Compliance and Monitoring Patients with OUD

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March 30, 2022

Learning Objectives

1. What are some monitoring tools for medication compliance with MAT
2. Interpretation of urine for buprenorphine compliance.
3. Should we be worried about diversion
4. Reasons to stop prescribing

QUESTION 1

Do you require attendance to a group or therapist in order to receive buprenorphine as a treatment option

A- Yes

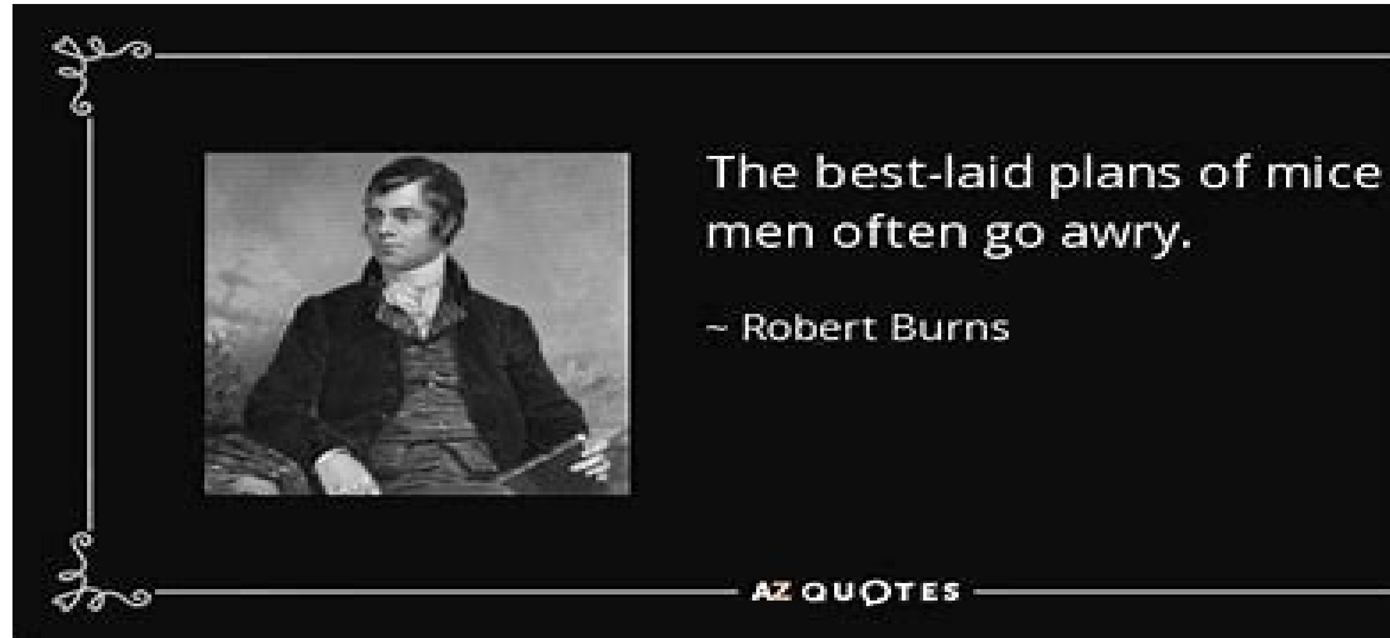
B- No

COMPLIANCE: "The act or fact of complying with a wish or demand."

- For the patient
  - following the treatment plan
  - taking medications as prescribed (medication compliance)
  - attending appointments/referrals
  - stopping drug use
  - submitting urine drug screens
- For the provider
  - following rules and regulations for provision of the medical care (documentation, required follow ups….)

Patient engagement: Treatment plans

- Engagement vs “compliance”
- Mutually agreed upon treatment plans vs “required” compliance
- When developed by the patient they are more accountable to their own plans
- Expect plans to change based on the patient’s response (individualized plans)



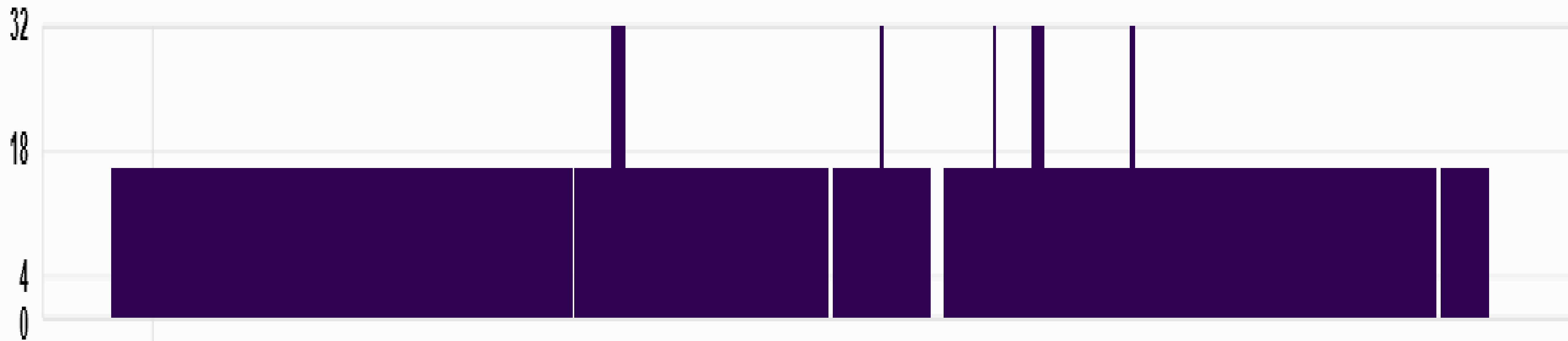
MEDICATION COMPLIANCE

- Is the patient taking the medication as prescribed
- How does one monitor medication compliance
- If noncompliant why?
- If noncompliant what are strategies to improve compliance?

MONITORING MEDICATION COMPLIANCE

- Patient history
- Refill history
- Urine drug screening
- Bring in medication bottles

INSPECT DATA ON OVER/UNDER USE

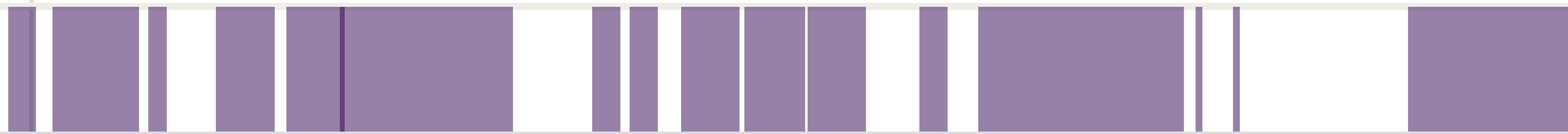


RX Graph

☐ Narcotic ☑ Buprenorphine ☐ Sedative ☐ Stimulant ☐ Other

Prescribers

1 - Christopher Suelz



Timeline 03/29 2m 6m 1y

RX Graph

☐ Narcotic ☑ Buprenorphine ☐ Sedative ☐ Stimulant ☐ Other

Prescribers	
1 - Christopher Suelz	
Timeline	03/29 2m 6m

Disclaimer

Why is the patient asking for an early refill

- took more for pain
- took more for cravings
- dose is not adequate
- vacation, work or travel plans
- stolen or lost prescriptions

USING URINE TO MONITOR COMPLIANCE

Buprenorphine Metabolism

- Mu receptor (euphoria, analgesia, respiratory depression, constipation, miosis)
  -partial agonist at mu receptor
  -antagonist at Kappa receptor (reduces stress/dysphoria responses)
  -high affinity (1.7 times hydromorphine, 5.4 times morphine, 6.2 times fentanyl, 120.0 times oxycodone)
  -low efficacy (partial agonist)-ceiling effect
  -slow dissociation kinetics (166 minutes)
  -potency (very difficult to measure due to ceiling effect)
  -mean time to maximal plasma concentration following SL administration ranges from 40 minutes to 3.5 hours

Buprenorphine Pharmacology and Metabolism

Metabolism

-metabolized to norbuprenorphine via CYP450-34A cytochrome
-norbuprenorphine is mu agonist but does not cross blood/brain

-both buprenorphine and norbuprenorphine undergo glucuronidation to buprenorphine 3- glucuronide and norbuprenorphine -3 glucuronide which are inactive

-most is eliminated in the feces, 10-30% excreted in urine
-elimination half lives vary (24-69 hrs.)

Buprenorphine Dosage and Urine Quantitative Buprenorphine, Norbuprenorphine, and Creatinine Levels in an Office-Based Opioid Treatment Program. Furo,H., et.al., Ann of Clin Biochemisty, Intern. J of Lab Med., 2021

- Samples of 41 patients in residential program on MAT
- 8mg daily dose (66 samples)
  - buprenorphine (range 8-1530, mean 260+/- 304
  - norbuprenorphine (range 45->2000 , mean 596+/- 468
  - bup:norbup ratio .51 +/- .75, range 04-5.8
- 12mg daily dose (83 samples)
  - buprenorphine (range 24->2000, mean 388 +/- 38-
  - norbuprenorphine (range 81-2000, mean 780+/- 583
  - bup:norbup ratio >.56 +/- .48 , range .05-2.56
- 16mg daily dose (35 samples)
  - buprenorphine (range 63-1220, mean 334 +/- 259
  - norbuprenorphine (range 164 > 2000, mean 870+/- 560
  - bup:norbup ratio > .44 +/- .25, range .47-7.8)

QUESTION: 2

- Which of the following most likely explains this urine result in a patient being prescribed buprenorphine 16mg daily

  A- The pt is likely diverting his buprenorphine
  B- The pt is overtaking and ran out before his drug screen
  D- The pt brought in someone else's urine

NORTRAMADOL LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
BUPRENORPHINE LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
NORBUPRENORPHINE LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
METHYLPHENIDATE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -

QUESTION 3
IS THS PATIENT TAKING HIS BUPRENORPHINE

A- Yes

B- No

C- You can not tell

	TRAMADOL LCMS	None Detected
	NORTRAMADOL LCMS	None Detected
	BUPRENORPHINE LCMS	>400
	NORBUPRENORPHINE LCMS	None Detected
	METHYLPHENIDATE LCMS	None Detected
	RITALINIC ACID LCMS	None Detected
	URINE CREATININE	18.8

Urine Buprenorphine testing

- Urine levels do not correlate well with dose, urine concentration can vary 10 fold
- Total norbup > buprenorphine but not always (90-100%) - time of dosing to collection impacts this ratio
- Bup without metabolite - adulterated specimen
  Bup > 1000 with metabolite- "likely" adulteration
  Bup:norbup ration > 50:1 spiked
- 95% is excreted after 144 hours
- IV, IN, SC routes bypass first pass and result in significantly lower norbuprenorphine formation

URINE VS SALIVIA

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

Do point of care testing for buprenorphine test for metabolite ?

Know about your specific test

NarcoCheck® Buprenorphine test (BUP 10)

compounds	cut-off (ng/ml)
Buprenorphine	10
Buprenorphine-3-B-d-gluconoride	10
Nor-Buprenorphine	>1000
Nor-Buprenorphine-3-B-d-gluconoride	>1000

TAKEHOME MESSAGE ABOUT URINE TESTING

- Urine testing should always be interpretated in the context of the clinical picture.
- When a concerning result is found the real question is what is the reason for the test result?

NONCOMPLIANCE AND DIVERSION

QUESTION 4

Have you treated a patient who reported obtaining buprenorphine off the street

1- Yes
2- No
3- Don't know

Increasing rates of buprenorphine diversion in the United States, 2002 to 2019: Butram ME., et. al, Phamracoepidemiology and Drug Safety., July 2021

-monitor of diversion case reports from law enforcement and regulatory agencies from 2002-2019

- Adjusted for prescription rates (per 100,000 prescriptions)
- 9670 cases reports during this time period
- Average of 30 per 100,000 prescriptions
- This is similar to hydrocodone/oxycodone

Increasing rates of buprenorphine diversion in the United States, 2002 to 2019

Number of Buprenorphine Diversion Cases per 100,000 Population

0.500
0.400
0.300
0.200
0.100
0.000

2002Q1 2002Q3 2003Q1 2003Q3 2004Q1 2004Q3 2005Q1 2005Q3 2006Q1 2006Q3 2007Q1 2007Q3 2008Q1 2008Q3 2009Q1 2009Q3 2010Q1 2010Q3 2011Q1 2011Q3 2012Q1 2012Q3 2013Q1 2013Q3 2014Q1 2014Q3 2015Q1 2015Q3 2016Q1 2016Q3 2017Q1 2017Q3 2018Q1 2018Q3 2019Q1 2019Q3

Year-Quarter

Pharmacoepidemiology and Drug, Volume: 30, Issue: 11, Pages: 1514-1519, First published: 24 July 2021, DOI: (10.1002/pds.5334)

Trends in and Characteristics of Buprenorphine Misuse Among Adults in the US . Hans B., et al., JAMA Network Open, 2022

- Data from National Survey on Drug Use and Health =, 2015-2019 214,505 individuals
- 2019
  estimated 2.4 million had used buprenorphine
  estimated 0.7 million misused buprenorphine

Buprenorphine misuse among those with OUD
Buprenorphine misuse among those without OUD

30
25
20
15
10
5
0

Weighted % of adults

2015 2016 2017 2018 2019

Study year

Source: Han et al.

Alcohol Drug Abuse Week, Volume: 33, Issue: 41, Pages: 1-4, First published: 22 October 2021, DOI: (10.1002/adaw.33234)

Use, without misuse
Misuse

No. of adults in millions

40
35
30
25
20
15
10
5
0

Hydrocodone (11.6)
Oxycodone (12.7)
Codeine (10.1)
Tramadol (7.8)
Morphine (9.1)
Fentanyl (11.5)
Buprenorphine (29.2)
Hydromorphone (11.8)
Methadone (22.2)
Meperidine (11.1)
Oxymorphone (37.5)

Prescription opioid (weighted % of misuse)

Data are from 42 739 respondents in the 2019 National Survey on Drug Use and Health (NSDUH). The 2015-2019 NSDUH did not collect information on the use of illicitly manufactured fentanyl; the fentanyl data shown are for prescription fentanyl. For each type of prescription opioid, the denominator for estimating the proportion of misuse is the number of adults with use but no misuse plus the number of adults with misuse.

Source: Han et al.

QUESTION 5

What percentage of patients on buprenorphine will at some point "misuse" their medication

A- 5%
B- 25%
C- 50%
D- 75%

QUESTION 6

What are reasons patients have given you they used buprenorphine off the street

1- They could not get into treatment
2- They ran out of their prescribed dose
3- To get high
4- To supplement their income

Buprenorphine in the United States: Motives for abuse, misuse, and diversion. Chilcoat H.D., et.al., J of Substance Abuse Treatment., 2019

Cicero et al, 2014; N 106

- 4% used bup as their primary drug of choice
- 3% felt it gave a better high
- 15% cheaper then other drugs
- 63% were trying to get off opioids
- 50% to treat withdrawal
- 50% used to treat pain
- 33% used to treat psychological symptoms

Buprenorphine in the United States: Motives for abuse, misuse, and diversion. Chilcoat H.D., et.al., J of Substance Abuse Treatment., 2019

Survey data among those who actually divert (N107)
- 59% helping a friend or partner
- 57% needing the money
- 27% not needing the entire prescription
- 59% saving some prescribed dose to get high

Can one get “high” on buprenorphine?

- Injected/snorting buprenorphine can cause a high in an individual without opioids on board.
- Higher bioavailability for both buprenorphine and naloxone
- - 30% sublingual vs 48% nasal (buprenorphine)
- - 10% sublingual vs 30% nasal (naloxone)
- Typically mixed with benzo
- Patient on stable doses do not experience euphoria or clouding

Does the addition of the naloxone really prevent IV abuse?

- Buprenorphine has a very long half life (24-60 hrs). Its euphoric effects would last appr 6 hours
- Naloxone half life 30 to 40 minutes
- Buprenorphine has a higher binding affinity for the mu receptor then naloxone
- If someone had pure agonist on board injected the buprenorphine alone they would precipitate a withdrawal
- If someone had no opioids on board and injected/snorted either buprenorphine product they could experience a euphoria (the reward would be delayed for half a hour in the combination product)

Exploring nonprescribed use of buprenorphine in the criminal justice system through qualitative interviews among individuals recently released from incarceration. Monico, L.B., el al J of Substance Abuse 2021Treatment,

- Interviews of 26 individual with OUD recently released from jail or prison

  - all noted a high prevalence of diverted buprenorphine in jail/prison
  - much more expensive then on the street so small doses are purchased (3-4 times more expensive)
  - predominately strips, typically dissolved in water and snorted
  - main reasons: to get high, to be energized, to fight depression

QUESTION 7

Can one fatally overdose on buprenorphine alone?

A- Yes

B- No

Concomitant drugs with buprenorphine user deaths: Mariottine C. et.al., Drug and Alcohol Dependence, (218), 2021

Finnish post mortem data base 2016-2019

792 buprenorphine findings in autopsy, 271 in which bup was implicated

- concomitant benzos 94%
- illicit drugs 63%
- gabapentinoids 53%
- alcohol 41%
- ONLY 3 cases only had buprenorphine

QUESTION 8

DOES CONCURRENT USE OF BENZOS OR ALCOHOL PRECLUDE USE OF BUPRENORPHINE?

A- Yes

B- No

C- It depends

DOES CONCURRENT USE OF BENZOS OR ALCOHOL PRECLUDE USE OF BUPRENORPHINE?

Requires a risk assessment
Document the reasoning
Address the other substances in the treatment plan

WHAT IF DIVERSION IS HIGHLY SUSPECTED

- Hx of diversion does not preclude treatment but it does require an action plan that minimizes the risk and maximizes the treatment

  - assess the patient for the benefit of treatment
  - active diversion often results in termination of treatment
  - more frequent monitoring
  - shorter prescriptions (1 week or less)
  - random pill counts
  - injectable formulations

Reasons to discontinue prescribing buprenorphine

- It is not working
- There is a safety concern
- There is active diversion
- Inconsistent with other employment/legal requirements

Summary

- Buprenorphine diversion is real but is the exception and is far outweighed by the benefit of the treatment
- Many, if not most of your patients will have a history of obtaining buprenorphine off the street at some time in their history. This does not mean they are drug seeking for buprenorphine.
- The majority are not obtaining it to get high (<5%) but “misusing” it for self treating, pain treatment, run out early
- At some point apparent noncompliance will occur, i.e. an early refill overtaking, stocking extras. Have a plan

Difficult conversations

- The patient has overused their buprenorphine and comes in for an early refill. This is the second time and you previously warned the patient there would be no more early refills.

Her response: I need the buprenorphine, it works. Now I am going to be sick and you are forcing me to go out and use.

Difficult conversations

- The patient reveals verbally he relapsed on heroin. As a consequence per clinic policy he loses his takehome bottles of methadone, he was getting 7.

His response: Angrily “I thought I could trust you to tell the truth and now I have to suffer. I would have been better off not telling the truth”

Difficult conversations

- The patient submits a urine screen that is positive for methamphetamine, high levels. The patient is vehement the lab made a mistake, it could not be his

His response: There is no way that can be right, I have not used in 2 weeks. I wouldn’t lie to you and I do not want to risk this treatment which has been the only thing that has helped.

Difficult conversations

- The patient is not attending the groups as per a mutually agreed treatment plan. He comes faithfully for the individual sessions with you when he obtains his next prescription but is not following the original treatment plan. He is no longer using opioids but still has intermittent positive urines for methamphetamines.

- His response: I can't make it to the groups, I have to work