

Urine Drug Toxicology and Pain Management Testing

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Learning Objectives

- Describe what chronic pain is, who is affected and how they are commonly treated
- Explain the common methodologies used in pain management testing
- Interpret urine drug testing results
- Create protocols to minimize the occurrence of false positive or false negative results



Pain – definition and types

- Pain - an unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Chronic pain - pain that extends beyond the expected period of healing
- Nociceptive Pain
 - Pain caused by tissue injury
 - Stimulus-evoked, high intensity
 - Opioid sensitive
- Neuropathic Pain
 - Caused by nerve injury
 - Spontaneous activity
 - Develops in days or month
 - Opioid insensitive



Chronic Pain Patients

- Arthritis
 - Osteoarthritis
 - Rheumatoid arthritis
 - Gout
- Cancer
- Chronic non-cancer pain
- Central pain syndrome
 - CNS damage
 - Multiple Sclerosis
 - Parkinson's disease
- Chronic abdominal pain
 - Intestinal obstructions
- Fibromyalgia
- Headaches
 - Migraine
 - Tension
 - Cluster
- Myofascial pain
- Neuropathic pain
 - Diabetic Peripheral Neuropathy
 - Postherpetic neuralgia
- Neck and Back Pain



Chronic Pain Medications

- Opiates
 - Codeine
 - Morphine
- Semi-synthetic opioids
 - Oxymorphone
 - Oxycodone
 - Hydromorphone
 - Hydrocodone
 - Buprenorphine
- Muscle Relaxers
 - Cyclobenzaprine
 - Carisoprodol
 - Metaxalone
 - Methocarbamol
- Synthetic opioids
 - Fentanyl
 - Methadone
 - Meperidine
 - Tramadol
 - Propoxyphene
 - Levorphanol
 - Tapentadol
- Anticonvulsant
 - Gabapentin
 - Pregabalin
 - Oxcarbazepine
 - Carbamazepine
 - Topiramate



Opiates or Opioids

- **Opioid** - psychoactive chemical that works by binding to opioid receptors – includes opiates (naturally occurring) and semi-synthetic opiate-like drugs
- **Opiate** - often used as a synonym for *opioid*, the term *opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy (codeine, morphine)



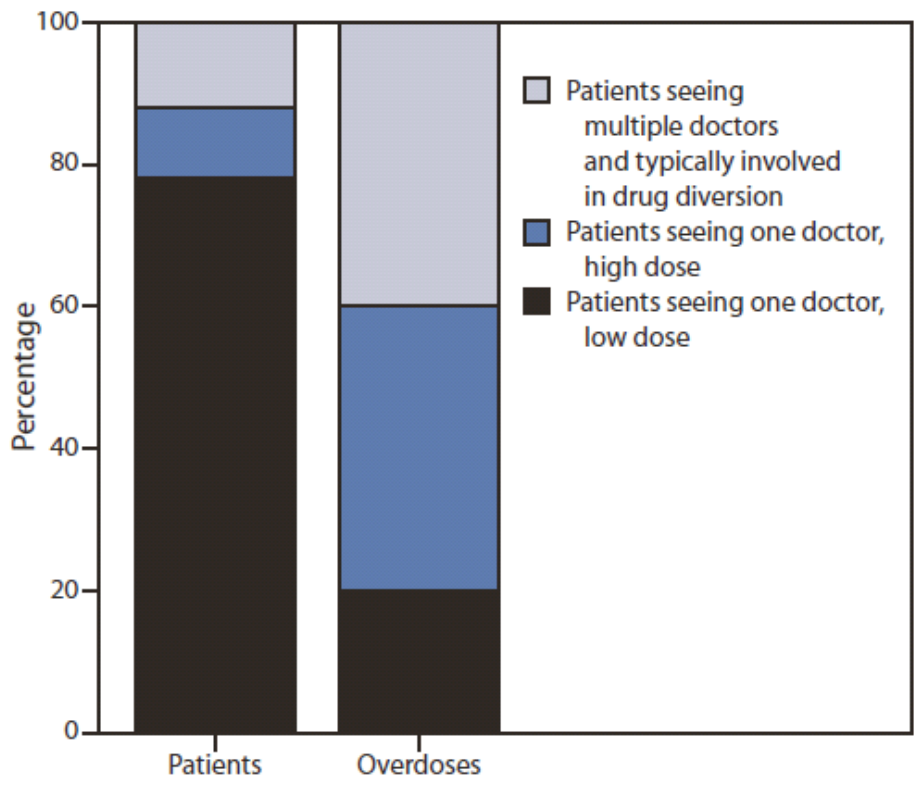
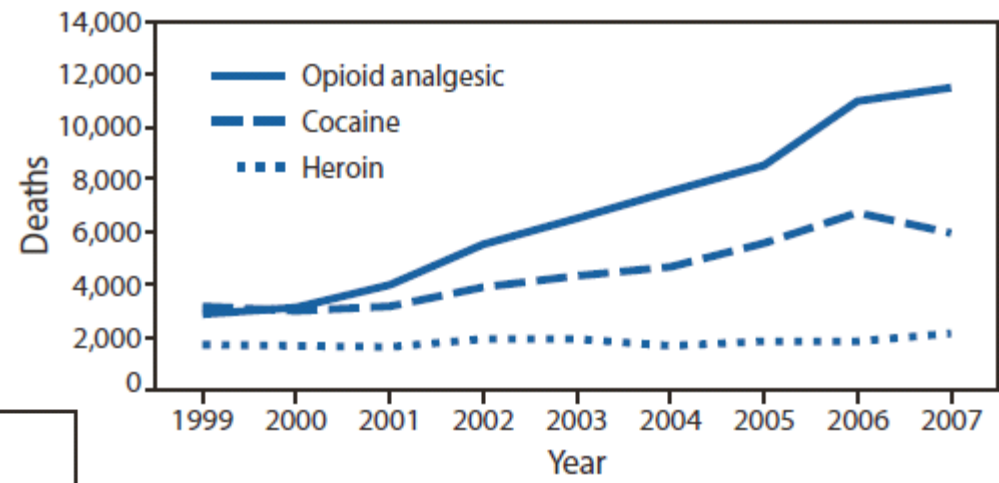
Chronic Pain Medications

- Benzodiazepines
 - Diazepam
 - Alprazolam
 - Clonazepam
 - Lorazepam
 - Nordiazepam
 - Oxazepam
 - Temazepam
 - Nitrazepam
 - Flunitrazepam
 - Flurazepam
 - Triazolam
- Tricyclic Antidepressant
 - Imipramine
 - Amitriptyline
 - Nortriptyline
 - Protriptyline
- SSRI
 - Fluoxetine
 - Paroxetine
 - Sertraline
- SNRI
 - Duloxetine



Pain – statistics

NSDUH (2010) – ~22.6 million (8.9%) illicit drug users in the US
~5.1 million use Rx opioids

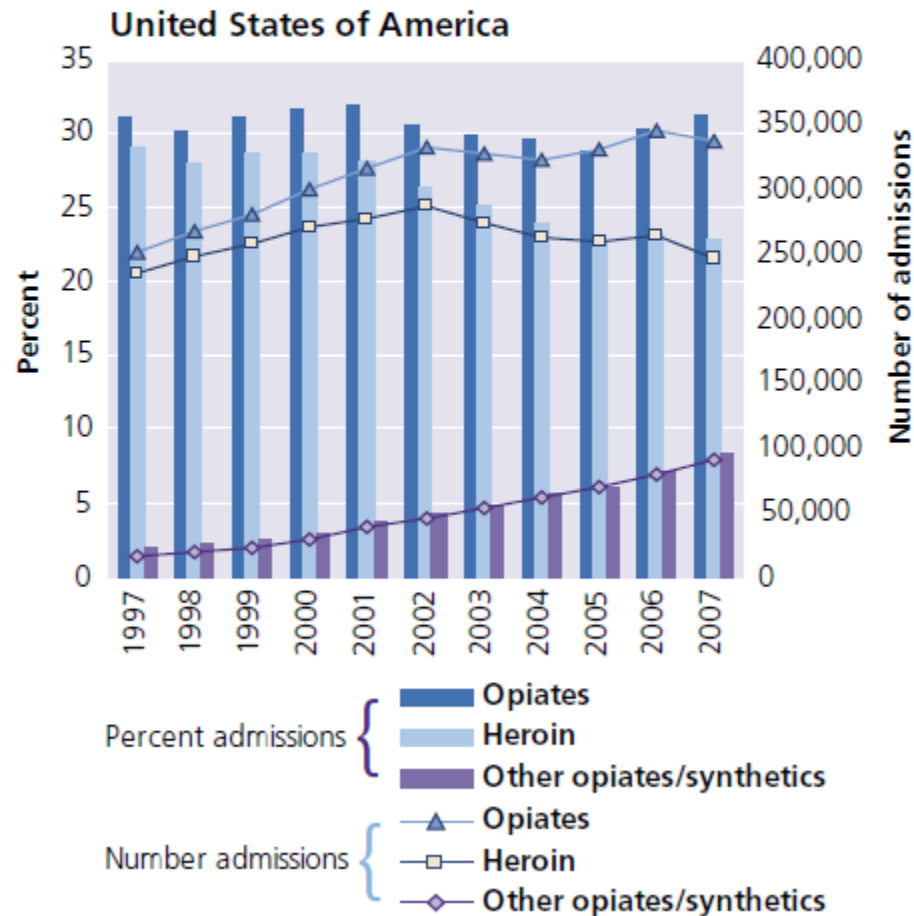


Drug Use Trends: SAMSHA / World Drug Report 2011

Fig. 102: Treatment admissions for opiates, 1997-2007 (North America)

Note: Percent of admissions excluding alcohol.

Source: Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS)





Drug Screening Panels

Drugs commonly in “Drug of Abuse” and/or “Pain Management” Panels
<i>Amphetamines</i>
<i>Opiates</i>
Benzodiazepines
<i>Cocaine</i>
Barbiturates
Methadone
<i>Phencyclidine (PCP)</i>
<i>Marijuana (THC)</i>
Oxycodone



Drug Screen – cut-off values

Laboratory #1

Drug/Drug Class	Cut-off
Amphetamines	1000
Barbiturates	200
Benzodiazepines	200
Cocaine Metabolite	300
Opiates	300
Heroin Metabolite	10
Methadone Metabolite	100
Oxycodone	100

Laboratory #2

Drug/Drug Class	Cut-off
Amphetamines	1000
Barbiturates	200
Benzodiazepines	200
Cocaine Metabolite	300
Opiates	2000
Cannabinoids	50

- Cut-offs were originally set for workplace drug testing – tolerant to false negatives
- SAMSHA cut-offs - significant number of pain patients are considered noncompliant
- Suggested cutoffs for pain patients are much lower (not standardized)



Average Windows of Detection

Drug of Abuse	Drug Detection Period
Amphetamines	2-4 days
Barbiturates	1-3 days (Phenobarb., 2 weeks)
Benzodiazepines	Up to 2 weeks
Cocaine (BE)	2-3 days
Methadone (EDDP)	2-4 days
Opiates	2-3 days
Oxycodone	1-3 days
Phencyclidine	3-8 days
Heroin Metabolite (6-MAM)	12-24 hours
Ethanol	Less than 1 day
THC	1-95 days



Pain Management – who to test?

- The guidelines for treating non-cancer pain patients with opioids stipulate that urine drug testing should be conducted:
 - When starting a new patient
 - When medications or dosages are changed
 - When behavior or appearance is suspicious
 - When patient asks for specific medications
 - Periodically or randomly



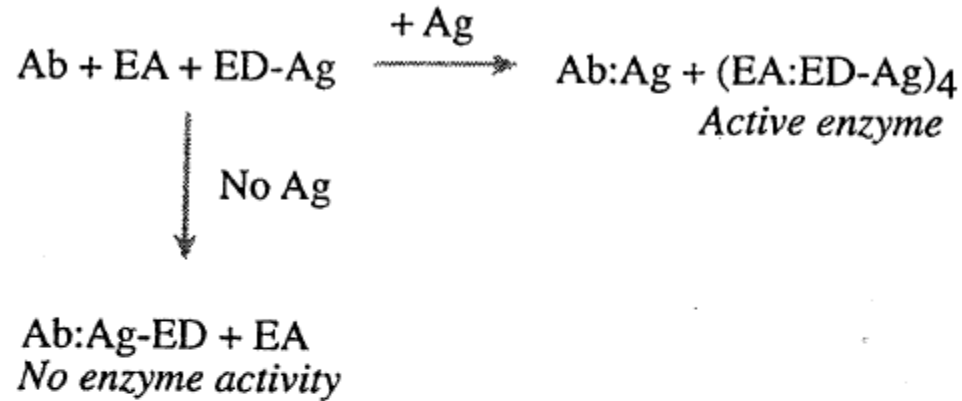
Testing Methodologies

Testing Methods	Abbreviation
Point-of-care assays	POC
Radio immunoassay	RIA
Enzyme linked immunosorbent assay	ELISA
Enzyme-multiplied immunoassay technique	EMIT
Cloned enzyme donor immunoassay	CEDIA
Fluorescence polarization immunoassay	FPIA
Liquid chromatography with ultraviolet detection	HPLC-UV
Gas chromatography mass spectrometry	GC-MS
Liquid chromatography tandem mass spectrometry	LC-MS/MS
Liquid chromatography time-of-flight mass spectrometry	LC-TOF
Liquid chromatography high resolution mass spectrometry	LC-HRMS

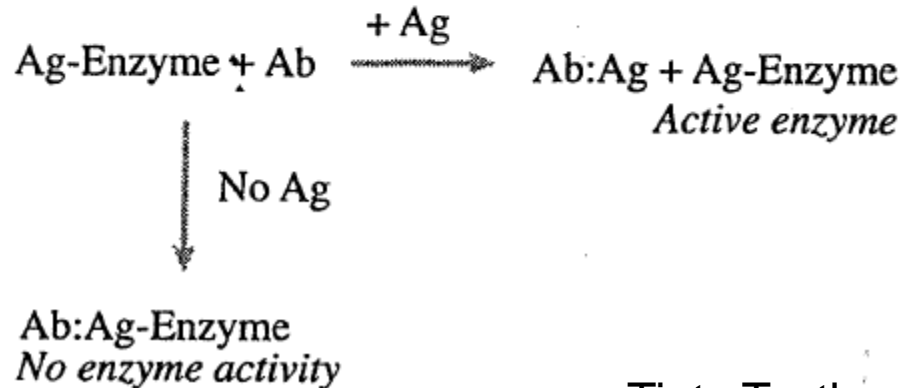


EMIT and CEDIA

CEDIA



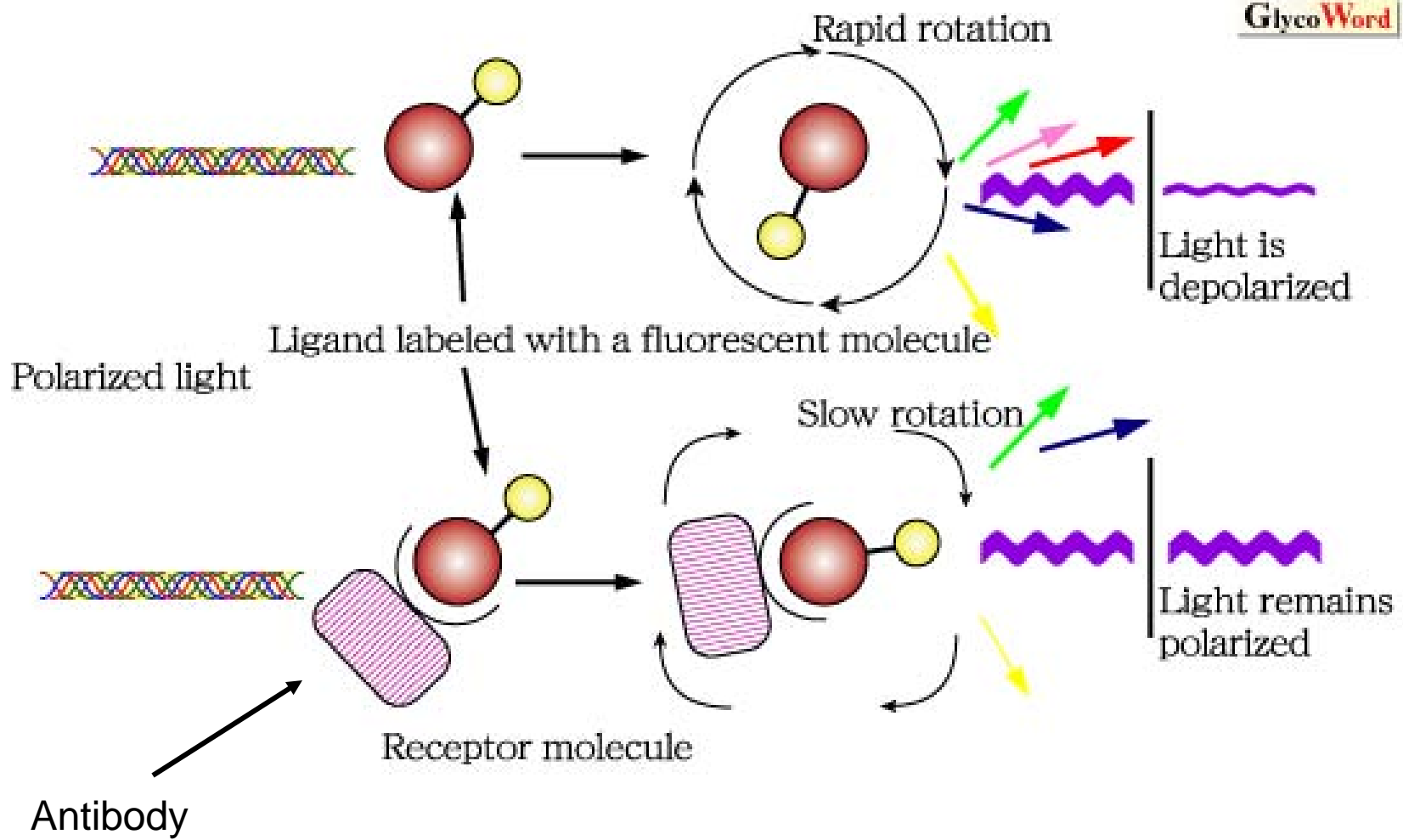
EMIT





FPIA – Fluorescent Polarization Immunoassay

GlycoWord





Methods used for Drug Screening and Confirmation

LC-UV

limited specificity

variability of UV spectra

REMEDi no longer supported

many compounds have little to no UV absorbance

GC-MS

increased sensitivity and specificity (compared to LC-UV)

cannot detect non-volatile, polar and thermally labile compounds

requires lengthy sample preparation (hydrolysis/derivatization)

high reproducibility of generated mass spectra

LC-MS/MS

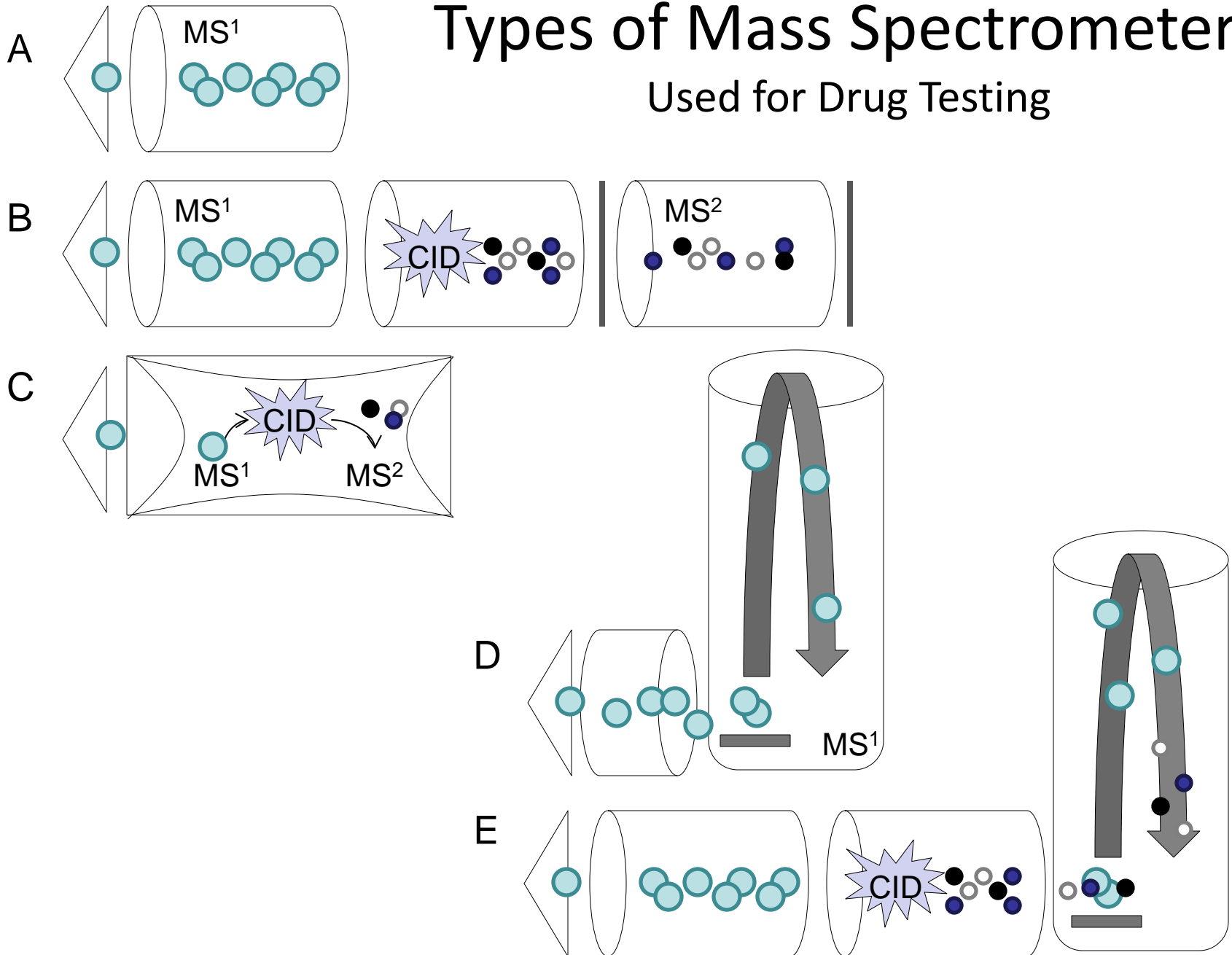
high sensitivity and specificity

minimal sample preparation (sample already in aqueous matrix)

can detect non-volatile, polar and thermally labile compounds

Types of Mass Spectrometers

Used for Drug Testing



Opiates

Is my patient taking what I am prescribing them?



Urine drug test interpretation: what do physicians know?

Reisfield GM et al. J Opioid Manag. 3(2):80-86, 2007

- 1) In a patient prescribed Tylenol #3, one would expect which of the following to be detectable in the urine? (29% correct)
- 2) In a patient prescribed MSContin, one would reasonably expect to find which of the following in the urine? (61% correct)
- 3) In a patient abusing heroin, one would be likely to detect which of the following in the urine? (7% correct)
- 4) A patient taking Oxycontin is given a urine drug test. He notifies you that he ate a poppy seed muffin for breakfast. What might reasonably be detected in the urine? (22% correct)
- 5) A patient on chronic opioid therapy tests positive for cannabis on a random drug screen. She explains that her husband sometimes smokes pot in their bedroom. Is this a plausible explanation for the test findings? (79% correct)
- 6) Which of the following are plausible explanations for a negative urine opiate screen in a patient on chronic opioid therapy? (17% correct)
- 7) A patient on q6h Dilaudid therapy tests opiate-negative on a urine drug screen. He claims use as prescribed. What is the appropriate next step? (52% correct)

Only 30% answered more than half of the questions correctly

Opiates - Case 1

47 y.o. male with history of chronic back pain

Taking “high dose” Oxycontin[®]

Urine Opiate Screen is negative

Is my patient taking his oxycontin? Should I stop prescribing it to my patient?



Case 1 - Dose and specimen information

20 mg/day for three weeks

Last dose 11 am on Tuesday

Specimen collected at 8 am on Wednesday

Also taking gabapentin, ibuprofen, citalopram, omeprazole

Half-life of oxycontin – 4.5 – 6.5 hours

Detection window in urine: 1 – 3 days



Opiates: Immunoassay cross-reactivity

	Online DAT opiates II ¹ assay	EMIT II+ opiate aassay ²	TDx/TDx- flex opiate opiate assay ³	Archetect/ Acroset	AsSym opiate ³	CEDIA opiate ⁴	DRI opiate ⁴	DRI oxycodone ⁴
Morphine	100	100	100	100	100	100	100	<29
Codeine	134	98	>3.6	167	>3.6	125	167	<20
Ethyl morphine	101		<10		>100			
Diacetyl morphine (heroin)	82					53	86	<33
6-Acetylmorphine	78	69	>20	67	<30	81	79	<200
Dihydrocodeine	69	103	>3.6	106	>3.6	50	67	<100
Morphine-3-glucuronide	54	48	>57	47	>57	81	50	<11
Morphine-6-glucuronide			>5.7		<8.6	47	100	
Hydrocodone	28	121	>8.0	158	>12	48	18	<133
Hydromorphone	21	60	>4.4	54	>6.7	57	7.5	<333
Norcodeine	2							<10
Normorphine							0	<10
Oxycodone	0	12	>1.1	11	<1.7	3.1	1.9	100
Oxymorphone		1.5	<10	0	<15	1.9	0.7	103
Noroxycodone								<0.1
Noroxymorphone								<0.1
Meperidine	0	<0.6	<2.0	0	<3.0	0.2	0	
Levallorphan		<4	<6.0	13	<6.0			
Levorphanol		29	>6.0	27	>6.0		2.1	<50
Nalorphine		3	<20	2.3	<30			
Naloxone	0	0.04	<20	0	<30		0	<50
Imiprimine	0					1.6		
Ranitidine						0	0	
Thebaine	25		<20		<30		<15	
Naltrexone	0						0	<20
Fentanyl			<40		<60			

Opiates - Case 2

38 y.o. female on vicodin (hydrocodone) for chronic pain

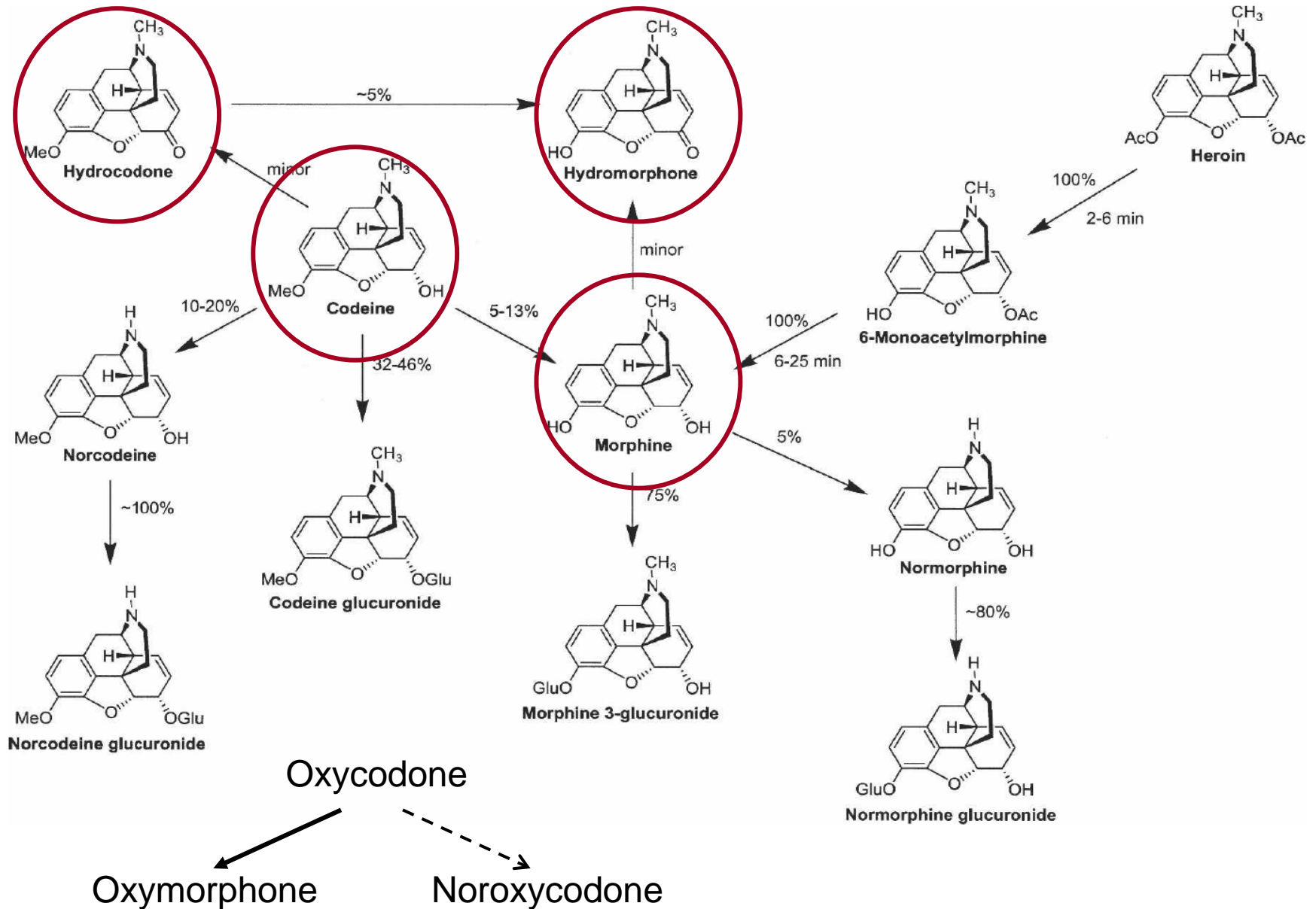
Opiate screen positive

Opiate confirmation is positive for hydromorphone and hydrocodone

Is my patient taking another opiate (Dilaudid - hydromorphone) in addition to the vicodin? Should I stop prescribing it to my patient?



Opiate Metabolism



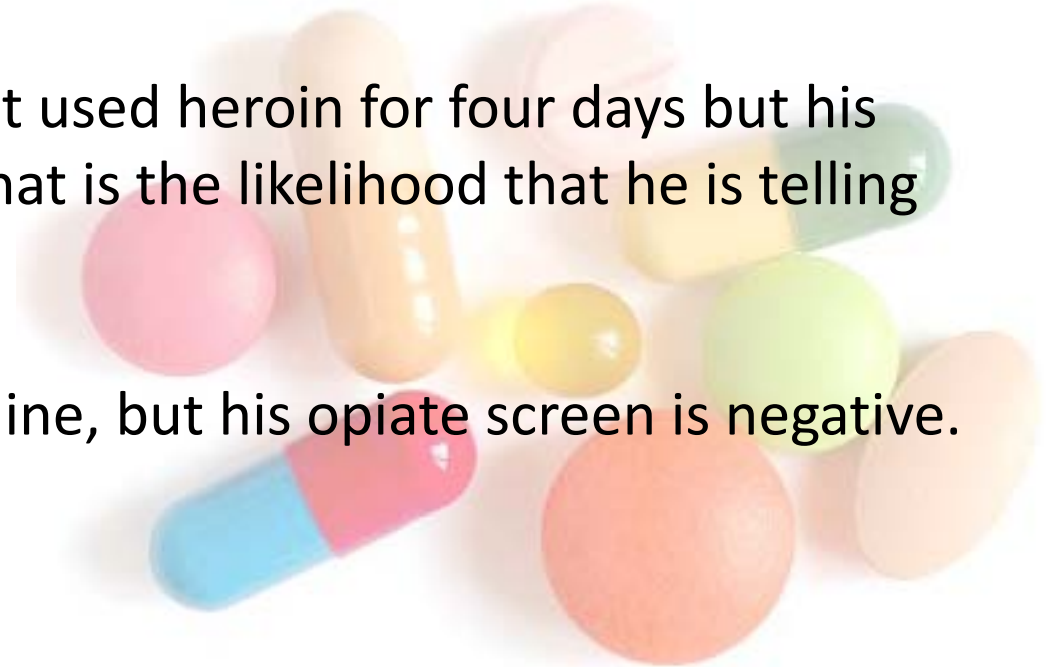
Opiates: Other questions

My patient swears he took his hydrocodone three days ago but his opiate screen is negative?

I am prescribing my patient codeine. Their opiate confirmation was positive for morphine and codeine are they taking heroin?

My patient swears he has not used heroin for four days but his opiate screen is positive? What is the likelihood that he is telling me the truth?

My patient is on buprenorphine, but his opiate screen is negative. Is he taking his prescription?



Amphetamines



Amphetamines - Case 1

Amphetamine screen is positive and the confirmation (LC-MS/MS) is negative for amphetamine, methamphetamine, MDMA and MDA. How can this be explained?

Methamphetamine

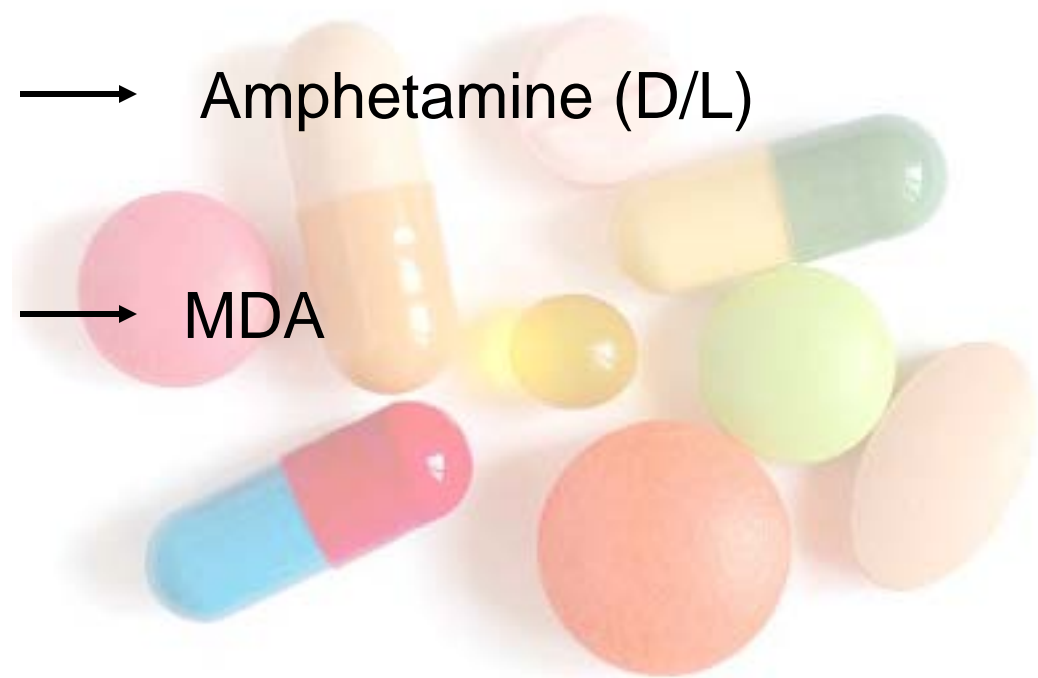


Amphetamine (D/L)

MDMA



MDA





Package insert 1: Amphetamine/Ecstasy Assay

Compound	Concentration Tested (ng/mL)	% Cross-Reactivity
d-Amphetamine	1000	104
l-Amphetamine	40,000	1.0
d,l-Amphetamine	1,250	88
d,l-Methamphetamine	1,000	77
l-Methamphetamine	8,000	18
3,4-Methylenedioxy-amphetamine (MDA)	1000	116
3,4-Methylenedioxy-methamphetamine (MDMA)	500	196
3,4-Methylenedioxy-ethylamphetamine (MDEA)	300	172
N-Methylbenzodioxazolylbutanamine (MBDB)	900	121
Benzodioxazolylbutanamine (BDB)	1000	76
Phentermine	25,000	3.3
d,l-Phenylpropanolamine	500,000	0.3
d-Pseudoephedrine	160,000	0.9
l-Ephedrine	250,000	0.5
p-Methoxyamphetamine (PMA)	2000	24
p-Methoxymethamphetamine (PMMA)	500	100



Package insert 2

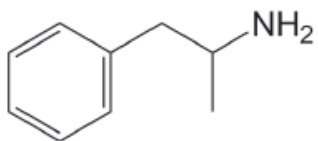
Specificity

Cross-reactivity was tested for amphetamine, methamphetamine and amphetamine metabolites. The following compounds **cross-react** above the sensitivity (100.00 ng/mL) of the AxSYM Amphetamine/Methamphetamine II assay.

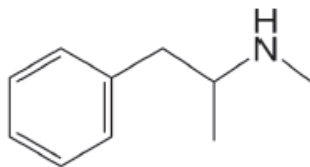
COMPOUND	CONCENTRATION TESTED (ng/mL)
d,l-Amphetamine	1,000
l-Amphetamine	3,000
4-Chloroamphetamine	1,000
d-Methamphetamine	1,000
d,l-Methamphetamine	3,000
l-Methamphetamine	8,000
4-Methyl-2,5-dimethoxy- amphetamine (DOM)	100,000
3,4-Methylenedioxyamphetamine (MDA)	3,000
3,4-Methylenedioxy-N- ethylamphetamine (MDE)	8,000
3,4-Methylenedioxy- methamphetamine (MDMA)	3,000

Cross-reactivity was also tested with compounds that have similar chemical structure or are used concurrently. The following compounds **cross-react** above the sensitivity (100.00 ng/mL) of the AxSYM Amphetamine/Methamphetamine II assay.

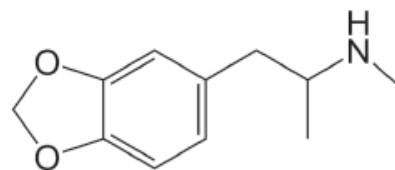
COMPOUND	CONCENTRATION TESTED (ng/mL)
Benzotropine Methanesulfonate	1,000,000
Benzylamine	1,000,000
Ciprofloxacin	1,000,000
Cyclohexylamine	1,000,000
Fenfluramine	50,000
Fluoxetine	1,000,000
Isometheptene	50,000
Isoxsuprine	100,000
Labetalol	100,000
Mephentermine	100,000
Methoxyphenamine	100,000
5-Methoxytryptamine	100,000
Metoprolol	1,000,000
Mexiletine	100,000
Norfloxacin	1,000,000
Nylidrin	100,000
Ofloxacin	1,000,000
Phenethylamine	100,000
Phenmetrazine	100,000
Phentermine	10,000
Phenyltoloxamine	1,000,000
Propylhexedrine	10,000
Ranitidine	1,000,000
Ritodrine	1,000,000
Sertraline	1,000,000
Timolol	1,000,000
Trimethobenzamide	100,000
Tryptamine	100,000
Tyramine	100,000



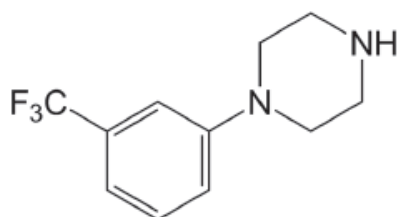
Amphetamine



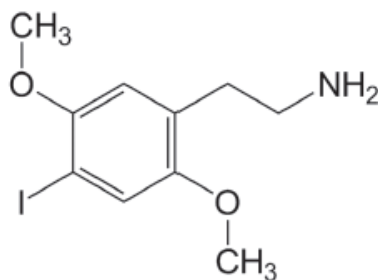
Methamphetamine



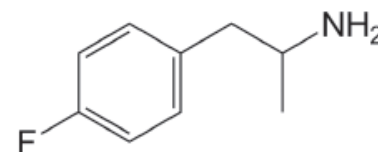
MDMA



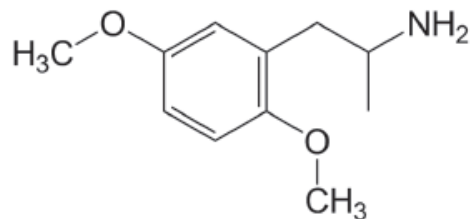
TFMPP
(Piperazine)



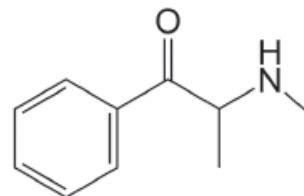
2C-I
(2C family)



4-Fluoroamphetamine
(4-substituted amphetamines)

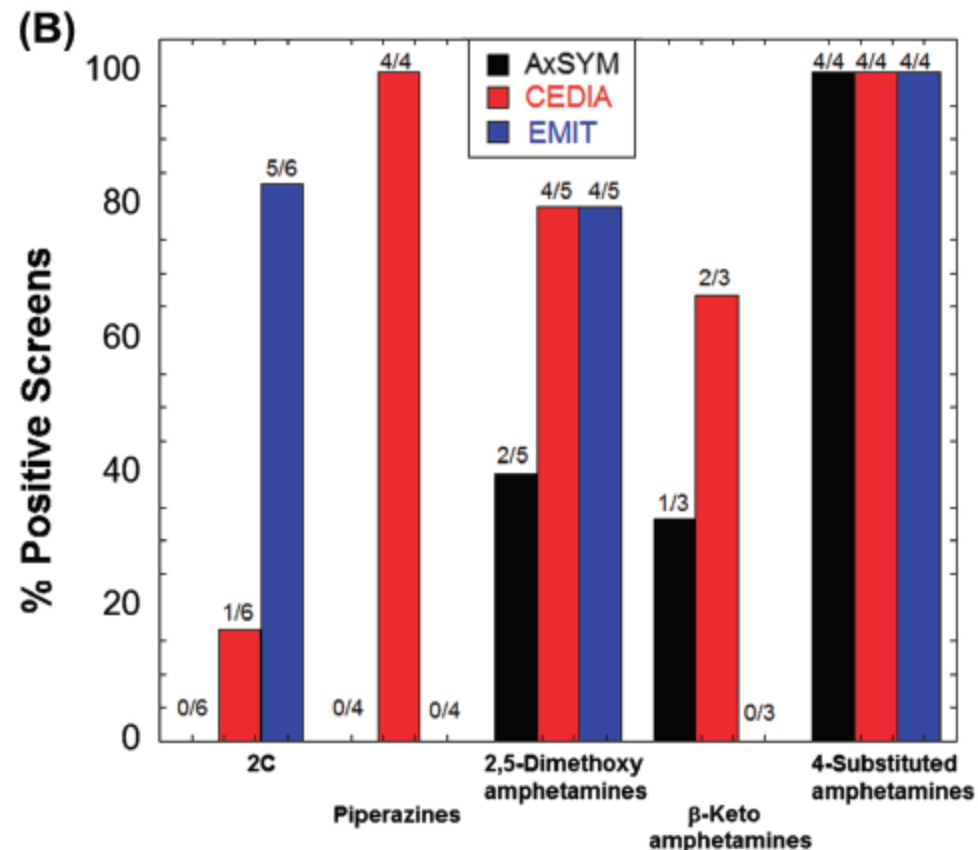
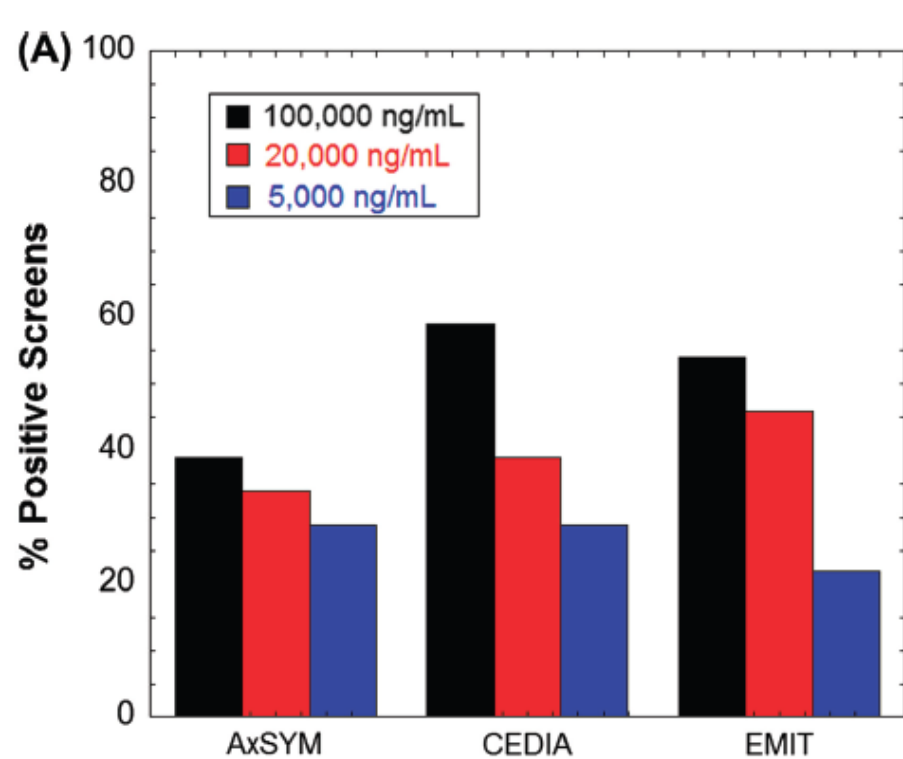


2,5-DMA
(2,5-Methoxyamphetamine family)



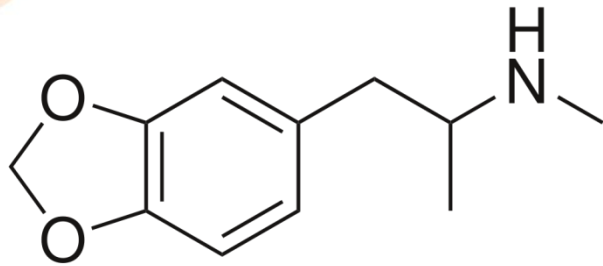
Methcathinone
(β -keto amphetamine family)

Amphetamines type stimulants

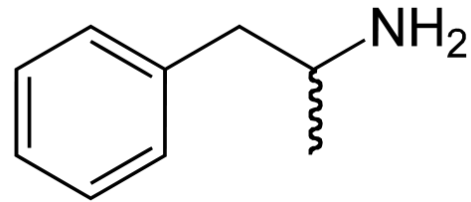




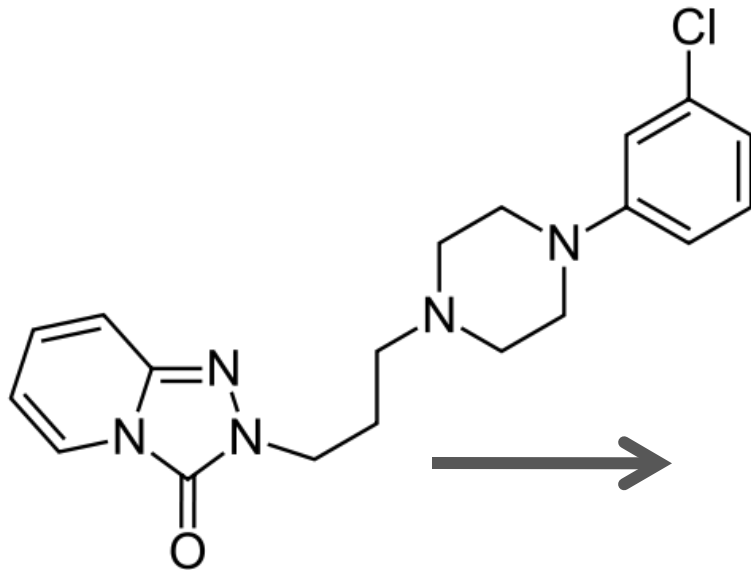
Amphetamines



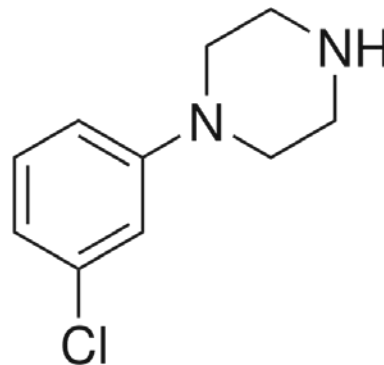
Ecstasy



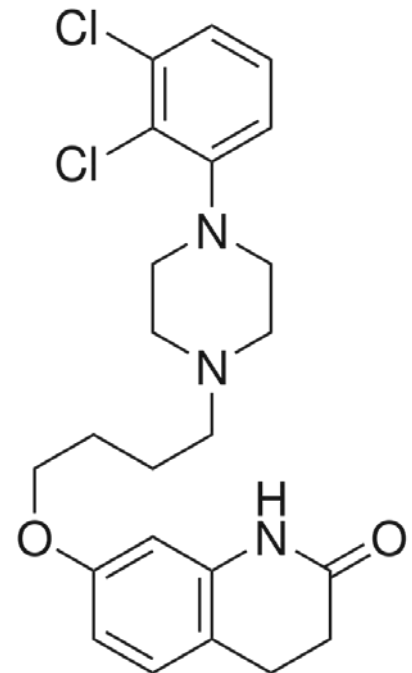
Amphetamine



Trazadone



mCPP



Aripiprizole

Amphetamine Assay Cross-reactivity

Trade Name	Generic Name	Immunoassay	LC-MS
Adderall, Dexedrine, Dextrostat, Vyvanse	d-amphetamine	+	+AMPH
Desoxyn	methamphetamine	+	+METH +AMPH
Anipryl, Zelapar	Selegiline	+	+METH +AMPH
Various Rx Drugs	Phentermine, Bupropion, Trazadone, Sildenafil	+ (at high [])	-
Ritalin, Concerta, Daytrana, Metadate, Methylin	methylphenidate	-	-
Focalin	dexmethylphenidate	-	-
Ephedrine, Pseudoephedrine		-	-

Benzodiazepines

What is the major limitation of most benzodiazepine assays?





Benzodiazepines: Immunoassay cross-reactivity

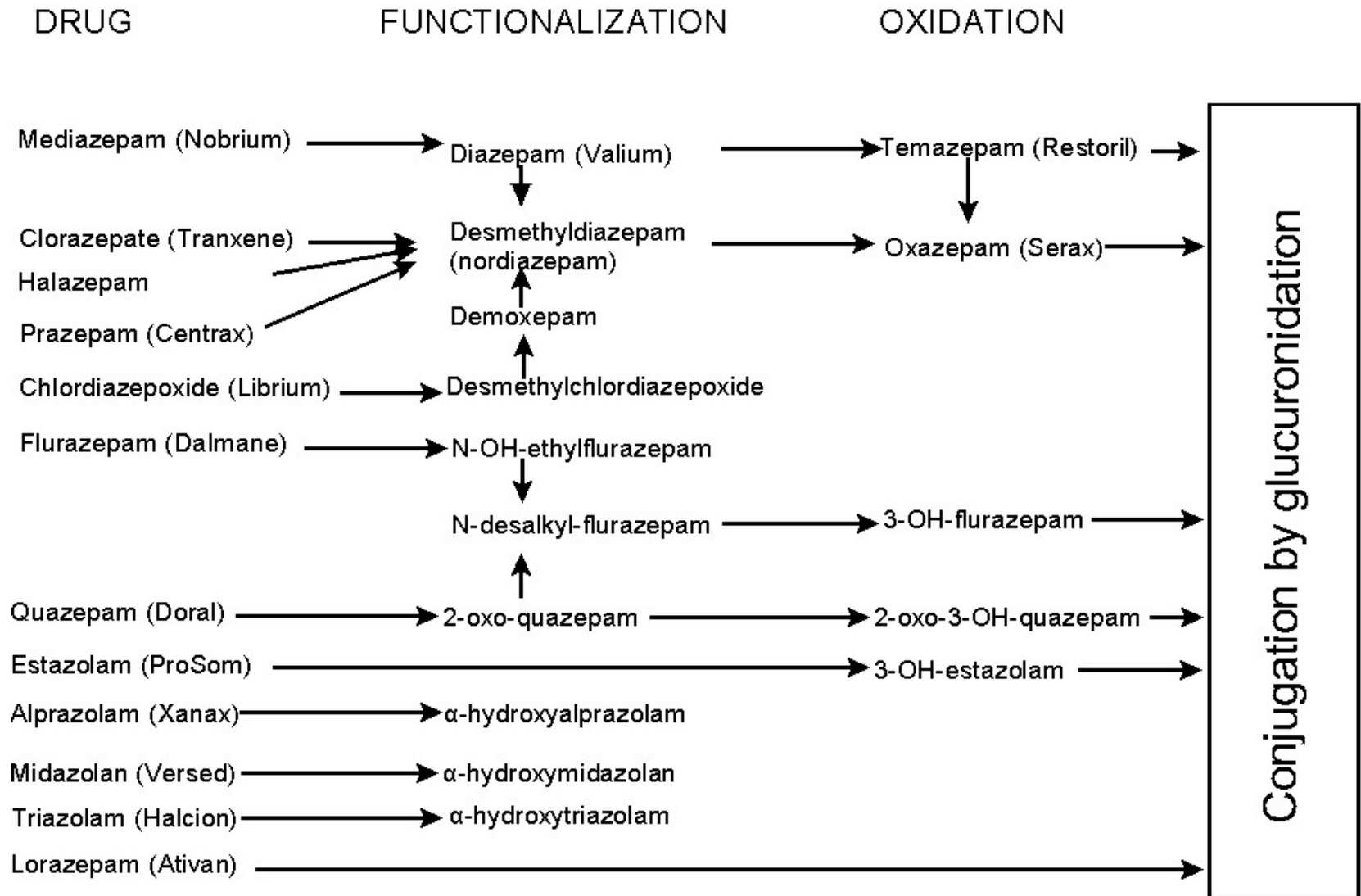
Benzodiazepines

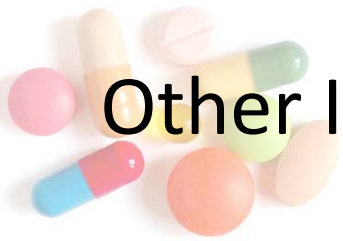
- Limited immunoassay crossreactivity
- Prone to false-negatives
- Some assays do not detect some common benzos – clonazepam, lorazepam, flunitrazepam
- Do not detect atypical benzodiazepine receptor ligands: eszopiclone (lunestra), zaleplon (sonata), zolpidem (ambien), etc.

Compound	Without β -Glucuronidase		With β -Glucuronidase	
	Tested ng/mL	%Cross-Reactivity	Tested ng/mL	%Cross-Reactivity
7-NH ₂ -Flunitrazepam	-	-	200	99
7-NH ₂ -Nitrazepam	-	-	250	83
α -OH-Alprazolam	163	188	115	167
α -OH-Triazolam	150	193	125	155
Alprazolam	138	205	100	220
Alprazolam glucuronide	-	-	200	100
Bromazepam	300	110	190	104
Chlordiazepoxide	2083	13	1200	16
Clobazam	400	62	300	59
Clonazepam	188	140	225	71
Clorazepate	325	84	300	75
Delorazepam	150	184	100	197
Demoxepam	1900	14	1000	19
Desalkylflurazepam	138	210	115	173
Diazepam	110	247	125	154
Estazolam	125	220	95	239
Flunitrazepam	188	135	175	109
Flurazepam	150	189	100	195
Halazepam	200	145	200	101
Lorazepam	208	122	175	115
Lorazepam glucuronide	10000	1	400	45
Lometazepam	163	165	150	137
Medazepam	200	135	150	118
NH ₂ -Clonazepam	-	-	200	96
Nitrazepam	300	100	200	100
Nordiazepam	150	211	120	173
Oxaprozin	10000	2	10000	2
Oxazepam	275	107	165	125
Oxazepam glucuronide	10000	1	800	25
Prazepam	150	184	160	116
Temazepam	175	144	180	93
Temazepam glucuronide	10000	1	750	25
Triazolam	138	191	90	217



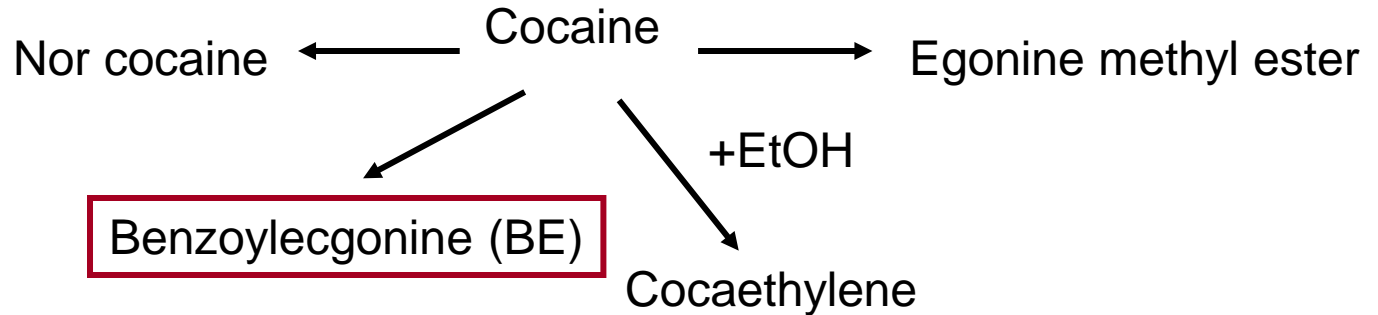
Benzodiazepine Metabolism





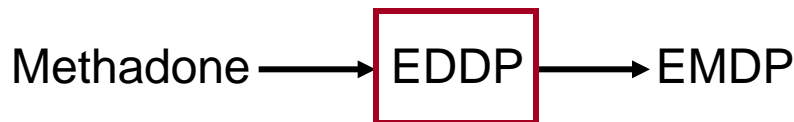
Other Immunoassays: what do I need to know?

Cocaine:



Compound	Concentration Tested (ng/mL)	% Cross Reactivity
Benzoyllecgonine	300	100
Cocaethylene	312	57
Cocaine	315	54
Ecgonine	10,000	1.1
Ecgonine methyl ester	10,000	< 0.1

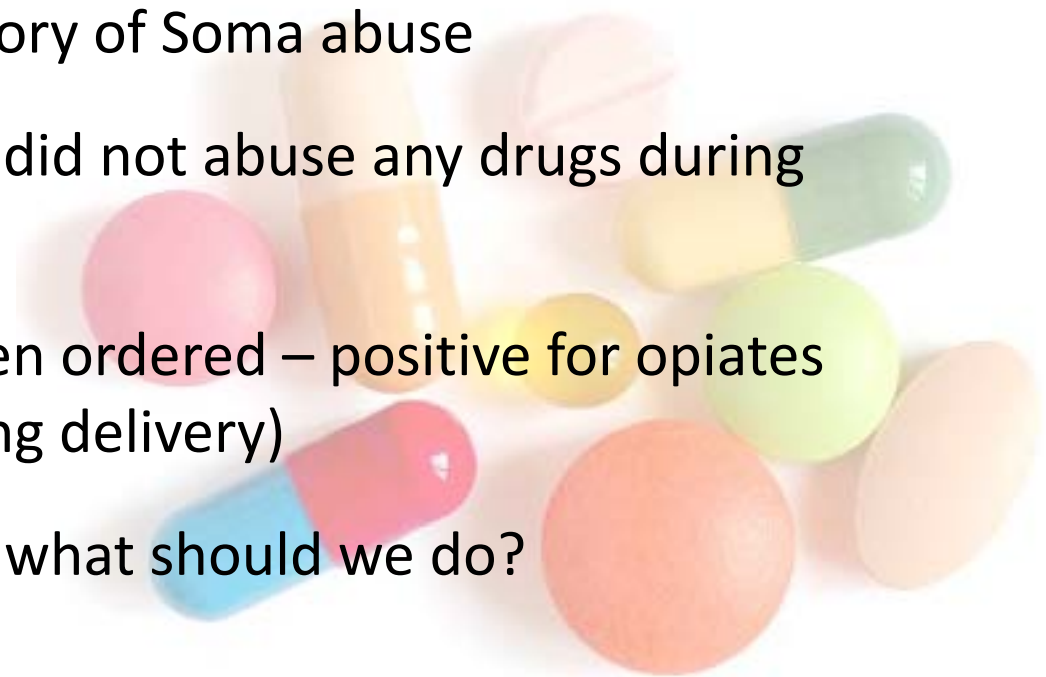
Methadone:



Compound	Concentration Tested (ng/mL)	% Cross Reactivity
EDDP	100	100
EMDP	200,000	0.004
Methadone	600,000	0.016
α -levo-acetylmethadol	1,000,000	0.000
α -levo-noracetylmethadol	1,000,000	0.001
α -levo-dinoracetylmethadol	1,000,000	0.000

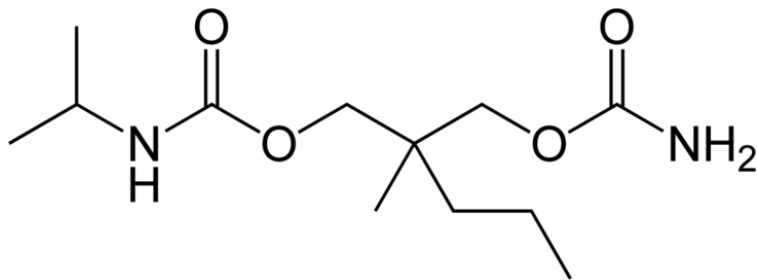
Case – immunoassays vs. LC-MS

- Mother gives birth to a baby girl at UCSF medical center
- Baby girl appeared lethargic and sedated (D1) and slightly agitated (D2) and symptoms consistent with neonatal drug withdrawal
- Mother has previous history of Soma abuse
- Mother claimed that she did not abuse any drugs during pregnancy
- Drug of abuse urine screen ordered – positive for opiates (hydrocodone given during delivery)
- SFGH called for consult – what should we do?

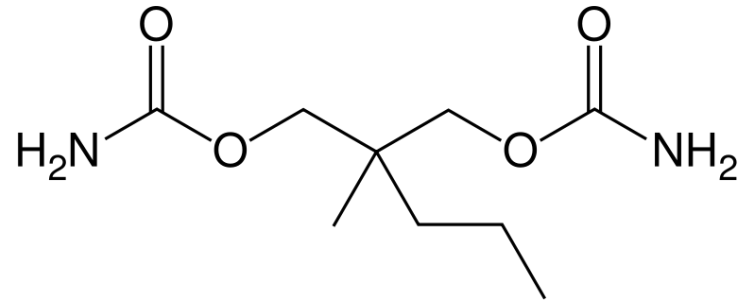
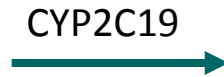


Soma - Carisoprodol

centrally acting skeletal muscle relaxant with high abuse potential

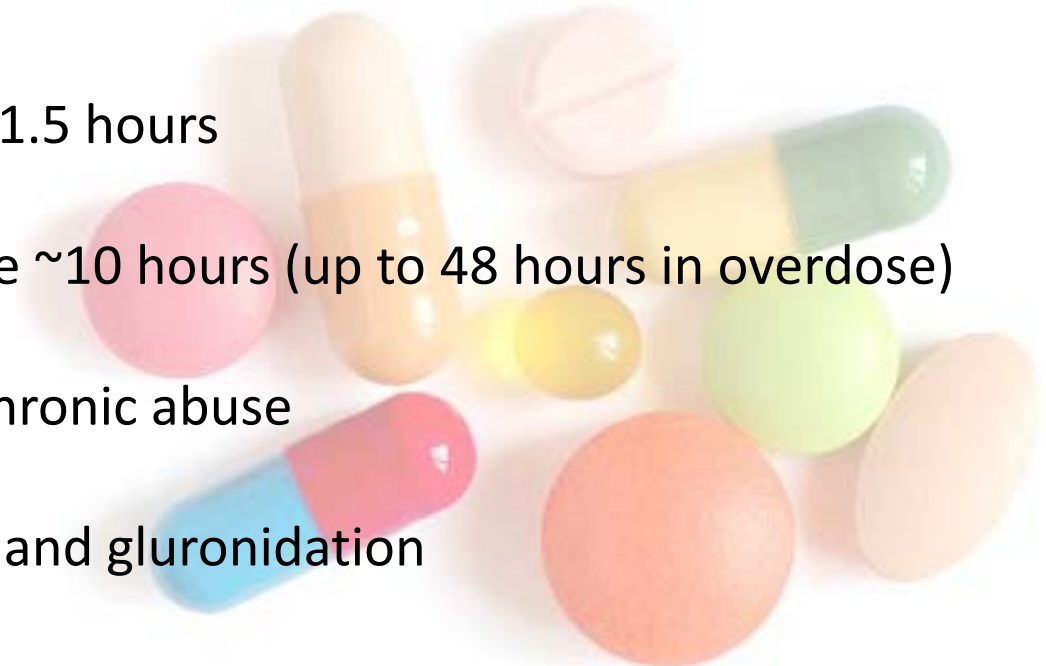


Carisoprodol

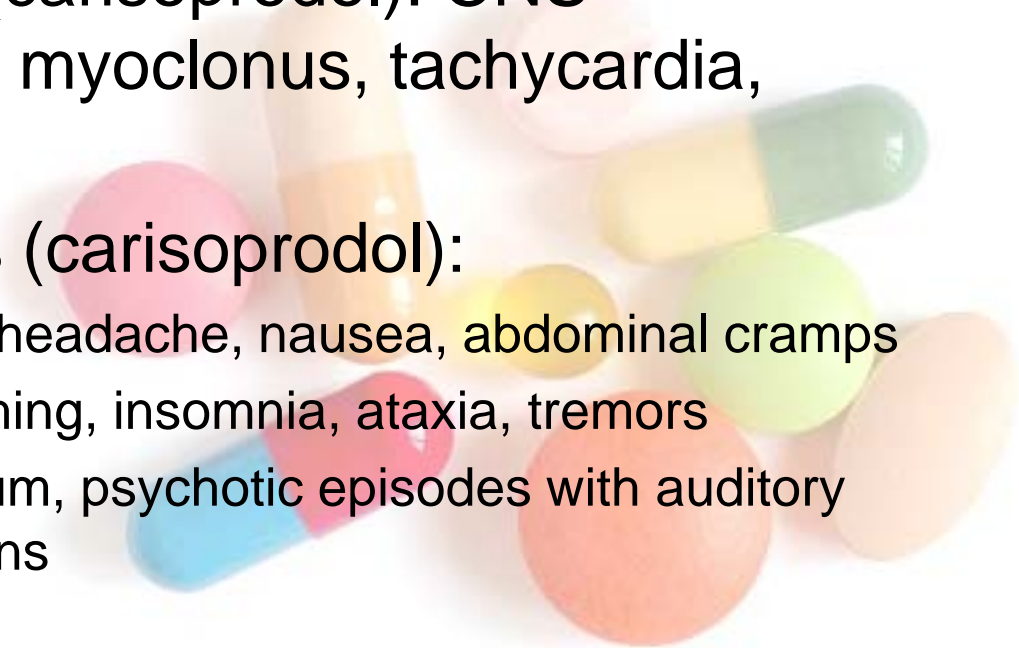


Meprobamate

- Carisoprodol – short half-life ~1.5 hours
- Meprobamate – longer half-life ~10 hours (up to 48 hours in overdose)
- More likely to accumulate in chronic abuse
- Metabolized via hydroxylation and glucuronidation

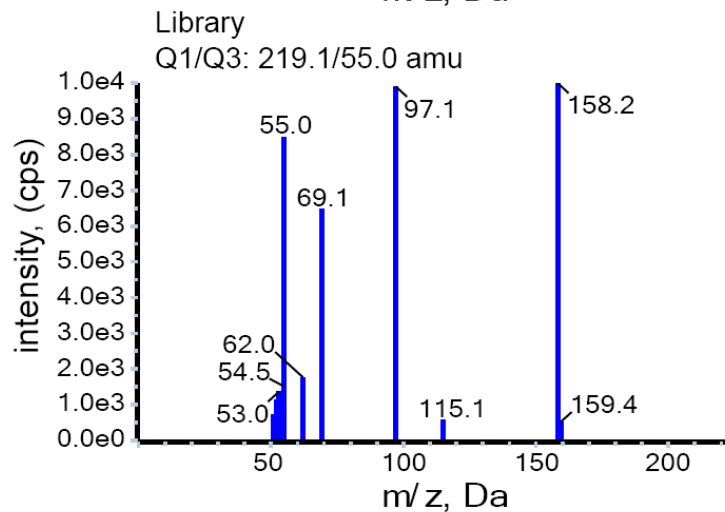
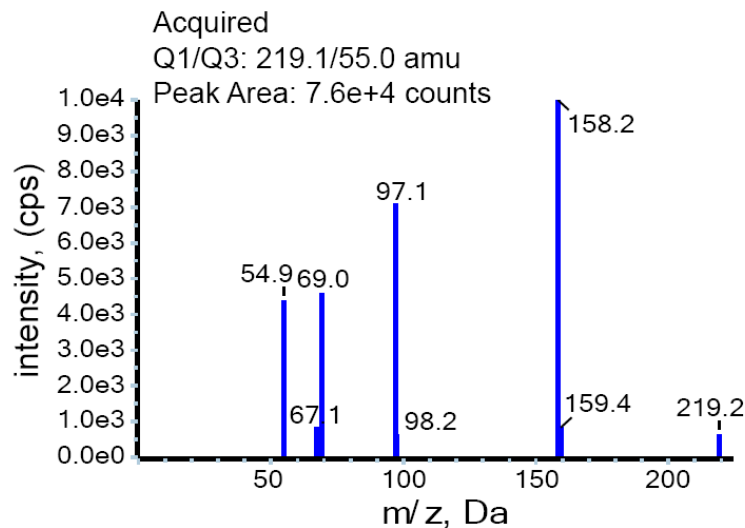


Soma – Abuse and Symptoms

- Abuse first reported in 1978
 - Potential for abuse recognized in 1990s
 - Number of ED episodes involving soma increased by 300% from 1994 to 2005
 - Overdose symptoms (carisoprodol): CNS depression, shivering, myoclonus, tachycardia, nystagmus
 - Withdrawal symptoms (carisoprodol):
 - Mild – anxiety, agitation, headache, nausea, abdominal cramps
 - Moderate – muscle twitching, insomnia, ataxia, tremors
 - Severe – seizures, delirium, psychotic episodes with auditory and/or visual hallucinations
- 

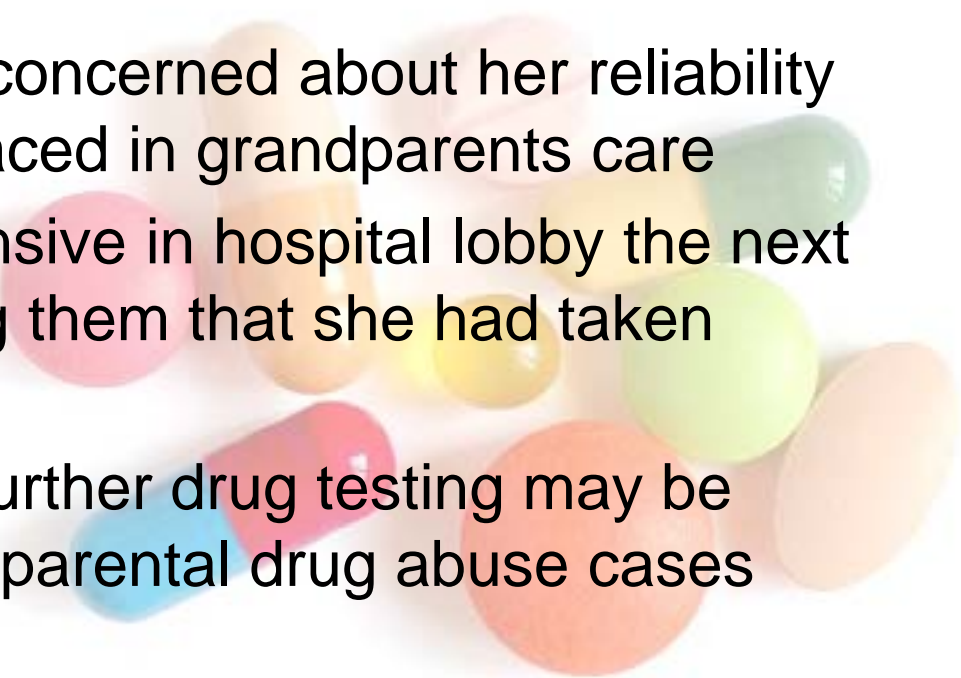
Drug Screen: Baby – meprobamate positive

Mother – negative for meprobamate and carisoprodol



	Compound Name	Purity (%)	Fit (%)	RFit (%)
1	Meprobamate	80.5	87.4	92.1

Case Study Conclusions

- CPS convened a meeting with extended family and the parents
 - Mother continued to deny use during pregnancy and asked “how did it get there....all of my previous UTOXs have been negative
 - All family members were concerned about her reliability and stability, child was placed in grandparents care
 - Mother found semi-responsive in hospital lobby the next day and went to ED telling them that she had taken SOMA and Benadryl
 - CPS acknowledged that further drug testing may be needed in many potential parental drug abuse cases
- 

The future of pain management testing

- Use of more sensitive and specific testing methodologies - LC-MS/MS, LC-HRMS
- Guidelines for standardized cut-off concentrations
- Alternative Matrices – Blood (use of therapeutic ranges) and/or oral fluid (non-invasive, observed collection)

Self-Assessment Questions

1. Which forms of chronic pain does not respond to opiates?
 - a) Neck and back pain
 - b) Headaches
 - c) **Diabetic peripheral neuropathy**
 - d) Chronic non-cancer pain

2. Which combination of methodologies are most frequently used in laboratories for pain management testing?
 - a) TLC and GC-MS
 - b) Radioimmunoassay and LC-MS/MS
 - c) ELISA and HPLC-UV
 - d) **Immunoassay and LC-MS/MS**

3. Which immunoassay(s) are prone to false negative
 - a) Amphetamines
 - b) Benzodiazepines
 - c) Opiates
 - d) Cocaine
 - e) **B and C**