

Pain Management Data: Synthetic Opioids

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This presentation was modified from its original format for
508 compliancy.

Outline

- Opioids and Pain Management
- The context: analytes and cutoff selections
- Datasets, characteristics
- Urine opioids
- Oral fluid opioids
- Recommendations

Urine & Oral Fluid

- What new opioid analytes should be added?
- What should be their cutoffs?

What Synthetic Opioid “Analytes” Should be Included?

- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Metabolites?

Increasing Environmental Availability of Rxs

Drug	1990	2010
Rx Opioids	5 million	30 million
Rx Stimulants	45 million	180 million

White House Drug Policy, 2011

http://www.whitehousedrugpolicy.gov/publications/pdf/rx_abuse_plan.pdf

- Epidemic: Responding to America's Prescription Drug Abuse Crisis 2011
 - Executive Office of the President of the United States
 - “Prescription drug abuse is the Nation’s fastest-growing drug problem.”
 - “...prescription drugs are the second most-abused category of drugs after marijuana.”
 - “In our military, illicit drug use increased from 5 percent to 12 percent among active duty service members over a three-year period from 2005 to 2008, primarily attributed to prescription drug abuse.”

Drug Testing of Pain Patients Serves Important Needs

- Compliance with prescribed medication(s)
- Non-authorized medications
- Patient safety
- Addiction
- Diversion to an illegal market
- Physician liability

Pain Management Has Enormous Data Resources

Specimen	Study	# Patients
Urine	Cone, et al., JAT, 2008	10,922
Urine	Heltsley, et al., JAT, 2010	20,089
Urine	Cone, et al., FSI, 2010	2,654
Urine	DePriest, et al., JAT, 2010	4 Databases (2,600 to 45,000)
Urine	Heltsley, et al., JAT, 2011	57,542
Oral Fluid	Heltsley, et al., JAT, 2011	6,441
Oral Fluid	Heltsley, et al., JAT, 2012	133 paired sets

- What Can We Learn From Pain Management Data?
 - Information on opioid analytes
 - Prevalence
 - Concentration distributions
 - Metabolites
 - Unique “metabolites”

Testing Advances Rapidly in Pain Management Arena

- Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. *J. Anal. Toxicol.* 2008;32.
- Heltsley R, Zichterman A, Black DL, Cauthon B, Robert T, Moser F, Caplan YH, Cone EJ. Urine drug testing of chronic pain patients. II. Prevalence patterns of prescription opiates and metabolites. *J. Anal. Toxicol.* 2011;35.
- DePriest A, Heltsley R, Black DL, Cawthon B, Robert T, Moser F, Caplan YH, Cone EJ. Urine drug testing of chronic pain patients. III. Normetabolites as biomarkers of synthetic opioid use. *J. Anal. Toxicol.* 2010;34.
- Heltsley R, DePriest A, Black DL, Robert T, Caplan YH, Cone EJ. Urine drug testing of chronic pain patients. IV. Prevalence of gabapentin and pregabalin. *J. Anal. Toxicol.* 2011;35.

The Analytical Challenge of Pain Management!!

- Multiple screens necessary
- Multiple drug categories for confirmation
- Continuing need for additional tests
- Extremely broad concentration ranges
- Interpretation can be simple or complex

Typical urine test panel used in pain management (abbreviated)

Drug (Metabolite)	Urine Confirmation LOQs, ng/mL
α-OH Alprazolam	50
Amphetamine	80
Buprenorphine	1
Norbuprenorphine	2
Butalbital	200
Carisoprodol	100
Meprobamate	100
7-Aminoclonazepam	50
Benzoylcegonine	20
Codeine	50
Diazepam	NT
(Nordiazepam)	50
(Oxazepam)	50
(Temazepam)	50
Fentanyl	1
(Norfentanyl)	1
Hydrocodone	50
(Hydromorphone)	50
(Norhydrocodone)	50
(Dihydrocodeine)	50
Hydromorphone	50
Lorazepam	50
Methadone	50
(EDDP)	50
Methamphetamine	80
Morphine	50
(Hydromorphone)	50
Oxycodone	50
(Oxymorphone)	50
(Noroxycodone)	50
Propoxyphene	50
(Norpropoxyphene)	50
Temazepam	50
(Oxazepam)	50
(THCCOOH)	2
Tramadol	50
(N-Desmethyltramadol)	50
(O-Desmethyltramadol)	50

Results: Overall Drug Prevalence

- 10,922 Patients, 15,859 Specimens with drug group positives

Drug	# Positives
Opiates	8986
Benzodiazepines	2397
Methadone	1209
THCCOOH	967
Cariso	611
Fentanyl	458
Propoxyphene	385
Cocaine	310
Barbiturates	308
Amphetamines	160
Meperidine	58

Interpretation:

Prescription Opioid Drugs and Metabolite Crossover to Other Drugs

Drug	Metabolite	Metabolite	Metabolite
Hydrocodone	Hydromorphone	Dihydrocodeine	Norhydrocodone
Codeine	Norcodeine	Morphine	Hydrocodone
Oxycodone	Oxymorphone	Noroxycodone	
Morphine	Hydromorphone		

- Morphine does not metabolize to codeine
- Hydromorphone does not metabolize to morphine or hydrocodone
- Hydrocodone does not metabolize to codeine

Opioid Abbreviations

- Morphine (MOR)
- Codeine (COD)
- Norcodeine (NCOD)
- Hydrocodone (HC)
- Hydromorphone (HM)
- Norhydrocodone (NHC)
- Dihydrocodeine (HC)
- Oxycodone (OC)
- Oxymorphone (OM)
- Noroxycodone (NOC)

Opioid Urine Dataset

- Dataset of 20,089 urine specimens from pain patients
- Aegis Sciences Corp., Nashville, TN
- Analyzed for 10 opioids by LC-MS-MS (LOQ = 50 ng/mL)
- Confirmed 13,126 specimens for at least one analyte
- Published data; Heltsley, et al., JAT, 2010

Opioid & Metabolite Prevalence in Pain Patients (n=20,089)

Heltsley, et al., JAT, 2010

- Opiate positives (N = 36,315)

Analyte*	N
Codeine	267
Norcodeine (metabolite)	50
Morphine (metabolite?)	2704
Hydrocodone	5595
Dihydrocodeine (metabolite/drug?)	3698
Norhydrocodone (metabolite)	5372
Hydromorphone (metabolite/drug?)	4282
Oxycodone	5046
Noroxycodone (metabolite)	4757
Oxymorphone (metabolite/drug?)	4544

Method of Frequency Analyses

Frequency Method		Cutoff Method
Bins (ng/mL)	Bin Limits (ng/mL)	Greater than (ng/mL)
50 to 100	100	>50
101 to 150	150	>100
151 to 200	200	>200
201 to 250	250	>300
251 to 300	300	>400
301 to 500	500	>500
501 to 1000	1000	>600
1001 to 2000	2000	>700
2001 to 5000	5000	>800
5001 to 10000	10000	>900
10001 to 15000	15000	>1000
15001 to 2000000	2000000	>2000
		>10000
		>15000
		>100000

Codeine/Morphine/Norcodeine

Codeine histogram

Bins	Frequency	Cumulative %
50 to 100	11	4.1%
101 to 150	16	10.1%
151 to 200	9	13.5%
201 to 250	10	17.2%
251 to 300	13	22.1%
301 to 500	23	30.7%
501 to 1000	34	43.4%
1001 to 2000	28	53.9%
2001 to 5000	52	73.4%
5001 to 10000	38	87.6%
10001 to 15000	15	93.3%
15001 to 2000000	18	100.0%

Morphine histogram

Bins	Frequency	Cumulative %
50 to 100	44	1.6%
101 to 150	60	3.8%
151 to 200	62	6.1%
201 to 250	39	7.6%
251 to 300	33	8.8%
301 to 500	95	12.3%
501 to 1000	152	17.9%
1001 to 2000	193	25.1%
2001 to 5000	350	38.0%
5001 to 10000	381	52.1%
10001 to 15000	264	61.9%
15001 to 2000000	1031	100.0%

Norcodeine histogram

Bins	Frequency	Cumulative %
50 to 100	5	10.0%
101 to 150	5	20.0%
151 to 200	3	26.0%
201 to 250	4	34.0%
251 to 300	6	46.0%
301 to 500	6	58.0%
501 to 1000	5	68.0%
1001 to 2000	3	74.0%
2001 to 5000	9	92.0%
5001 to 10000	2	96.0%
10001 to 15000	0	96.0%
15001 to 2000000	2	100.0%

Hydrocodone/Hydromorphone/ Dihydrocodeine/Norhydrocodone

Hydrocodone histogram

Bins	Frequency	Cumulative %
50 to 100	237	4.2%
101 to 150	295	9.5%
151 to 200	241	13.8%
201 to 250	217	17.7%
251 to 300	205	21.4%
301 to 500	624	32.5%
501 to 1000	1041	51.1%
1001 to 2000	1077	70.4%
2001 to 5000	1097	90.0%
5001 to 10000	385	96.9%
10001 to 15000	99	98.6%
15001 to 2000000	77	100.0%

Hydromorphone histogram

Bins	Frequency	Cumulative %
50 to 100	483	11.3%
101 to 150	529	23.6%
151 to 200	488	35.0%
201 to 250	368	43.6%
251 to 300	324	51.2%
301 to 500	822	70.4%
501 to 1000	762	88.2%
1001 to 2000	300	95.2%
2001 to 5000	126	98.1%
5001 to 10000	43	99.1%
10001 to 15000	18	99.6%
15001 to 2000000	19	100.0%

Dihydrocodone histogram

Bins	Frequency	Cumulative %
50 to 100	557	15.1%
101 to 150	576	30.6%
151 to 200	438	42.5%
201 to 250	348	51.9%
251 to 300	302	60.1%
301 to 500	647	77.6%
501 to 1000	556	92.6%
1001 to 2000	201	98.0%
2001 to 5000	72	100.0%
5001 to 10000	1	100.0%
10001 to 15000	0	100.0%
15001 to 2000000	0	100.0%

Norhydrocodone histogram

Bins	Frequency	Cumulative %
50 to 100	151	2.8%
101 to 150	210	6.7%
151 to 200	189	10.2%
201 to 250	181	13.6%
251 to 300	178	16.9%
301 to 500	543	27.0%
501 to 1000	926	44.3%
1001 to 2000	1058	64.0%
2001 to 5000	1204	86.4%
5001 to 10000	507	95.8%
10001 to 15000	121	98.1%
15001 to 2000000	104	100.0%

Oxycodone/Oxymorphone/ Noroxycodone

Oxycodone histogram

Bins	Frequency	Cumulative %
50 to 100	123	2.44%
101 to 150	150	5.41%
151 to 200	137	8.13%
201 to 250	129	10.68%
251 to 300	118	13.02%
301 to 500	348	19.92%
501 to 1000	673	33.25%
1001 to 2000	836	49.82%
2001 to 5000	1153	72.67%
5001 to 10000	709	86.72%
10001 to 15000	274	92.15%
15001 to 2000000	396	100.00%

Hydromorphone histogram

Bins	Frequency	Cumulative %
50 to 100	138	3.04%
101 to 150	150	6.34%
151 to 200	136	9.33%
201 to 250	167	13.01%
251 to 300	115	15.54%
301 to 500	460	25.66%
501 to 1000	692	40.89%
1001 to 2000	761	57.64%
2001 to 5000	898	77.40%
5001 to 10000	513	88.69%
10001 to 15000	237	93.90%
15001 to 2000000	277	100.00%

Noroxycodone histogram

Bins	Frequency	Cumulative %
50 to 100	76	1.60%
101 to 150	65	2.96%
151 to 200	73	4.50%
201 to 250	72	6.01%
251 to 300	62	7.32%
301 to 500	209	11.71%
501 to 1000	433	20.81%
1001 to 2000	579	32.98%
2001 to 5000	1022	54.47%
5001 to 10000	859	72.52%
10001 to 15000	420	81.35%
15001 to 2000000	887	100.00%

Percentage Of Specimens That Would Be Reported As “Negative” At Selected Cutoff Concentrations

Cutoff, ng/mL	COD	NCOD	MOR	HC	DHC
100	4.1%	10.0%	1.6%	4.2%	15.1%
300	22.1%	46.0%	8.8%	21.4%	60.1%
2000	53.9%	74.0%	25.1%	70.4%	98.0%

Cutoff, ng/mL	NHC	HM	OC	NOC	OM
100	2.8%	11.3%	2.4%	1.6%	3.0%
300	16.9%	51.2%	13.0%	7.3%	15.5%
2000	64.0%	95.2%	49.8%	33.0%	57.6%

The Distribution Of Positive Results Greater Than (>) Selected Concentration Thresholds

	COD	NCOD	MOR	HC	DHC	NHC	HM	OC	NOC	OM
N	267	50	2704	5595	3698	5372	4282	5046	4757	4544
%>50	100	100	100	100	100	100	100	100	100	100
%>100	95.9	90.0	98.4	95.8	84.9	97.2	88.7	9.6	98.4	97.0
%>200	86.5	74.0	93.9	86.2	57.5	89.8	65.0	91.9	95.5	90.7
%>300	77.9	54.0	91.2	78.6	39.9	83.1	48.8	87.0	92.7	84.5
%>400	71.9	44.0	89.1	72.5	29.4	77.6	37.6	83.3	90.4	79.2
%>500	69.3	42.0	87.7	67.5	22.4	73.0	29.6	80.1	88.3	74.3
%>600	66.3	40.0	86.4	63.1	17.8	68.7	23.8	76.8	86.3	70.4
%>700	64.8	40.0	85.0	59.1	14.4	64.9	19.3	73.9	84.3	67.3
%>800	61.8	34.0	83.7	55.1	11.6	61.9	16.4	71.2	82.7	64.7
%>900	58.4	34.0	82.8	52.2	9.5	58.9	13.9	68.9	81.0	62.1
%>1000	56.6	32.0	82.1	48.9	7.4	55.7	11.8	66.7	79.2	59.1
%>2000	46.1	26.0	74.9	29.6	2.0	36.0	4.8	50.2	67.0	42.4
%>10000	12.4	4.0	47.9	3.1	0.0	4.2	0.9	13.3	27.5	11.3
%>15000	6.7	4.0	38.1	1.4	0.0	1.9	0.4	7.8	18.6	6.1
%>100000	0.7	0.0	2.9	0.0	0.0	0.0	0.0	0.1	0.2	0.0

The Distribution Of Positive Results Greater Than (>) Selected Concentration Thresholds

ng/mL	HC	HM	OC	OM
N	5595	4282	5046	4544
%>100	95.8	88.7	97.6	97.0
%>300	78.6	48.8	87.0	84.5

Urine Specimen Combinations Containing Parent Drug And /Or Normetabolite

Drug/Metabolite	# Total Positives (Drug and/or Normetabolite)	Drug Present Without Nor-metabolite # (%)	Drug and Normetabolite Present # (%)	Normetabolite Present Without Drug # (%)
Codeine/ norcodeine	275	225 (81.8)	42 (15.3)	8 (2.9)
Hydrocodone/norhydrocodone	6538	1166 (17.8)	4429 (67.7)	943 (14.4)
Oxycodone/noroxycodone	5748	991 (17.2)	4055 (70.5)	702 (12.2)

Recommendations

- Opioid analytes
 - Oxycodone
 - Hydrocodone
 - Oxymorphone
 - Hydromorphone
- Cutoff concentration
 - Screen & confirm @ 100 ng/mL?
 - Screen & confirm @ 300 ng/mL?
- Consider normetabolites?
 - Noroxycodone
 - Norhydrocodone

Oral Fluid Information

- Spit happens!

Testing Advances Rapidly in Pain Management Arena

- Heltsley R, DePriest A, Black DL, Robert T, Marshall L, Meadors VM, Caplan YH, Cone EJ. Oral fluid drug testing of chronic pain patients. I. Propositive prevalence rates of licit and illicit drugs. J Anal Tox 2011;35
- Heltsley R, DePriest A, Black DL, Crouch DJ, Robert T, Marshall L, Meadors VM, Caplan YH, Cone EJ. Oral fluid drug testing of chronic pain patients. II. Comparison of paired oral fluid and urine specimens. J Anal Tox 2011;00:1-6

Oral Fluid Methodology

- N = 6441 patients
- Screened by ELISA for 14 drug/metabolite categories
- Confirmed by LC-MS-MS for 40 analytes at LOQs

Drug (Metabolite)	Oral Fluid LC-MS-MS LOQs, ng/mL	Urine Confirmation LOQs, ng/mL
Alprazolam	0.5	NT
(α -OH Alprazolam)	NT	50
Amphetamine	5	80
Buprenorphine	0.5	1
(Norbuprenorphine)	2	2
Butalbital	25	200
Carisoprodol	10	100
(Meprobamate)	10	100
Clonazepam	1	NT
(7-Aminoclonazepam)	NT	50
Cocaine	2	NT
(Benzoyllecgonine)	2	20
Codeine	1	50
Diazepam	1	NT
(Nordiazepam)	1	50
(Oxazepam)	0.5	50
(Temazepam)	0.5	50
Fentanyl	0.1	1
(Norfentanyl)	0.5	1
Hydrocodone	1	50
(Hydromorphone)	1	50
(Norhydrocodone)	1	50
(Dihydrocodeine)	1	50
Hydromorphone	1	50
Lorazepam	1	50
Methadone	2	50
(EDDP)	1	50
Methamphetamine	8	80
Morphine	1	50
(Hydromorphone)	1	50
Oxycodone	1	50
(Oxymorphone)	1	50
(Noroxycodone)	1	50
Propoxyphene	5	50
(Norpropoxyphene)	1	50
Temazepam	0.5	50
(Oxazepam)	0.5	50
Tetrahydrocannabinol	1	NT
(THCCOOH)	2	2
Tramadol	20	50
(N-Desmethyltramadol)	20	50
(O-Desmethyltramadol)	20	50

Oral Fluid: Confirmation Results

(Heltsley et al., JAT, 2011)

Drug	% Confirmed
Opiates	27
Oxycodone	24
Propoxyphene	2
Tramadol	4
Amphetamines	2
Barbiturates	1
Benzodiazepines	11
Buprenorphine	2
Cannabinoids	4
Carisoprodol	7
Cocaine	4
Fentanyl	5
Methadone	7
Methamphetamine	0

- Oral fluid (n = 9337)

Oral Fluid: Oxycodone & Oxymorphone Data Sorted by Selected Cutoff Concentrations

(Screened @ 20 and Confirmed at LOQ = 1)

- Oxycodone (n = 1847)

Positives	N	%
>=LOQ (1)	1847	100%
>=30	1432	77.5%
>=20 to 29.99	109	5.9%
>=10 to 19.99	135	7.3%
>=1 to 9.99	171	9.3%

- Oxymorphone (n =1046)

Positives	N	%
>=LOQ (1)	1046	100%
>=30	81	7.7%
>=20 to 29.99	48	4.6%
>=10 to 19.99	142	13.6%
>=1 to 9.99	775	74.1%

Oral Fluid Hydrocodone & Hydromorphone Data Sorted by Cutoff Concentrations

(Screened @ 10 and Confirmed at LOQ = 1)

- Hydrocodone (n = 1843)

Positives	N	%
>=LOQ (1)	1843	100%
>=30	1250	67.8%
>=20 to 29.99	131	7.1%
>=10 to 19.99	185	10.0%
>=1 to 9.99	277	15.0%

- Hydromorphone (n = 305)

Positives	N	%
>=LOQ (1)	305	100%
>=30	32	10.5%
>=20 to 29.99	11	3.6%
>=10 to 19.99	25	8.2%
>=1 to 9.99	207	77.7%

Oral Fluid Morphine & Codeine Data Sorted by Cutoff Concentrations

(Screened @ 10 and Confirmed at LOQ = 1)

- Morphine (n = 619)

Positives	N	%
>=LOQ (1)	619	100%
>=30	222	35.9%
>=20 to 29.99	68	11.0%
>=10 to 19.99	130	21.0%
>=1 to 9.99	199	32.1%

- Codeine (n = 136)

Positives	N	%
>=LOQ (1)	136	100%
>=30	40	29.4%
>=20 to 29.99	11	8.1%
>=10 to 19.99	9	6.6%
>=1 to 9.99	76	55.9%

Recommendations

- Opioid analytes
 - Oxycodone
 - Hydrocodone
 - Oxymorphone
 - Hydromorphone
 - Morphine
 - Codeine
- Cutoff concentration
 - Screen @ 30 ng/mL
 - Confirm @ 15 ng/mL

And...If there is time???

- Time flies
 - We could make a few urine to oral fluid comparisons

Drug Prevalence: Urine vs. Oral Fluid

Two separate pain
patient populations

- Urine (n=10,922)
- Oral fluid (n=9,337)

Drug	Urine % Pos	Oral Fluid % Pos
Opiates	56.7	51.0
Amps	1.0	2.0
Cannabis	6.1	4.0
Cocaine	2.0	4.0
Benzos	15.1	11.0
Methadone	7.6	7.0
Cariso/Mep	3.9	7.0
Propox	2.4	2.0
Fentanyl	2.9	5.0
Barbs	1.9	1.0

Oral Fluid vs. Urine (paired specimens) Overall Agreement Comparison

(n=1544 Paired Tests)

	OF Positive	OF Negative
Urine Positive	329++	148+-
Urine Negative	83--	984--

- Sensitivity = 69%
- Specificity = 92.2%
- Agreement = 85%
- Agreement expected by chance 58.9%
- Cohen's Kappa = 0.64 ("Substantial")

Oral Fluid vs. Urine (paired specimens)

DHHS Agreement Comparison (4 Drug Categories)

(n=263 Paired Tests)

	OF Positive	OF Negative
Urine Positive	35++	11+-
Urine Negative	9-+	208--

- Sensitivity = 76.1%
- Specificity = 95.9%
- Agreement = 92.4%
- Agreement expected by chance 71.6%
- Cohen's Kappa = 0.73 ("Substantial")

Summary

- Comparisons of urine to oral fluid appear to be favorable
 - Approximately equal positivity
 - Some differences in drug group detection rates should be expected