



DIFFICULT INDUCTIONS and DRUG TESTING PITFALLS

Christopher Suelzer, MD.





Learning Objectives

- 1- Discuss micro or macro -dosing as a strategy to transition patients to buprenorphine
- 2- Discuss use of drug testing to monitor compliance concerns for diversion
- 3- Discuss drugs that may not show up on standard drug testing



Cases for micro-induction

- Patient is a 30 yo female with history of heroin use disorder who recently has been using fentanyl over the last 6 months. History of multiple overdoses requiring naloxone, often seen in the emergency room. She has not been able to stop long enough to transition to buprenorphine but is interested in starting it



Traditional induction process

- Wait till the opioid used is metabolized and frees the mu receptors
- The patient starts to experience withdrawal
- Start buprenorphine which will bind to the unoccupied receptor and provide relief from the withdrawal





Cases for micro or macro-induction

- Patient is a 30 yo female with history of heroin use disorder who recently has been using fentanyl over the last several months. History of multiple overdoses requiring naloxone. She has not been able to stop long enough to transition to buprenorphine but keeps coming back to start it.

How can we get her on MAT when she can not stop
(painless conversion?)



Is methadone dangerous to use in patients addicted to Fentanyl

Concern:

- 1- Is adding a pure agonist in someone who is using another pure agonist increasing the risk of overdose
- 2- The length of time to achieve a therapeutic dose



Is methadone dangerous to use in patients addicted to Fentanyl

- 123 patients enrolled in methadone who tested positive for fentanyl
- 32% left treatment before 6 months (2 died after leaving)
- 89% achieved abstinence (3 consecutive neg UDS)
- 71% tested positive for fentanyl who stayed in treatment
- 0 deaths while on methadone



The concern with starting buprenorphine or naltrexone

- **Precipitated withdrawal**





Precipitated withdrawal vs Abstinence-related withdrawal

- Rapid displacement of the pure agonist with a partial agonist or full antagonist
- Tends to be much more severe in symptoms and more acute
- Delirium/autonomic hyperactivity
- Restless limb movements
- Can be life threatening in certain situations



BINDING AFFINITIES TO MU RECEPTOR

- Sufentanil 0.1
- Buprenorphine .21-1.5
- Naltrexone .4 -.6
- Fentanyl .70-1.9
- Methadone .70-5.6
- Naloxone 1.0-3.0
- Morphine 1.0-4.0

Pharmacytimes.com, Jan 6, 2018



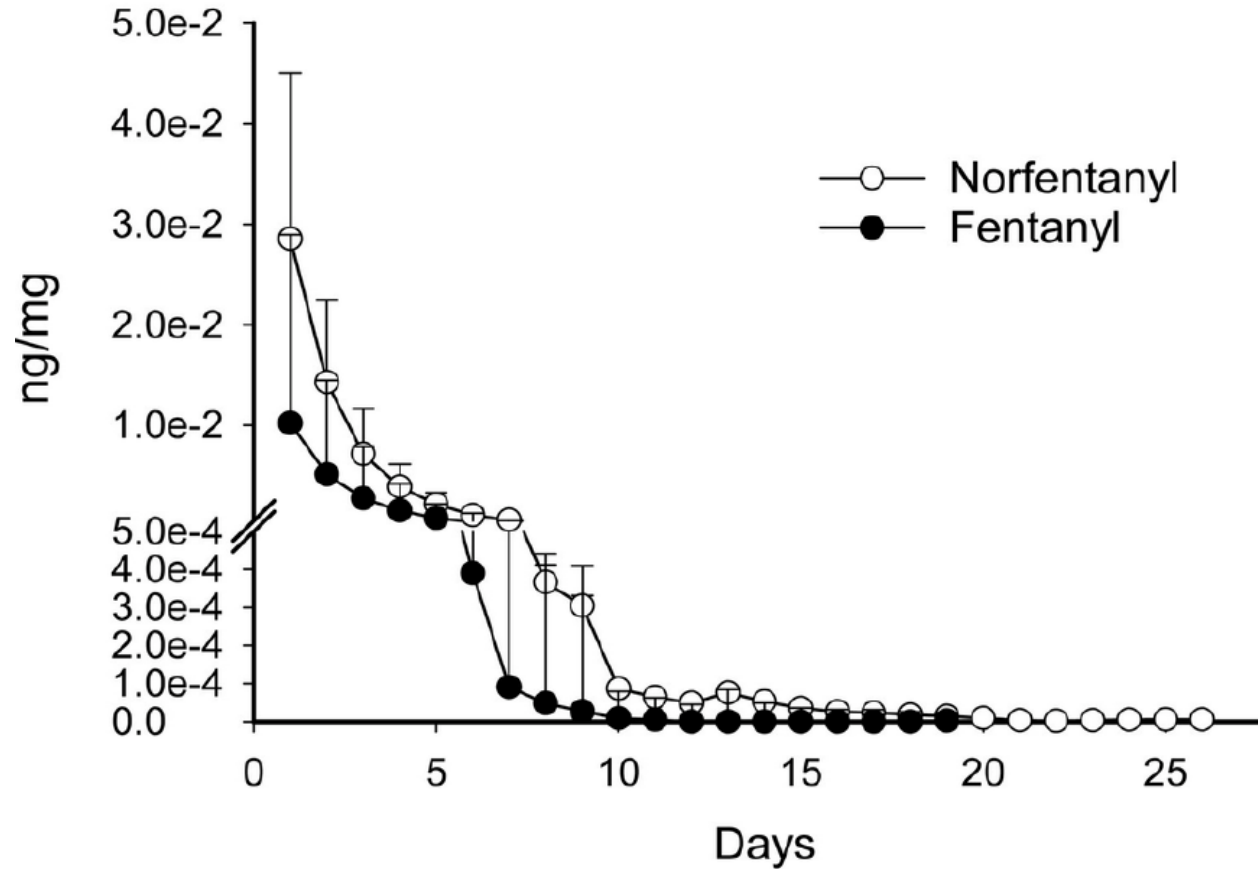
FENTANYL PHARMACOKINETICS

ROUTE	HALF LIFE
Single IV bolus	1.5-6 hrs
Continuous IV infusion	8 -12 hrs
Intranasal	1.5-7hrs
Transdermal	20-27 hours

Fentanyl is lipophilic so it accumulates in the fatty tissue extending the elimination
Great deal of variation in the pharmacokinetics among individuals



Urine detection for fentanyl and norfentanyl



HuhnSA et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depen. 2021



Precipitated opioid withdrawal

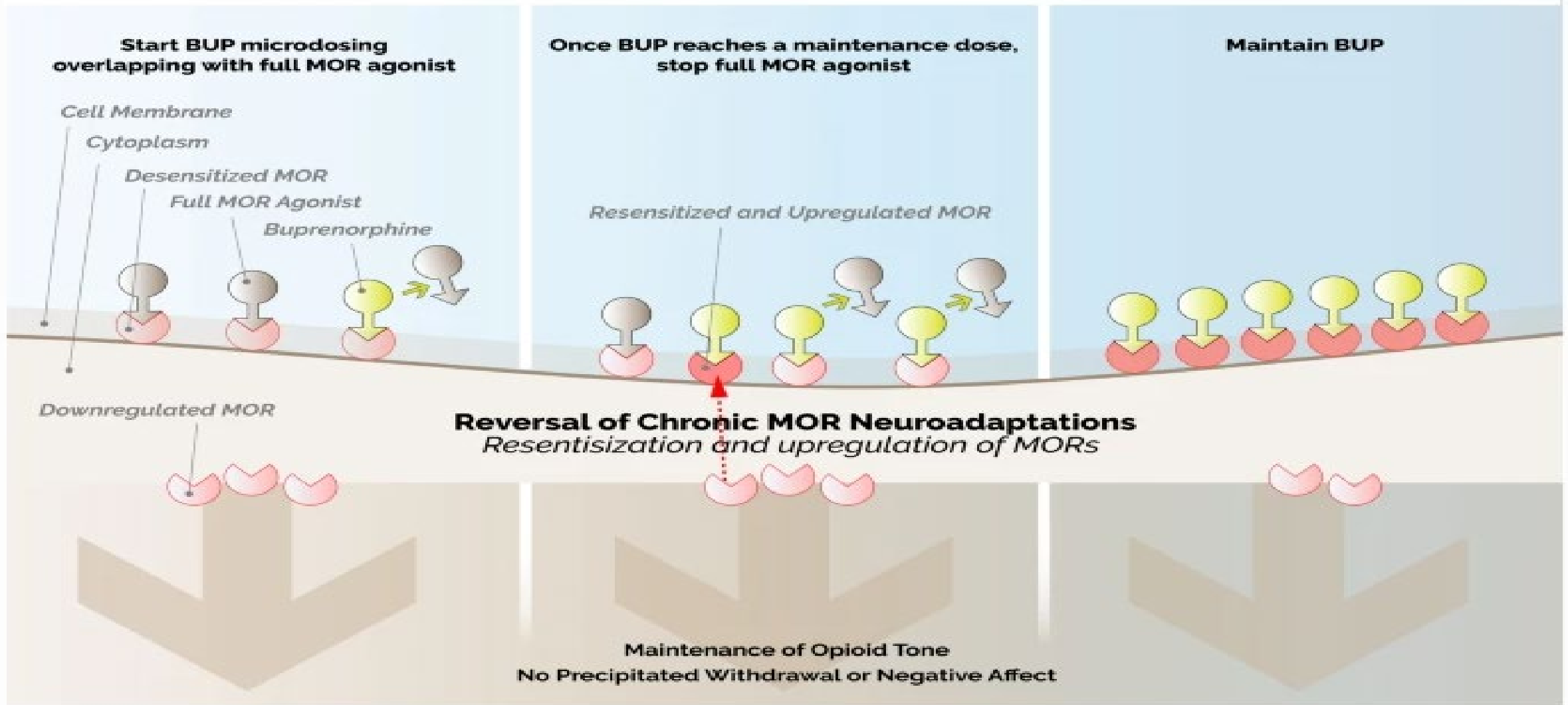
High dose fentanyl increases risk of precipitated withdrawal

Fentanyl is lipid soluble and may results in delayed withdrawal

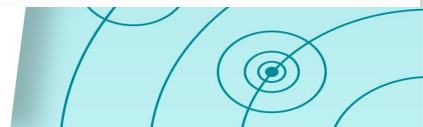
Increasing reports of using microdosing to successfully transition the patient to buprenorphine without requiring patient to experience withdrawal

Fig. 2

Buprenorphine Microinduction in Opioid-dependent Persons



De Aquino, J.P., et. Al., The pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clinical Drug Investigation* 41, 425-436, 4/2021





Micro-dosing conversion

- Allows conversion from methadone to buprenorphine without stopping the methadone
- Literature:
 - case report of 2 patients 2016 (Vogel M et al., 2016)
 - case report of 2 patients on heroin (Hamming R et al., 2016)
 - case report of 3 hospitalized patients (Terasaki et al., 2019)
 - case report of 2 hospitalized patients (Sukhpreet et al., 2019)
- Now multiple case reports (>20) and different microinduction protocols



BERNESE METHOD-7 day

Day	Order	Number of tablet(s) per dose when using buprenorphine-naloxone 2 mg – 0.5 mg tablet	Agonist
1	buprenorphine 0.5 mg – naloxone 0.125 mg sublingual BID	One quarter tablet	Full dose
2	buprenorphine 0.5 mg – naloxone 0.125 mg sublingual TID	One quarter tablet	Full dose
3	buprenorphine 1 mg – naloxone 0.25 mg sublingual BID	One half tablet	Full dose
4	buprenorphine 2 mg – naloxone 0.5 mg sublingual BID	1 tablet	Full dose
5	buprenorphine 2 mg – naloxone 0.5 mg sublingual QID	1 tablet	Full dose
6	buprenorphine 4 mg – naloxone 1 mg sublingual TID	2 tablets	Full dose
7	buprenorphine 12 mg – naloxone 3 mg sublingual daily	Refer to MAR for directions	Stop



5 day Vancouver protocol

Day	Order	Number of tablet(s) per dose when using buprenorphine-naloxone 2 mg – 0.5 mg tablet	Agonist
1	buprenorphine 0.5 mg – naloxone 0.125 mg sublingual BID	One quarter tablet	Full dose
2	buprenorphine 1 mg – naloxone 0.125 mg sublingual TID	One quarter tablet	Full dose
3	buprenorphine 2 mg – naloxone 0.25 mg sublingual BID	One half tablet	Full dose
4	buprenorphine 4 mg – naloxone 0.5 mg sublingual BID	1 tablet	Full dose
5	buprenorphine 12 mg – naloxone 0.5 mg sublingual QID	1 tablet	Full dose
6	Titrate as needed		
7			



Rapid micro-induction protocols

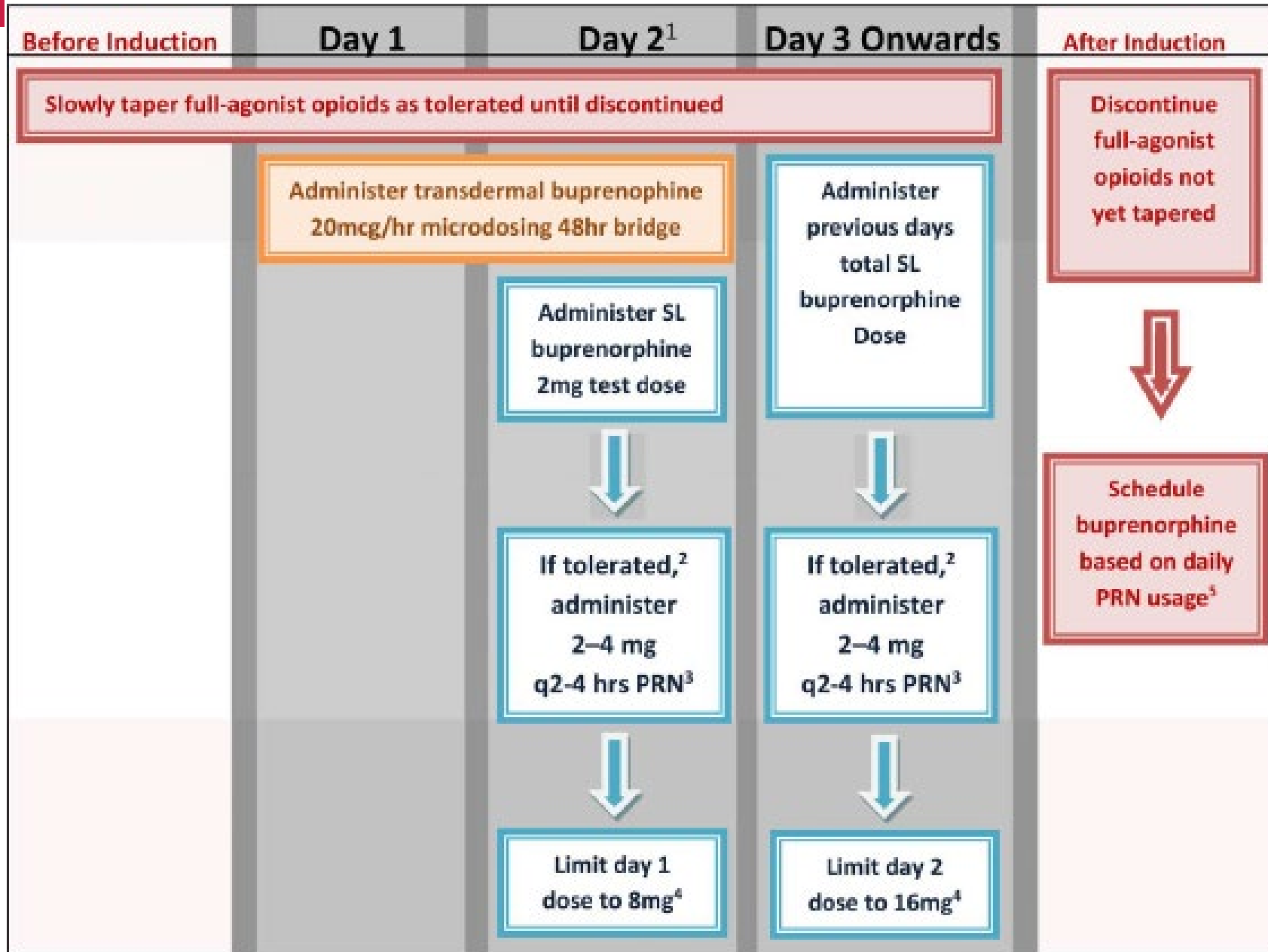
	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

KlaireS, ZivanovicR, BarbicSP, Sandhu R, Mathew N, Azar P.
Rapid micro-induction of buprenorphine/naloxone for opioid
use disorder in an inpatient setting: a case series. *Am J Addict.*
2019;28(4):262-26



BUPRENORPHINE TRANSDERMAL METHOD





Another micro dosing method

- Ingestion of the sublingual buprenorphine?





Caveat for micro-inductions

- The patient continues the full agonist while receiving these low doses of buprenorphine
- Better suited for inpatient settings or a methadone clinic/ pain medication conversion where the dose of full agonist can be monitored
- However some inpatient pharmacies will not split pills or strips



Macro-dosing buprenorphine / inducing withdrawals with Narcan then bup

- Concept: Give very large doses of buprenorphine 16-32mg when withdrawal starts (COWS 12 or more, may be >24hrs)
- Emergency room inductions after being given Narcan reversal following overdoses
- Does not require the patient to continue their opioids
- Probably not an outpatient process yet



Case 2

- Patient in methadone maintenance for 12 years wanting to convert to buprenorphine. Currently on 70mg daily.



Transferring from Methadone to Buprenorphine

- Strategies for conversion

A- abstinence from methadone long enough to make conversion

B- micro-inductions with buprenorphine (Bernese method)

C- inducing a rapid withdrawal (naloxone) quickly followed by high dose buprenorphine



Transferring from Methadone to Buprenorphine

- Reasons patients may want to convert to buprenorphine:
 - believe it is easier to come off buprenorphine
 - side effects of methadone (impotence, nodding, sleep apnea)
 - methadone “not holding”
 - want more flexibility in their dosing
 - toxicity: prolonged QT, constipation
 - discharged from a methadone program



Transferring from Methadone to Buprenorphine –abstinence method

- Clarify why patient is transferring
- Methadone is especially long-acting opioid; risk of precipitated withdrawal is higher and dose dependent.
- Confirm patient is in withdrawal prior to induction – the timeline will vary amongst patients (72 or longer hours typically)
- Ideally patient should be stable around 30-35mg for one week, success has been shown for pts up to 100 mg, higher conversions seek expertise and hospitalization
- Use small test dose , i.e. 2 mg, repeat, but if no PW then escalate dose the 1st day for total of 4-8mg
- Patients need lots of support – ok to go back to methadone if buprenorphine fails



Transferring from Methadone to Buprenorphine – microdosing

- Many patients can not reduce their methadone to 30mg
- Better suited for micro-induction at higher doses







Drug testing Difficulties

- It is **a monitoring tool** to see if the treatment plan needs to be improved. The real outcome is RECOVERY

It is not mainly to confirm the patient is telling the truth.

It is not to indicate the patient has failed

A positive does not mean the patient isn't making progress

It must always be interpreted in the context of the clinical picture. ****

Hgba1c analogy



The Trust Issue

- Its ok to be fooled sometimes
- - How do YOU feel when a sample is adulterated/substituted?
- - What does it really mean?



Flushing

-16 oz

-32 oz

-44 oz





Interpretation of Urine Dilution

- Value < 20 mg/dL suggests water ingestion
- The amount of H₂O required to dilute the urine will vary greatly (can be as little as 16 ounces) – it is not always intentional
- Must interpret with the clinical history
- Ask about diuretics, diabetes, polydipsia
- Value < 5 inconsistent with urine
- If dilute a confirmation , which has lower cutoffs, may pick up suspected drugs
- **The urine was too dilute to interpret the results**



SUBJECT	Time	H2O	Creatinine(mg/dl)
D	22.82	12 oz	216
	23.82		157
	24.82		177
D	69.15	12 oz	215
	71.98		119
	72.82		64
	73.85		122
E	22.73	12 oz H2O	49
	23.48		111
	25.37		35
	28.07		45
F	21.68		88
	22.18	12 oz H2O	128
	29.18		105
G	32.93		33
	70.10	12 oz H2O	72
	71.93		28
C	78.27		206
	21.62		66
	22.87	12 oz H2O	109
	24.29		23
	24.62		19



Compliance testing for buprenorphine

Case: you suspect diversion of the buprenorphine you are prescribing. You obtain a urine bup level and it returns buprenorphine level 800
Norbuprenorphine level 50
 $Nbup/bup = .06$



Urine Buprenorphine testing

- Urine levels do not correlate well with dose
- Total norbup > buprenorphine but not always (80-100%)
 - time of dosing to collection impacts this ratio
 - ratio of Nbup/bup < .02
- Bup without metabolite - adulterated specimen
Bup > 750-1000 with metabolite- likely adulteration
- 95% is excreted after 144 hours
- IV, IN, SC routes bypass first pass and result in significantly lower norbuprenorphine formation



Prescription Status	Number	Both Positive (106)	Oral Fluid Only (4)	Urine Only (37)	Negative (113)
Suboxone	130	100 (77%)	1 (1%)	26 (20%)	3 (2%)
>8 mg/day	88	70 (80%)	1 (1%)	14 (16%)	3 (3%)
≤8 mg/day	42	30 (71%)	0 (0%)	12 (29%)	0 (0%)

Urine is superior to oral fluid for detecting buprenorphine compliance in patients undergoing treatment for opioid addiction; Ransohoff, J.R., et al., Drug and Alcohol Dependence, Volume 203, 1 October 2019, 8-12



Resources

- Vogel M et al., Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Substance Abuse and Rehabilitation*, 2016:7, 98-105
- Sandu R et al., Buprenorphine/naloxone induction for treatment of acute on chronic pain using a micro-dosing regimen: A case report. *Canadian Journal of Pain*, 2019 (3), issue 1
- Sukhpreet K et al., Rapid Micro-induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A case series. *The American Journal of Addictions* (28)issue
- Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a Period of Opioid Abstinence Using a Microdosing Protocol. *Pharmacotherapy: The J of Human Pharm and Drug Therapy* 2019



Resources

De Aquino, J.P., et. Al., The pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. Clinical Drug Investigation 41, 425-436, 4/2021