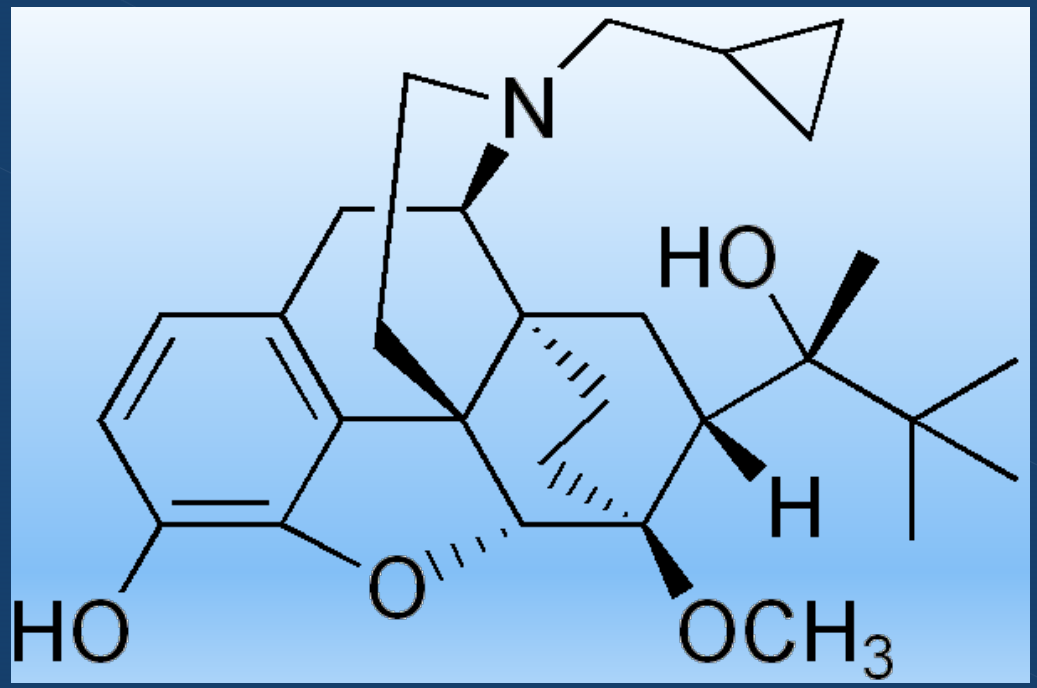
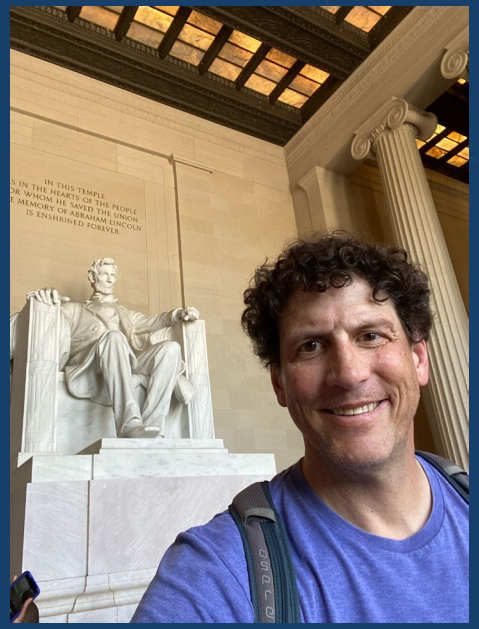
Buprenorphine



May 2024

Ari Greenberg, PAC



Community Medical Services, Billings MT

Montana Women's Prison, MT DOC

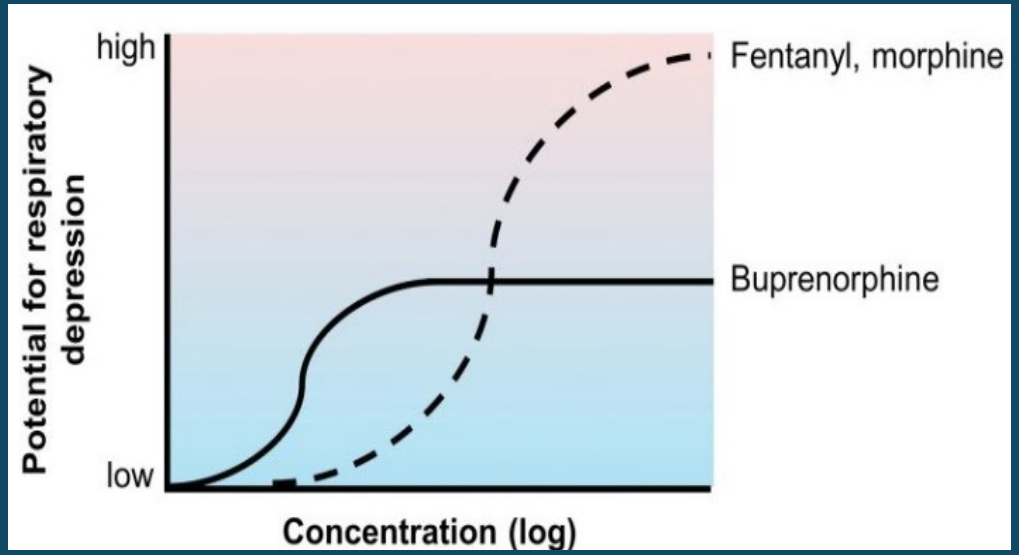
No Disclosures

Objectives

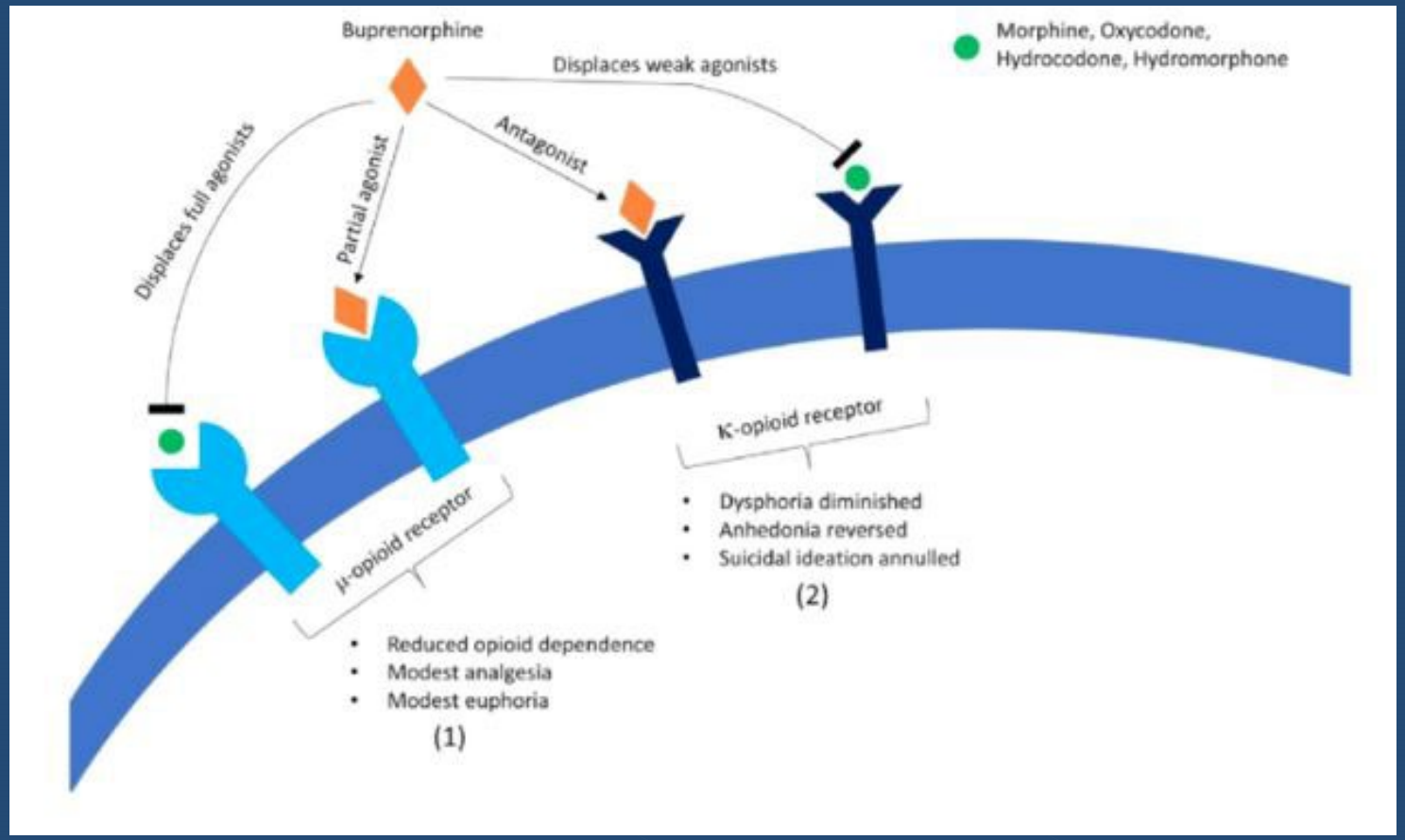
- Discuss mechanism of action (MOA) for Buprenorphine (Bup), along with adverse events and available formulary products.
- Discuss the impact of illicitly manufactured fentanyl products in today's drug market.
- Discuss methods to assist a provider in a clinical setting initiate patients on Bup.

Bup MOA

- Partial agonist/partial antagonist
- Onset 30-60 min, peak 100 min
- Ceiling effect for respiratory drive
- Metabolites eliminated/excreted via urine (30%), feces (69%)
- Renal or hepatic impairment does not appear to significantly impact buprenorphine's effects.



Pergolizzi 12/19 Journal of Pain Research
Tung, Wong, Fairbairn



- Partial agonist for MOR
- Antagonist for KOR

Benhamou, Lynch, Klepacz

Affinity

- **Powerful affinity for the Mu opioid receptor (MOR)**

Medication	K_i (nM)
Codeine	734.2
Meperidine	450.1
Oxycodone	25.87
Methadone	3.378
Naloxone	1.518
Fentanyl	1.346
Morphine	1.168
Hydromorphone	0.3654
Buprenorphine	0.2157
Sufentanil	0.1380

Tung, Wong, Fairbairn

Adverse events – Bup

Sedation	
Nausea/Constipation/Wt gain	
Headaches	Can be associated w/ Naloxone component
Tooth Decay	Poor oral hygiene Reduced saliva output Temporary increase in oral acidity
Endocrine disruption	

Q&A w/ Dr. Rena Souza, NIDCR Director

Concerns for Sedation with Treatment

Effect of WD sx's

- Sleep wave disruption

Sleep maintenance and repair

- NREM Recovery
- REM Rebound

Drug Using Dreams

- Emotional intensity attached to memories

Simon, Walker
Feriante, Singh
Gujat, Rashida, McDonald, Walker

Most Commonly Used Bup Formularies For MOUD

Sublingual film/tablet - Suboxone/Subutex (generic versions – B/N or Bup only)

- **$** (~$80/mo generic vs ~$274/mo brand films)

Long acting injectable (LAI) – Sublocade/Brixadi

- **$$$$$** (~$1900/$1650-monthly inj.)

SQ Buprenorphine LAI's

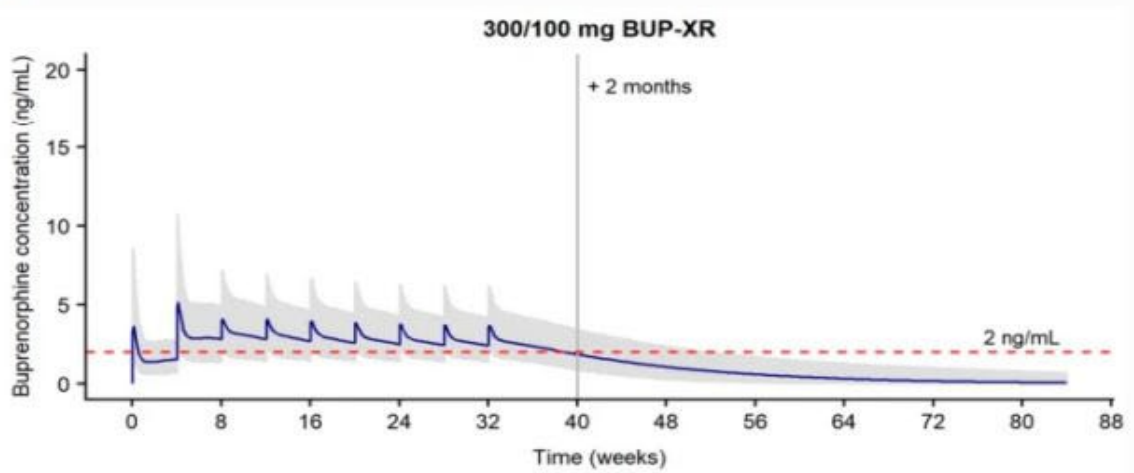
Requires Bup use prior to injection

- **Sublocade**
  - Refrigeration
  - Dosing: 300mg (loading) and 100mg (maintenance)
  - Injection site reactions
- **Brixadi**
  - Room temp
  - Dose adjustment
  - Weekly/monthly dosing
  - Injection site reactions

Daily Sublingual Buprenorphine Dose*	BRIXADI Weekly	BRIXADI Monthly
≤6 mg	8 mg	-
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Sublocade

Fig. 6



Predicted decrease in buprenorphine plasma concentrations for BUP-XR dosing regimens following treatment interruption. **a** 300/100-mg dosing regimen 2; **b** 300/300-mg dosing regimen. Blue solid lines: median of the simulated data; gray shaded areas: 90% prediction intervals of simulated data. A total of nine subcutaneous injections were simulated in 5000 subjects. The horizontal red dashed line

Patients stable on 100 mg will have blockade for 2 months (1 missed shot)

Patients stable on 300 mg will have blockade for 5 months (4 missed shots)

https://link.springer.com/article/10.1

Aksana, et al. Clin Pharm 2021

Fentanyl Era

- **Fentanyl is currently the primary choice of illicit opioid use**
  - **HPSO, novel synthetic analogs**

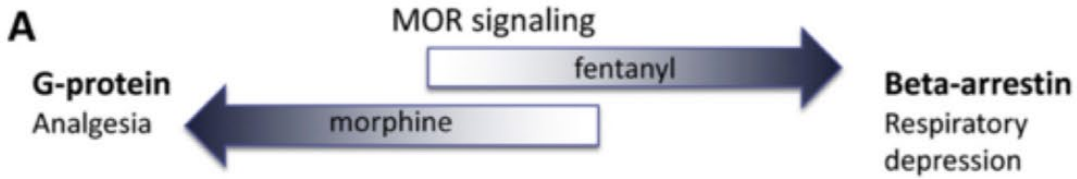
- **OD risks**
  - IV use
  - **Smoking** - Lesser risk d/t greater sensitivity to an open flame

  Multiple illicit drugs are adulterated w/ fentanyl
  - Snorting

- **EMS accidental exposure**
  - **Transdermal transmission requires constant direct contact**

Fentanyl Era

S.D. Comer, C.M. Cahill



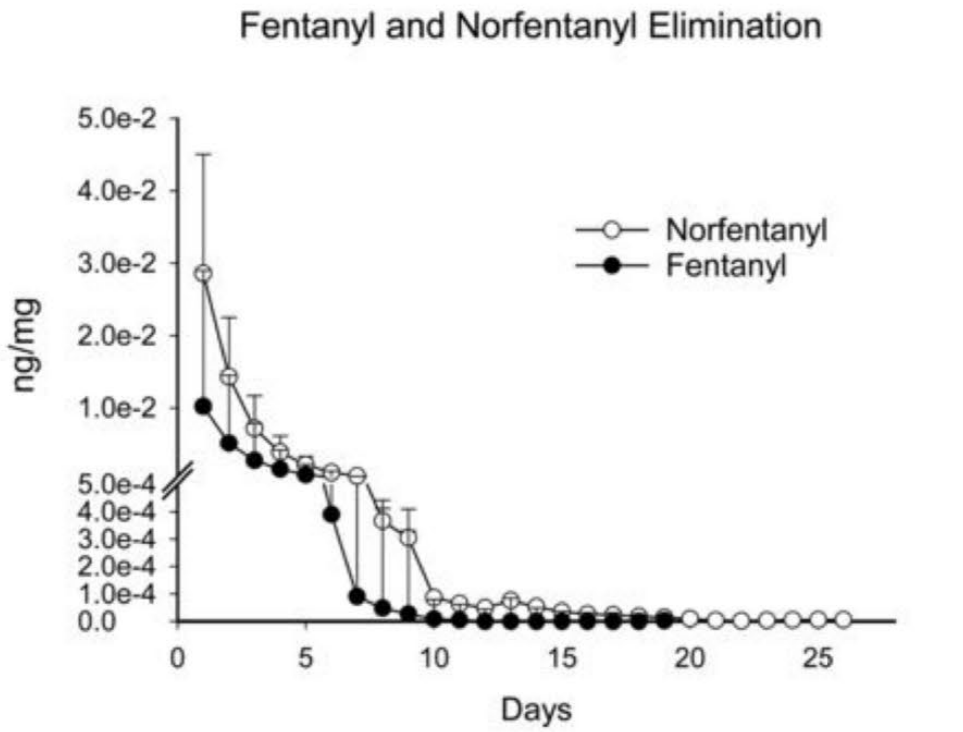
Morphine	Fentanyl
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry

Fentanyl and analogs account for >70% of opioid overdose deaths

Illicit fentanyl is illegally synthesized, forming many different analogs

Comer SD, et al. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Sep 1;214:108147.

Drug and Alcohol Dependence 214 (2020) 108147



Kliewer, et al BJP 2020

Fentanyl POCT

- 10/23 - 1st CLIA waived/FDA approved
  - Single test
  - Alltest cassette

Why should Bup gather more Attention?

- **Methadone –** Limitations to access
- **XR Naltrexone**
  - High drop-out rates in trial settings during initiation
  - Retrospective study looking at mortality benefit of MOUD did not find improved mortality
  - Lower tolerance may increase OD risk in the age of fentanyl.

Larochelle MR, et al. Ann Intern Med. 2018 Aug 7;169 (3) 137-45
Lee JD, et al. Lancet. 2018 Jan 27;391(10118). 309-18

Induction or Transition

“It makes me sick” Patients report POW’s

“It doesn’t work for me” Patient WD sx’s persist despite Bup initiation

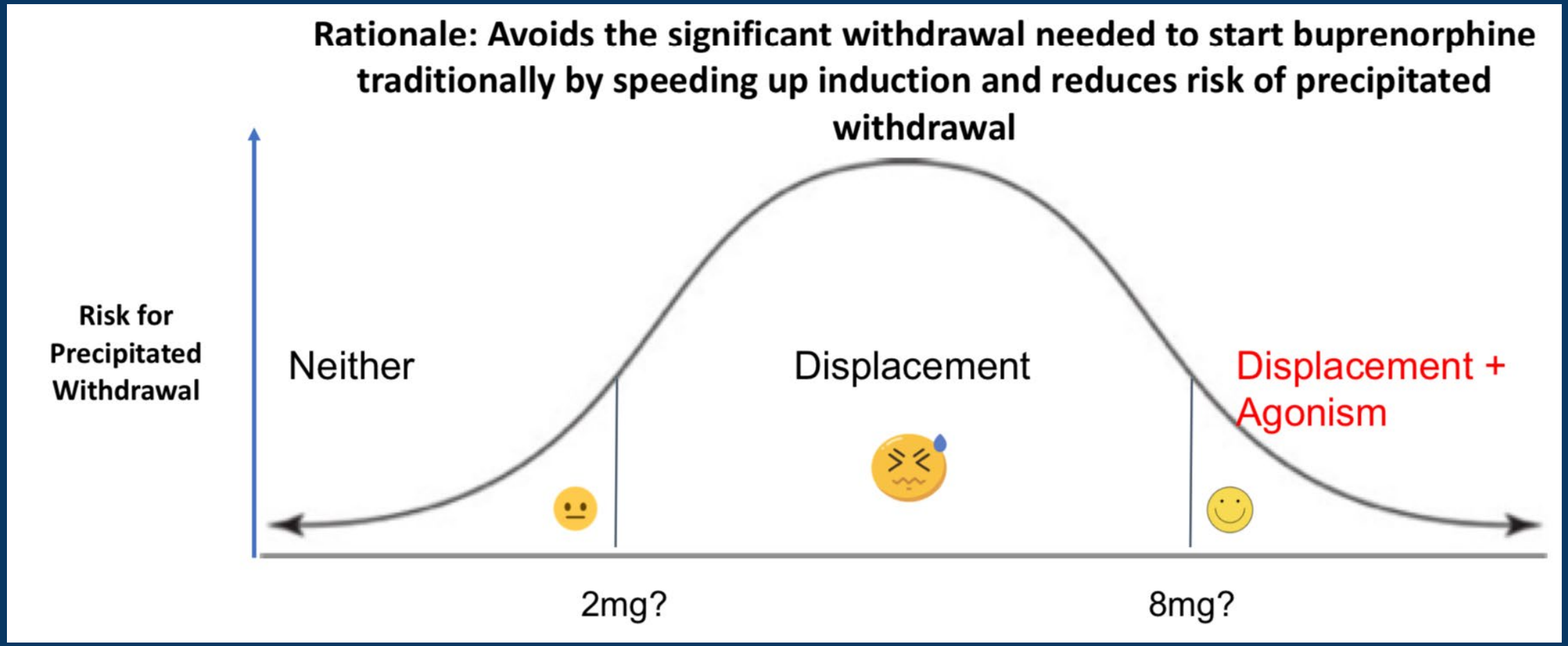
“I can’t wait long enough” Pts are unable to tolerate abstinence long enough to allow sufficient WD’s to develop permitting successful Bup induction w/ standard dosing.

Methods:

- **Micro Induction**
- **Macro Induction**
- **CA Bridge Inductions**
- **Bernese Method**

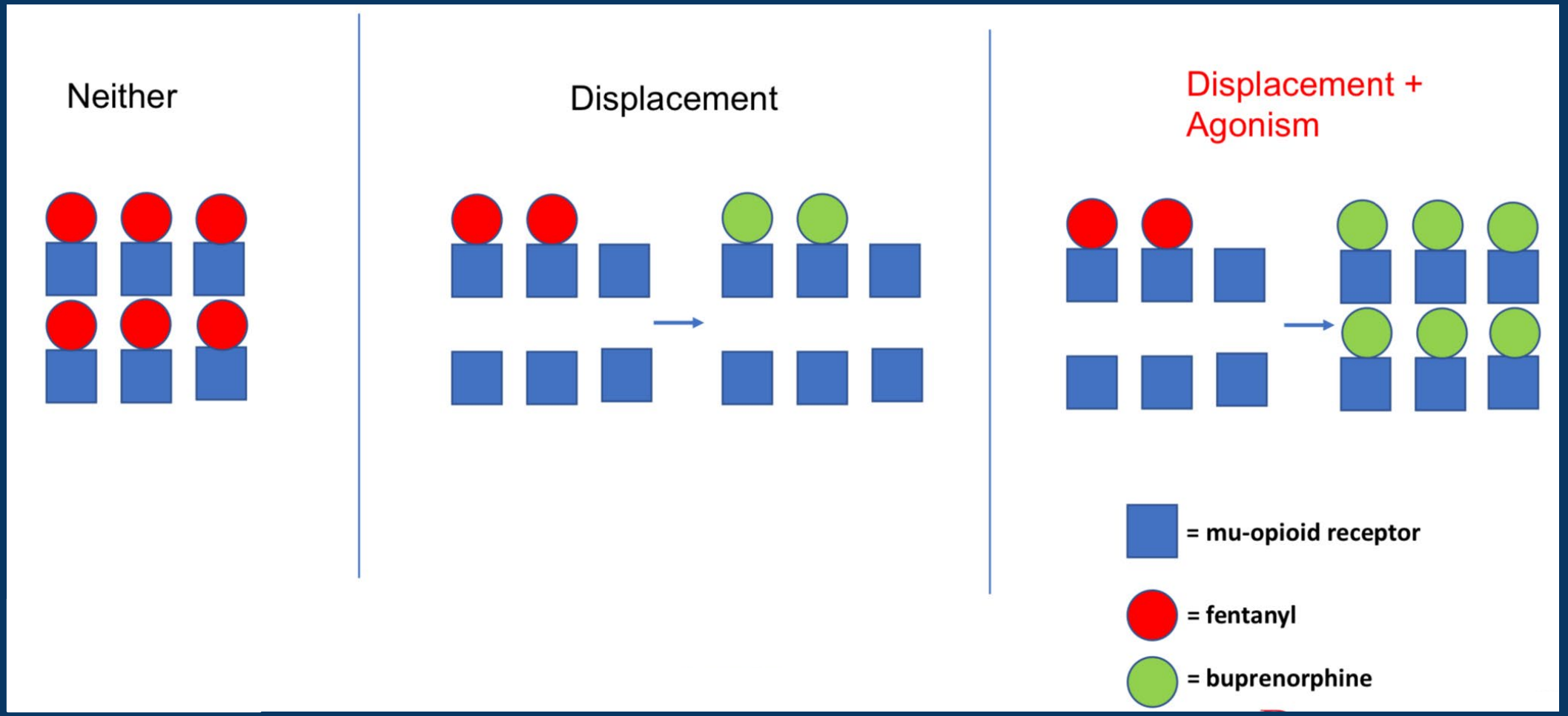
CA Bridge ASAM 2024

Micro vs Macro Dose Induction



Rutgers

Micro vs Macro Dose Induction



Rutgers

Micro Dose Induction

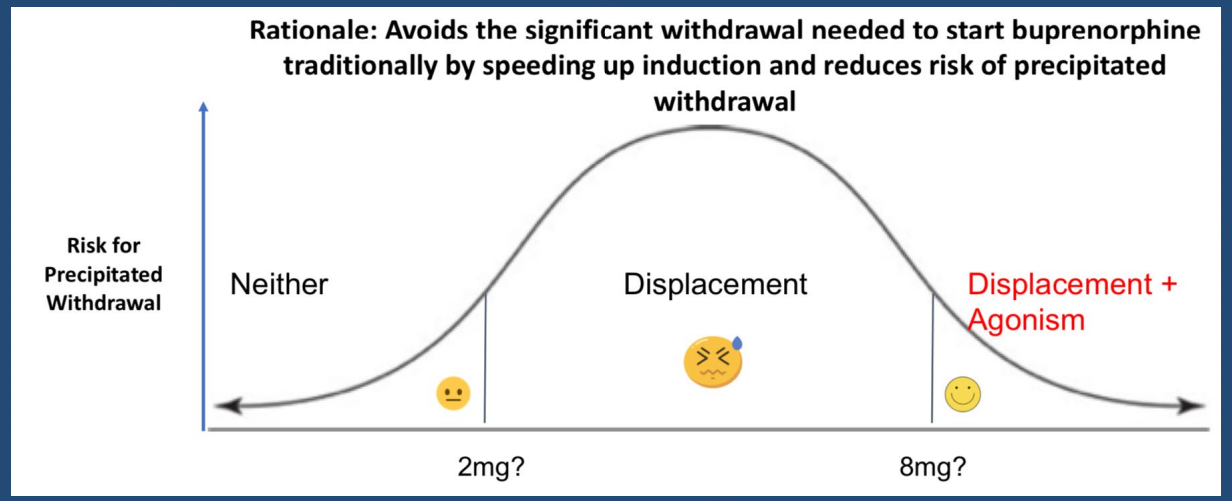
Office or home induction

- Start with a dose of 2-4mg of buprenorphine when patient exhibits mild-moderate withdrawal (COWS 6-10)
- Provided 24mg.
- Take 2-4mg every 30 minutes as needed, or up to 16mg.
- If POW's occur, progress immediately to taking remaining does up to 24mg.

Provide supportive treatment options

SAMHSA, Tip 63
Casadonte, PCSS, Bup Induction

Limitations?



Macro Dose Induction

Canadian presentation @ 2024 ASAM Conf

- **Video telehealth**
  - Nurse assessment and vitals/COWS provided

Bup induction

- 24-32-40mg (dependent on extent of use)
- >1h since last fentanyl use
- Bup ceiling effect on respiratory depression

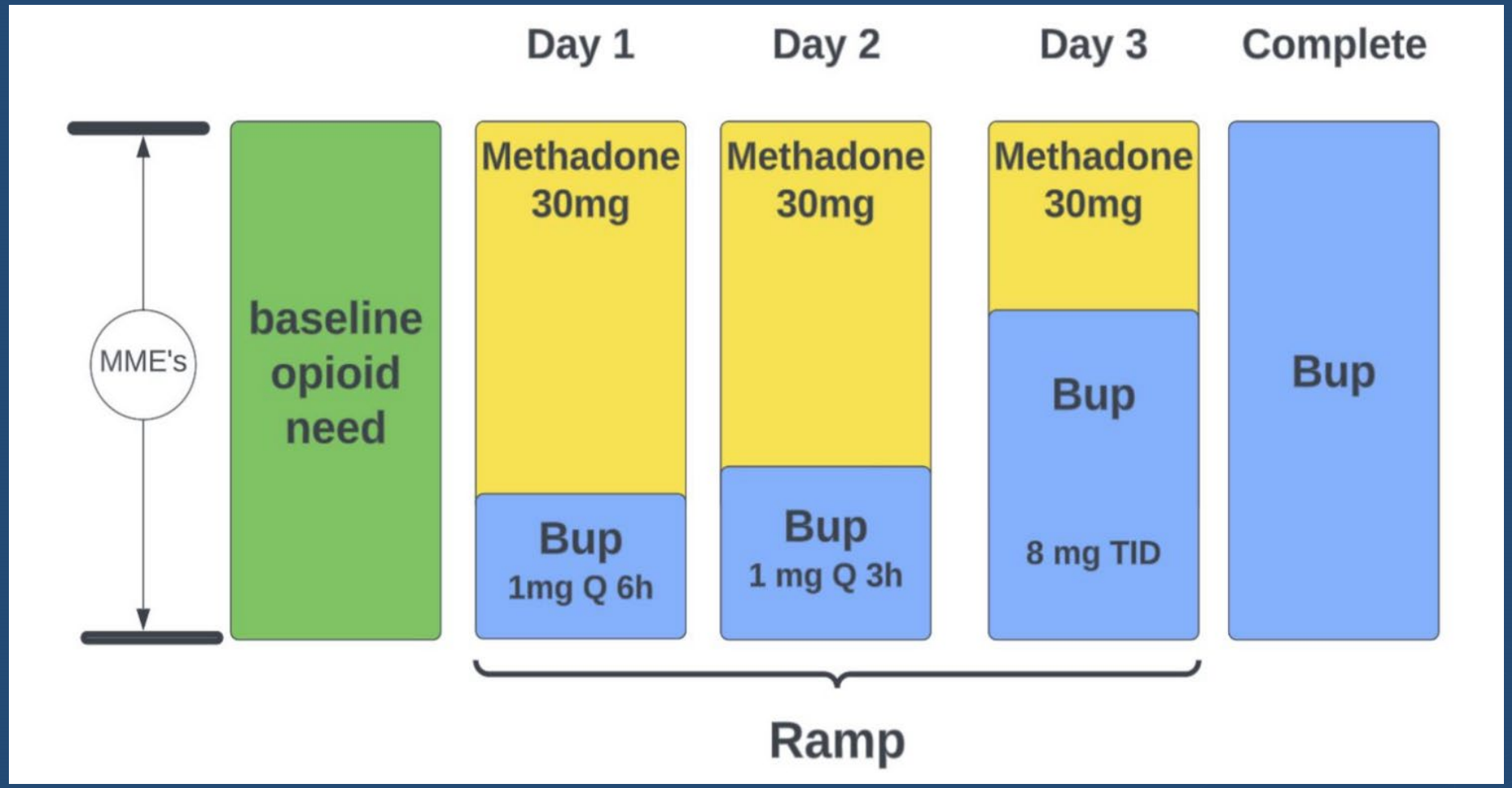
Dahan
Zobell, Nasr, Davis

Clinical approach

- Home induction
- Wait for WD sx's to become significant – 7/10
- Take 24mg at once, 3x8mg tabs sublingual until they dissolve
- Take another 8mg if sx's worsen w/in the first 100 min
- Follow up dosing may require 24mg if sx's poorly controlled after 24h
- Expect 16mg maintenance dose – patient dependent

CA Bridge LDB-OC Induction

- **Low dose Bup w/ opiate continuation**



Weimer, Herring, Kawasaki, Meyer, Kleykamp, Ramsey

CA Bridge HDB Induction

- **Rapid high dose Bup**
  - **COWS ≥8**
  - **Quickly escalate to 16-32mg**
  - **Prospective cohort study ED pts w/ >75% HPSO exposure reported POWs <1%**

    D'Onofrio, Hawk, Perrone JAMA 2023

  - **Cohort study HPSO exposure w/ similar results POWs ≤2%**

    Snyder, Chau JAMA 2023

  - **Risks for worsening sedation and/or respiratory depression:**
    - **Advanced age, acute medical illness, chronic lung disease, and those already sedated d/t other drugs or medications**

Weimer, Herring, Kawasaki, Meyer, Kleykamp, Ramsey

Methadone to Buprenorphine Transition

Reasons to transition

- Medical, Rx-Rx interactions, Increase TH's, Sober Living, Tx facilities, Bup LAI, Incarceration, Moving, SE's……
- Easier at lower doses <120mg, but not impossible

Methods

Novel Methods, Ghosh, 12/19

- MTD reduction to 30mg, stop 4-7d (Best <60mg)
  - Rapid Microdosing
  - Transdermal Bup or Fentanyl patches
  - Calgary SROM
- Bernese Method
  - microdose cross-titration

Bernese Transition

Most common protocol to transition from Methadone to Bup at OTP

Involves slowly replacing Methadone at the MOR w/ Bup over 11-13 days.

Best at a lower dose <120mg

Managing WD sx's:

- Splitting the daily dose
- Symptomatic tx w/ Clonidine, Ondansetron
- Frequent contact

Bernese Method
Switching from Methadone to Buprenorphine

Day	Mg	Bup/Nal 2mg strips	Date
1	0.125	0.0625 = 1/16	____
2	0.25	0.125 = 1/8	____
3	0.5	0.25 = 1/4	____
4	1.0	0.5 = 1/2	____
5	2.0	1	____
6	3.0	1.5	____
7	4.0	2	____
8	5.0	2.5	____
9	6.0	3	____
10	7.0	3.5	____
11	8.0	4	____
12	12.0	6	____
13	16.0	8	**(Stop Methadone, continue w/ CMS)**

- Pt will pick up generic Bup/Nal strips from Pharmacy, and will be cutting their strips at home.
- 13 days = #35 generic Bup/Nal 2mg strip (will use GoodRx)
  Then continue w/ SL tablets at CMS
- Expect some some mild WD sx's with each increase.
- **Reminded to adhere to instructions and not to take more Suboxone to help with increase in withdrawal symptoms.**

Generic Film

Use 1/16 strip on Day-1, 1/8 on Day-2, 1/4 on Day-3, 1/2 on Day-4, 1 strip on day-5, 1.5 strips on day-6, 2 on day-7, 2.5 on day-8, 3 on day-9, 3.5 on day-10, 4 on day-11, 6 on day-12, 8 on day-13

Bernese Transition template

Case #1

- **28yo female has come to your primary clinic setting at 1pm asking to start MOUD. She is both smoking and using IV fentanyl pills, averaging 10-15 pills a day. This has been going on for the last 2+ years and she can't stop.**
- **She has been trying to cut down the last week and has only been smoking 5 pills throughout the day. She last smoked one pill at 11pm last night. Her WD's in general are terrible: RLS, agitation, sweating, nausea, hot/cold flashes. She rates her current sx's as 5/10. She has tried Sbx off the streets and had an "allergic" reaction.**

Why did this pt do poorly with illicit Sbx?

Do you start dosing Sbx in the clinic? At home?

Symptomatic relief?

Case #2

- 39yo male pt has arrived at the ED on his own accord around 3pm with sx's of withdrawals from OUD. He is suffering from sneezing, hot/cold flashes, lacrimation, loose stools. He rates his current WD's as 8/10.
- His history includes using opiates since his motorcycle accident 8yo ago. Started w/ oral hydro's, then progressed to heroin IV. He reports currently smoking fentanyl blue pills daily, averaging 20-30 pills per day. He last smoked 5 pills early around 3am this morning. He also has a history of smoking methamphetamine on occasion when he can't find blues. He takes no other medications. He couch surfs for keeping a roof over his head.
- Today's POC urine tox screen results only reveal +amph/methamp.

Do you believe him? How come fentanyl did not show up?

Do you start in him on MOUD? Possible protocols?

Case #3

- 42 yo female pt comes into your primary clinical setting asking for help to make the transition from Methadone to a long-acting shot. She's been treated w/ Methadone for over 3 years and is frustrated by the medication. She feels ready to get off treatment. She has tried several times to take herself off, but WD sx's from Methadone were too terrible. Her friends have told her the shot is easier to wean off and wants to switch.
- She asks you, "I'm ready to get off treatment… Will it hurt?"

How do you discuss current state of tx?

Are WD sx's different from Methadone vs Buprenorphine?

What is the safest protocol to transition?

Is a LAI a better option to wean off MOUD? Why?

FREE RESOURCES

CA Bridge

ASAM Buprenorphine Clinical Consideration Document

ASAM Advanced Buprenorphine Education

Low Dose Bup 1 hr Education with Resources (fee)

QUESTIONS?

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