Opioid Addiction Treatment ECHO

For Providers and Primary Care Teams

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Learning Objectives

1. Discuss common clinic concerns in taking care of patients on buprenorphine
    - Drug testing, the pitfalls
    - Compliance testing and diversion
    - Continued use / early refills / discontinuing treatment


URINALYSIS.
I'M PISSED.

Drug testing

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

  It is not 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.

State Law Requirements for OBOT providers

- Perform toxicology screening for the following
  -Stimulants, Alcohol, Opioids including oxycodone, methadone and buprenorphine, THC, Benzodiazepines and Cocaine
- If toxicology screening shows the presence of an illegal or nonprescribed drug the provider shall assess the risk of the patient to be successfully treated and document
- The provider may perform a subsequent confirmation toxicology screening if the provider considers it medically necessary
- Rules regarding frequency are to be developed in consultation with the State Dept of Health and office of Secretary of Family and Social Services

Interpretation of drug testing requires:

- Understanding the limitations of the test
  - screening (ELISA)
  - issue of false positives and false negatives
  - what are the detection levels for the screening
- Understanding of the metabolism of the drug
  - half lives, fat solubility (windows of detection)
  - should metabolites be present
- Understanding how to identify appropriate samples
  - when is dilution intentional
  - bringing in other urine

Oral Fluid Drug Testing

- Urine
  - Collection is difficult
  - Opportunity for adulteration
  - Reflects excretion
  - Longer window of detection

Oral fluid

-Ease of collection
-Better sample integrity
-Reflect serum levels
-Direct oral deposition

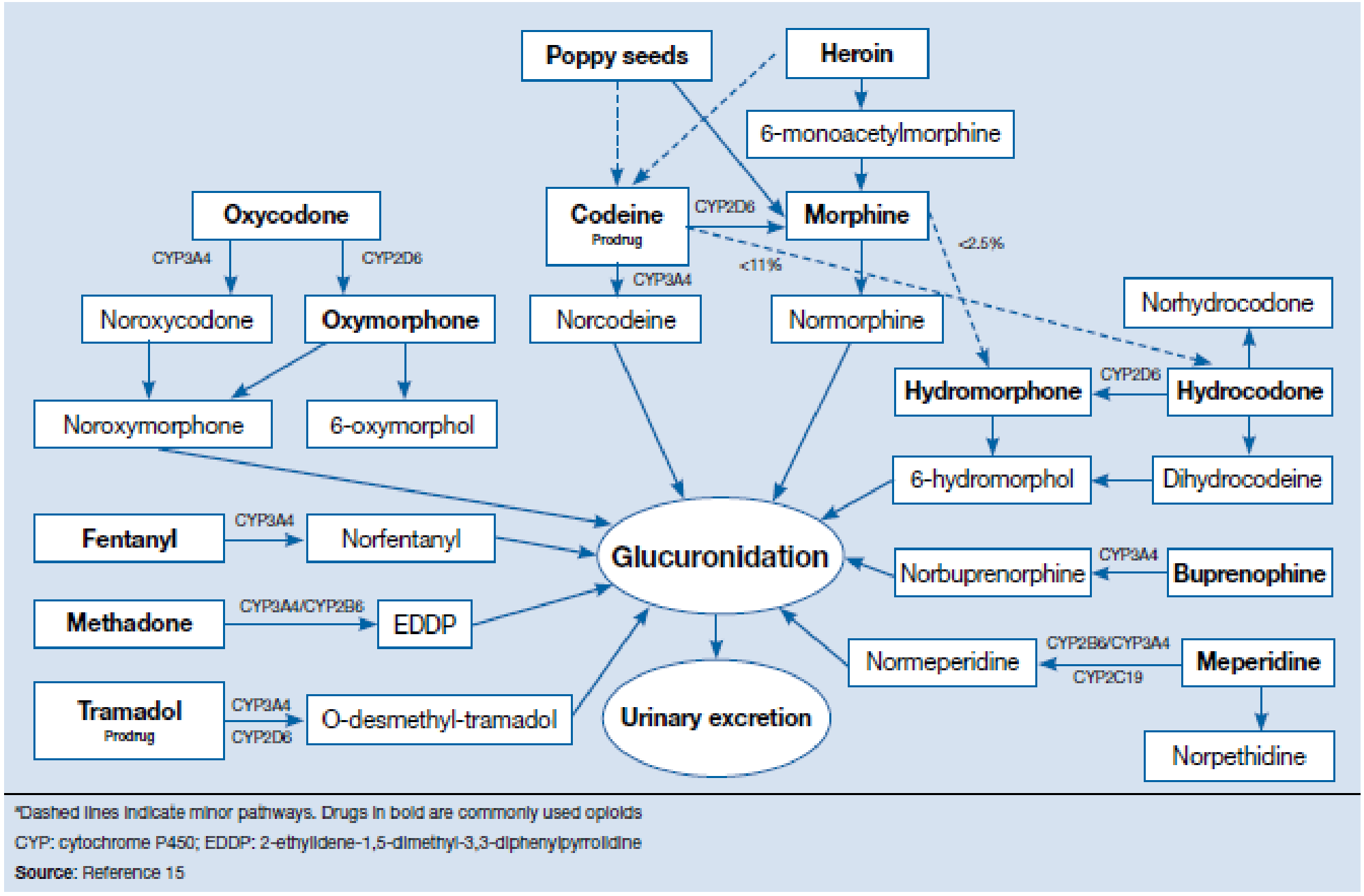
False positives and negatives

DRUG	FALSE POSITIVES	FALSE NEGATIVES
Amphetamines	Buproprion, trazadone, desipramine, doxepin, labetaolol, metformin, ephedrine, pseudoephedrine, Phentermine, atomoxetine, ranitidine, aripiprazole	
Benzodiazepines	Sertaline, Efavirenz	Clonazepam
Cocaine	None (medical anesthesia)	
THC	Efavirenz, ibuprofen, naproxenm dronabinol, CBD	Synthetic cannabinoids
Methadone	Quetiapine, verapamil, diphenhydramine, chlorpromazine	
Opioids	Quinolones, naltrexone, diphenhydramine,	Synthetic opioids
PCP	Velafaxine, lamotrigine, ibuprofen, zolpidem, …	

Confirmation testing

- Eliminates the doubt (unless the collection or lab processing is in error)
- It allows evaluation of metabolites
- The lower cut offs mean the drug use may have been earlier (weeks before) if the levels come back very low
- The lower cut offs expand the possibility of unknowing exposure
  - poppy seeds
  - passive inhalation
  - skin exposure

Comprehensive LCMS	Complete			
MORPHINE LCMS	92.04		ng/mL	Cutoff: 50 ng/mL -
CODEINE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
HYDROCODONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
HYDROMORPHONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
6-ACETYLMORPHINE LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
OXYCODONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
OXYMORPHONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
BENZOYLECGONINE LCMS	None Detected		ng/mL	Cutoff: 30 ng/mL -
METHAMPHETAMINE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
AMPHETAMINE LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
NORDIAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
OXAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
TEMAZEPAM LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
ALPRAZOLAM LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
a-OH-ALPRAZOLAM LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
7-AMINO-CLONAZEPAM LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
LORAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
METHADONE LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
EDDP LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -

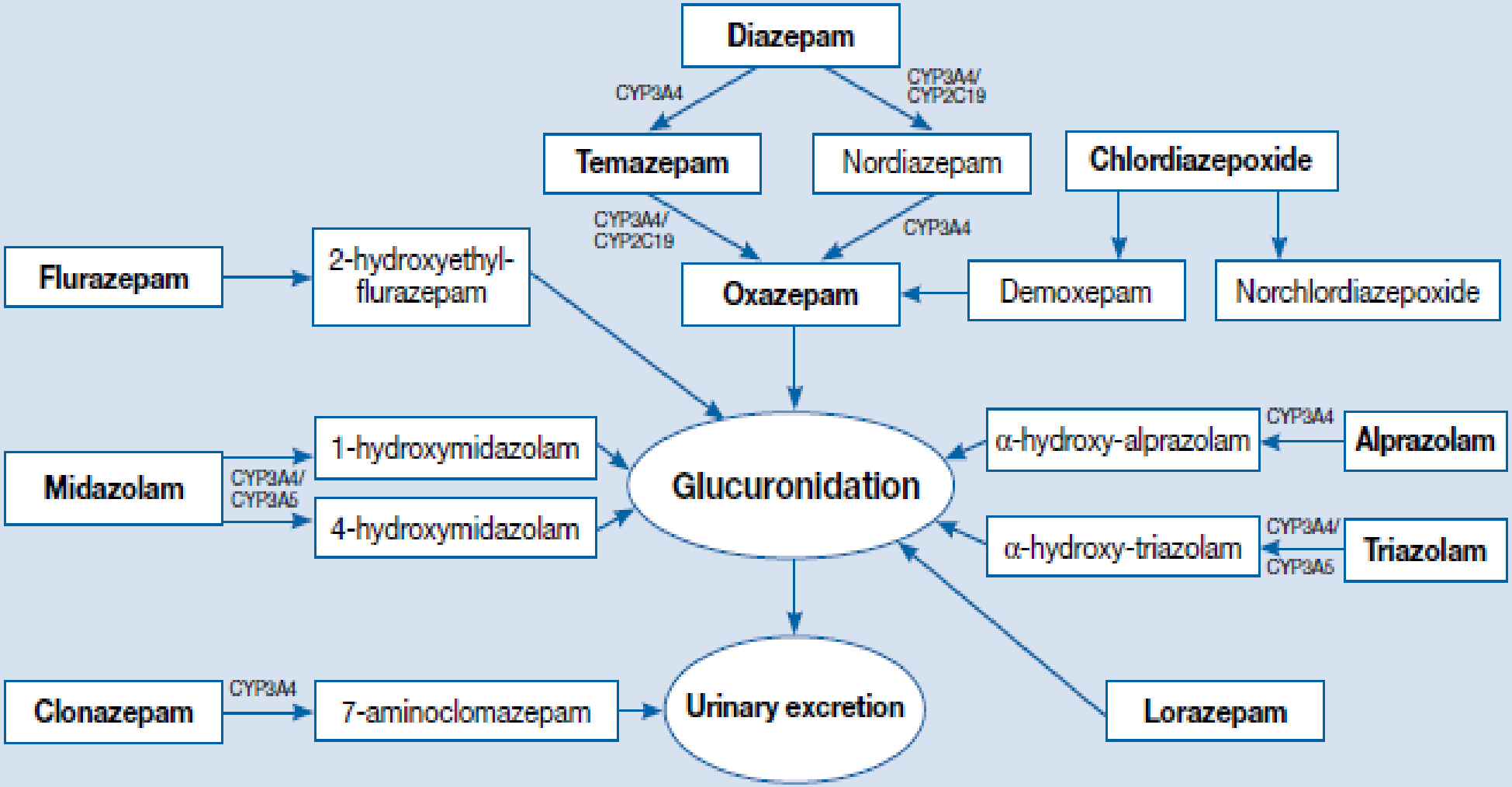


*Dashed lines indicate minor pathways. Drugs in bold are commonly used opioids

CYP: cytochrome P450; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine

Source: Reference 15

Benzodiazepines	Presumptive Positive, Confirmato
NORDIAZEPAM LCMS	171.50
OXAZEPAM LCMS	>800
TEMAZEPAM LCMS	123.76
ALPRAZOLAM LCMS	None Detected
a-OH-ALPRAZOLAM LCMS	None Detected
7-AMINO-CLONAZEPAM LCMS	None Detected
LORAZEPAM LCMS	None Detected



*Drugs in bold are commonly used benzodiazepines

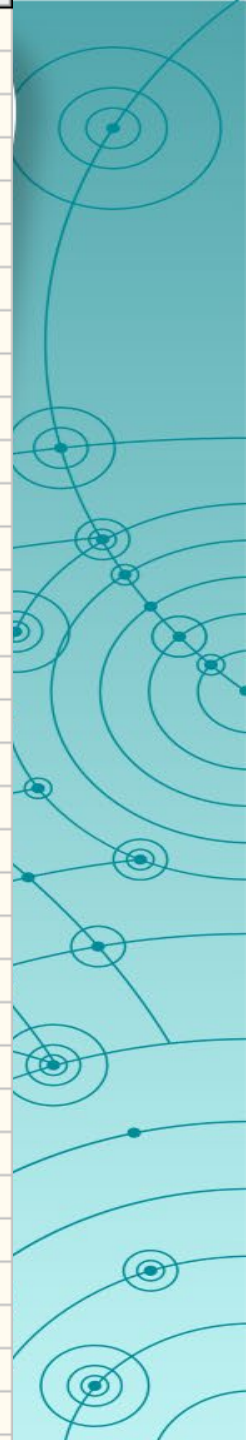
CYP: cytochrome P450

Source: Reference 14

Pre and Post Test Probability

Jul 20, 2018 10:14	Opiates	Presumptive Negative
	Oxycodone	Presumptive Negative
	Cocaine	Presumptive Negative
	Amphetamines	Presumptive Positive
	Benzodiazepines	Presumptive Negative
	Methadone	Presumptive Negative
	Phencyclidine	Presumptive Negative
	Cannabinoids	Presumptive Negative
	Barbiturates	Presumptive Negative
	URINE CREATININE	161.3
	CHROMATE(SVT)	<2.00
	NITRITE(SVT)	174
	SPECIFIC GRAVITY(SVT)	1.007
	pH(SVT)	7.6
	OXIDANT(SVT)	<5

Jul 12, 2019 12:06	OXYMORPHONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	Cocaine	Presumptive Negative		mAbs	Ref: Presumptive Negative
	BENZOYLECGONINE LCMS	None Detected		ng/mL	Cutoff: 30 ng/mL -
	Amphetamines	Presumptive Negative		mAbs	Ref: Presumptive Negative
	METHAMPHETAMINE LCMS	<50		ng/mL	Cutoff: 50 ng/mL -
	AMPHETAMINE LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
	Benzodiazepines	Presumptive Negative		mAbs	Ref: Presumptive Negative
	NORDIAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
	OXAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
	TEMAZEPAM LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	ALPRAZOLAM LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	a-OH-ALPRAZOLAM LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
	7-AMINO-CLONAZEPAM LCMS	None Detected		ng/mL	Cutoff: 20 ng/mL -
	LORAZEPAM LCMS	None Detected		ng/mL	Cutoff: 40 ng/mL -
	Methadone	Presumptive Negative		mAbs	Ref: Presumptive Negative
	METHADONE LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
	EDDP LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
	Phencyclidine	Presumptive Negative		mAbs	Ref: Presumptive Negative
	PCP LCMS	None Detected		ng/mL	Cutoff: 10 ng/mL -
	Cannabinoids	Presumptive Negative		mAbs	Ref: Presumptive Negative
	THC-COOH LCMS	None Detected		ng/mL	Cutoff: 30 ng/mL -
	Comprehensive LCMS	Complete			
	Barbiturates	Presumptive Negative		mAbs	Ref: Presumptive Negative
	BUTALBITAL LCMS	None Detected		ng/mL	Cutoff: 200 ng/mL -
	PHENOBARBITAL LCMS	None Detected		ng/mL	Cutoff: 200 ng/mL -
	FENTANYL LCMS	None Detected		ng/mL	Cutoff: 2 ng/mL -
	NORFENTANYL LCMS	None Detected		ng/mL	Cutoff: 8 ng/mL -
	MDPV LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	MEPHEDRONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	METHYLONE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	MDMA LCMS	None Detected		ng/mL	Cutoff: 100 ng/mL -
	MEPERIDINE LCMS	None Detected		ng/mL	Cutoff: 50 ng/mL -
	ZOLPIDEM METABOLITE LCMS	None Detected		ng/mL	Cutoff: 10 ng/mL -

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DATA FROM DEA AGENTS

Table II. All Samples Containing Detectable Methamphetamine from the 101 Samples Tested*

Sample Number	Concentration (ng/mL)	Date Sample Collected	Sample Number	Concentration (ng/ml)	Collected
1†	9.	5/8/2002	28	27	1/28/2004
2	43.	5/8/2002	29	3.	6/15/2004
3	15	5/8/2002	30	2.3	6/15/2004
4†	16	9/24/2002	31	10.	6/15/2004
5	36	9/24/2002	32	11.	6/15/2004
6	1.6	9/24/2002	33	2.6	6/15/2004
7	11	9/24/2002	34	10.	9/9/2004
8	13	9/24/2002	35	5.4	9/9/2004
9	6.7	31/2003	36	10.	9/9/2004
10	15	1/31/2003	37	12.	9/9/2004
11	3.1	1/31/2003			
12	4.	1/31/2003			
13	12	1/23/2003			
14	5	1/23/2003			
15	262	1/23/2003			

Journal of Analytical Toxicology, Vol. 30, October 2006

* Note that the limit of quantitation was 15 ng/mL, and the limit of detection was 1 ng/mL. Values less than 15 ng/mL are given because all chromatographic acceptance criteria were acceptable, indicating the presence

Flushing

-16 oz
-32 oz
-44 oz

SUBJECT	Time	H20	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 H20	49
	23.48		111
	25.37		35
	28.07		45
F	21.68		88
	22.18	12 oz H20	128
	29.18		105
	32.93		33
G	70.10	12 oz H20	72
	71.93		28
	78.27		206
C	21.62		66
	22.87	12 oz H20	109
	24.29		23
	24.62		19

J. of Analytical Tox. Vol 22, Oct 1998

Interpretation of Urine Dilution

- Value < 20 mg/dL suggests water ingestion
- The amount of H20 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 < 20 mg/dl suggest intentional ingestion
- Value < 5 inconsistent with urine
- If dilute a confirmation , which has lower cutoffs, may pick up suspected drugs

- The urine was too dilute to accurately interpret the results.

How to approach patient who absolutely denies use despite positive urine

- Consider confirmatory testing with quantitative levels
- Do not focus on patient characteristics ”this must mean you used” but focus on result “the urine was positive for opioids”and I am concerned about your recovery
- If patient reluctant to intensify treatment, present this as standard care and not a personal decision
- Invite the patient “If you had a patient with this result who denied it what would you do?”

Compliance monitoring for buprenorphine

Buprenorphine Metabolism

- Mu receptor (euphoria, analgesia, respiratory depression, constipation, miosis)

-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

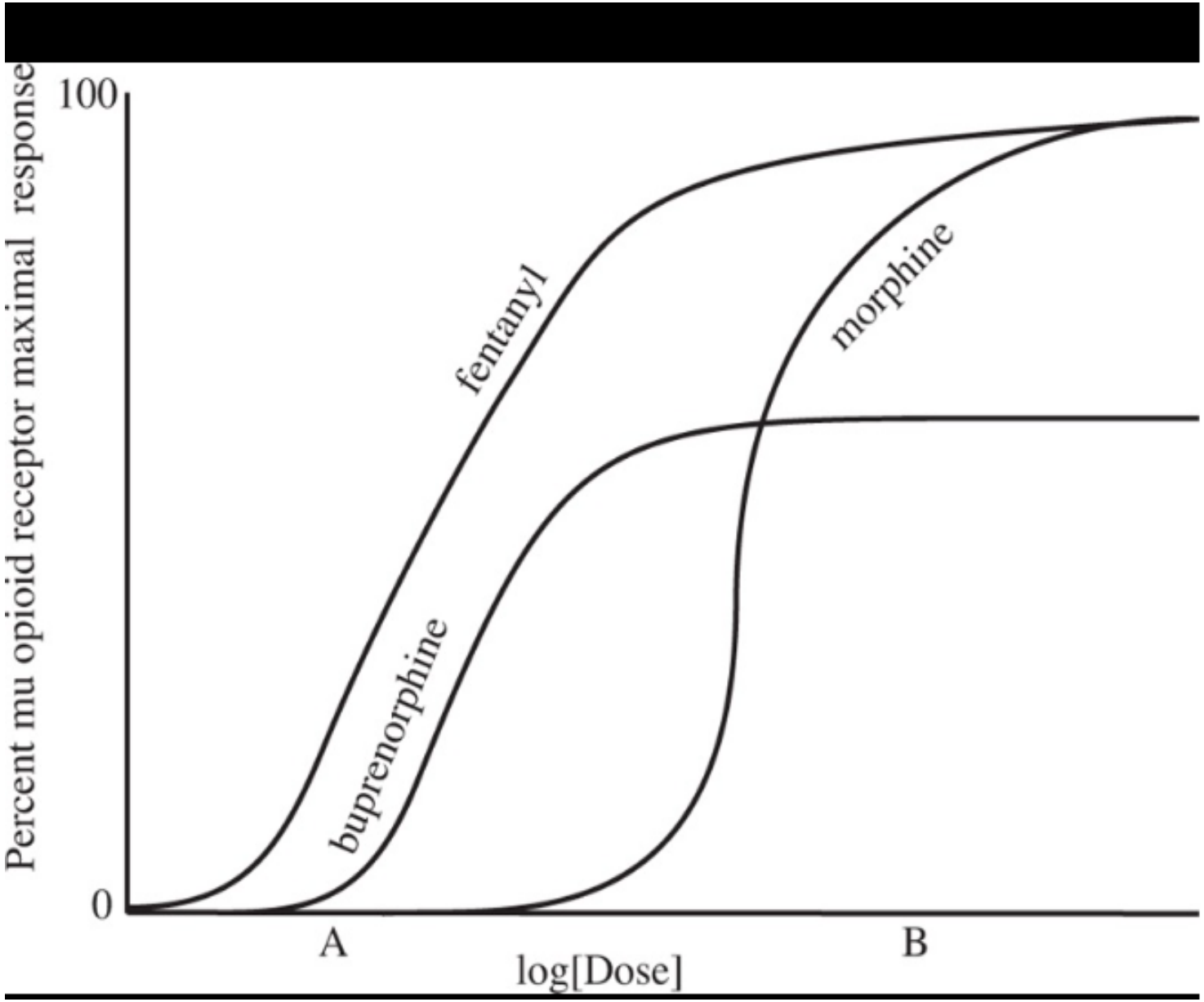


FIGURE 1

Dose-response curve schematic of 3 opioid agonists. At a low dose (dose A), fentanyl and buprenorphine produce significantly greater responses than morphine (ie, fentanyl and buprenorphine are more potent than morphine). While fentanyl response is dose-related until reaching 100% maximal response, buprenorphine effects reach a ceiling, at which point further increases in dose do not increase the magnitude of response. Because buprenorphine is a partial agonist, it cannot not produce a 100% response like a full agonist (ie, fentanyl) can. At higher doses (dose B), morphine (a full agonist with low potency) produces greater response than buprenorphine.

Source

Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations

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

Buprenorphine Pharmacology and Metabolism

Metabolism

-most is eliminated in the feces, 10-30% excreted in urine

-elimination half lives vary (24-69 hrs)

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
- Bup without metabolite - adulterated specimen
  Bup > 750-1000 with metabolite- likely adulteration
- Norbup/bup ratio <.02
- 95% is excreted after 144 hours
- IV, IN, SC routes bypass first pass and result in significantly lower norbuprenorphine formation

	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

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

Diversion

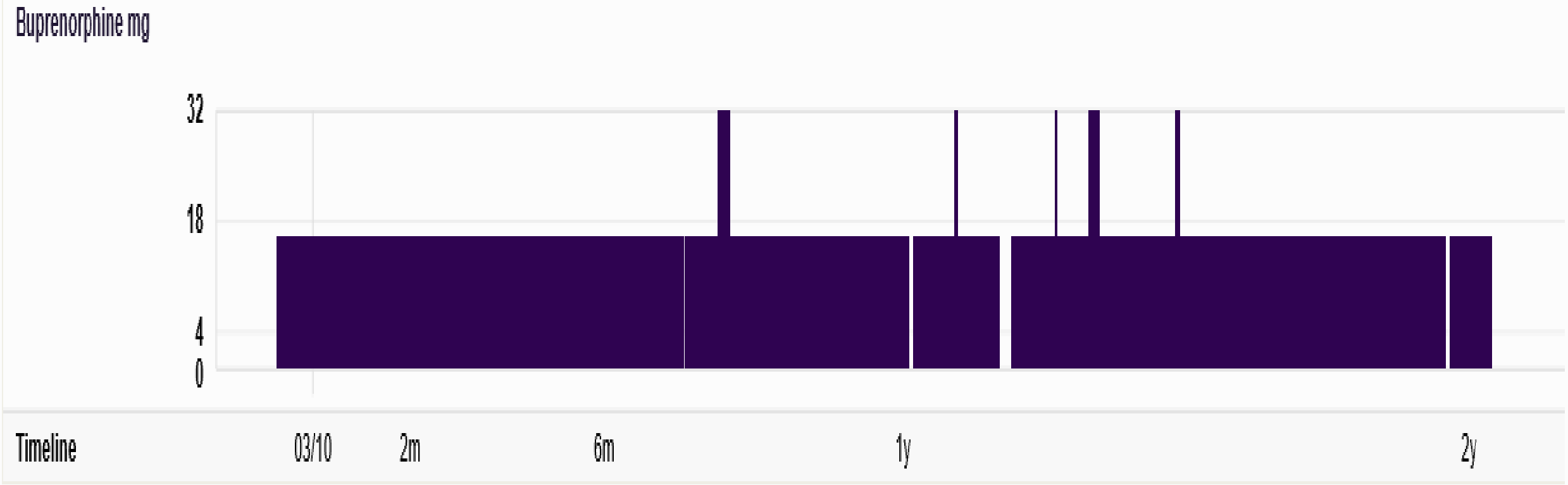
- Use of non-prescribed buprenorphine on the street is most often to self-treat withdrawal (64% in one study)
- Patients may divert to help another friend/family member
- Educate patients up front about importance of not diverting
- Take steps to minimize the risk but do not become the police
  - communicate, more frequent visits, monitored dosing, smallest dose that is effective, monitored urines with bup levels, pill count policy
- 30 day injectable formulation

* A Review of Buprenorphine Diversion and Misuse: J Addict Medicine 2014 Sep-Oct 8(5)

What to do with the patient who requests a early refill

- lost / stolen prescription
- took more for pain
- took more for cravings
- need to come in before my next scheduled appointment (vacation, traveling, work)

INSPECT DATA ON OVER/UNDER USE



Addressing Continued Use

- Return to use is expected and will vary in severity
- Do not stop treatment for positive urine alone
- Intensify treatment plan through more frequent visits, urine drug screens, and psychosocial supports
- Have a guide for when you will refer for higher level of care (i.e., IOP, new MAT, more therapy)
- Is the patient on an adequate dose?

Should treatment ever be stopped????

- When there are safety concerns (overdosing on the medications being used to treat)
- Disruptive behaviors to other clients and staff
- Total nonengagement
- Weigh the risk of overdose on the street vs continued treatment
- Some patients require the structure of a choice