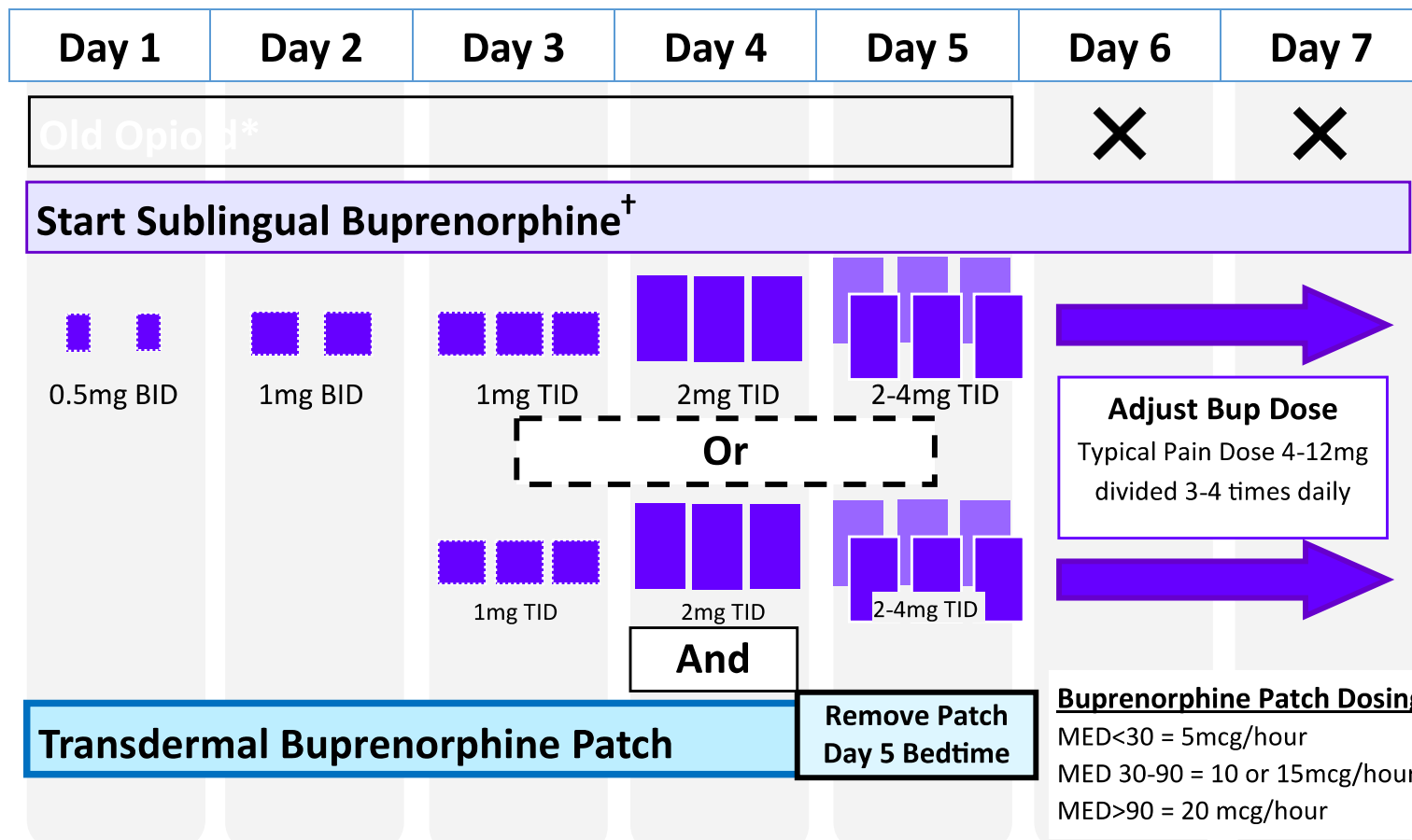
https://pcl.psychiatry.uw.edu/wp-content/uploads/2021/12/Buprenorphine_Microdosing_with_Patch_protocol-Perez95.pdf



Ghosh, S. M., Klaire, S., Tanguay, R., Manek, M., & Azar, P. (2019). A review of novel methods to support the transition from methadone and other full agonist opioids to buprenorphine/naloxone sublingual in both community and acute care settings. *Canadian Journal of Addiction*, 10(4), 41-50. <http://doi.org/10.1097/CXA.000000000000072>

How to Switch to Buprenorphine from Opioids (Microdosing)

Goal: Start buprenorphine without period of withdrawal



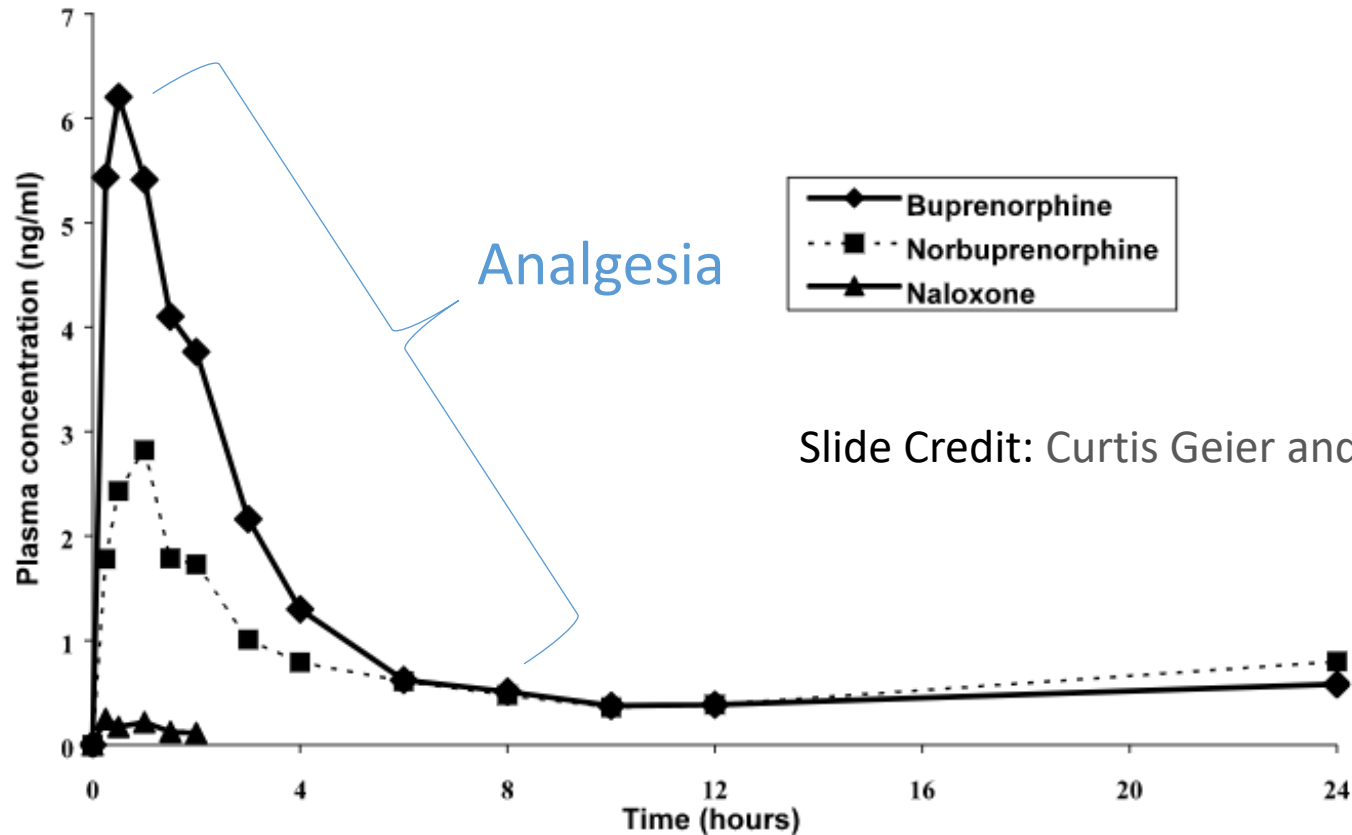
*Discontinue after 5 days or begin taper day 2-3

†Prescribe buprenorphine/naloxone 2/0.5mg film or tab. MEDD<40 may stabilize on 1mg TID-QID. MEDD = Morphine Equivalent Daily Dose

Buprenorphine Pharmacokinetics

S44

C.N. Chiang, R.L. Hawks / Drug and Alcohol Dependence 70 (2003) S39–S47



Slide Credit: Curtis Geier and Ben Smith

Fig. 4. The time course of plasma levels of buprenorphine, norbuprenorphine and naloxone for a subject receiving a sublingual dose of the combination tablet of buprenorphine (16 mg) and naloxone (4 mg) (data from Jones et al., 1997).

Controlled Environment Starts

Starting SL Buprenorphine in a Controlled Setting After Withdrawal

How to start buprenorphine/naloxone after the patient is no longer in withdrawal?

- Week 1: 1mg/0.25mg daily x7d
- Week 2: 2mg/0.5mg daily x7d
- Week 3: 3mg/0.75mg daily x7d
- Week 4: 4mg/1mg daily x7d
- Week 5: 6mg/1.5mg daily x7d
- Week 6: 8mg/2mg daily x14d
- Week 7: 16mg/4mg daily QOD



Vocci FJ, Schwartz RP, Wilson ME, Gordon MS, Kinlock TW, Fitzgerald TT, O'Grady KE, Jaffe JH. Buprenorphine dose induction in non-opioid-tolerant pre-release prisoners. *Drug Alcohol Depend.* 2015 Nov 1;156:133-138. doi: 10.1016/j.drugalcdep.2015.09.001. Epub 2015 Sep 7. PMID: 26409751; PMCID: PMC4633333. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4633333>

Starting SL Buprenorphine in a Controlled Setting After Withdrawal

However... *participants started onto buprenorphine at a rate faster than the induction schedule.*

- In another trial:
- Initial dose 4 mg which could be stepped up to a maximum of 8 mg on the first day. On subsequent days the subject could be stepped up to a maximum of 32 mgs, if clinically indicated and the patient agreed.



Magura S, Lee JD, Hershberger J, Joseph H, Marsch L, Shropshire C, Rosenblum A. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug Alcohol Depend.* 2009 Jan 1;99(1-3):222-30. doi: 10.1016/j.drugalcdep.2008.08.006. Epub 2008 Oct 18. PMID: 18930603; PMCID: PMC2658719. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2658719>

Medication FIRST Model

- People with OUD receive pharmacotherapy treatment as quickly as possible, prior to lengthy assessments or treatments planning sessions;
- Maintenance pharmacotherapy is delivered without arbitrary tapering or time limits;
- Individualized psychosocial services are continually offered but not required as a condition of pharmacotherapy;
- Pharmacotherapy is discontinued only if it is worsening the person's condition.

Medication FIRST Model

- Medication *first* **does not mean** Medication *only*
- Medication is contingent upon the pt's benefit, not based upon a timeframe, patient's participation in counseling, an unexpectedly positive test result, etc

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Funding for this initiative was made possible (in part) by grant no. 6H79TI081968 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.