A Primary Care Perspective of Opioid-Use Risk Reduction, Addiction Management and Withdrawal Support

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Objectives

1. Describe clinical tools to reduce opioid-use risk
2. Discuss naloxone intranasal spray and Alaska laws for prescribing and dispensing
3. Review pharmacology of medications used for opioid addiction treatment
4. Discuss medications commonly used to assist with opioid withdrawal symptoms

Disclosures

Drs. Crowe and Li have nothing to disclose.

Pre-Test

1) Which method of urine drug testing is the most prone to false positives?

2) What criteria does the CDC recommend for naloxone prescribing?

3) Of morphine, buprenorphine and naltrexone, place these in order of affinity at the mu opioid receptor.

4) What is the purpose of hydroxyzine in opioid withdrawal?

Tools for Opioid Risk Reduction

Pill Counts

Urine Drug Screens

AK Prescription Drug Monitoring

Intranasal Naloxone

Introduction

- The 2016 CDC guideline for opioid use in chronic pain explored the following risk reduction strategies in their analysis
  - instruments for predicting risk for opioid overdose, addiction, abuse or misuse
  - patient education
  - urine drug testing
  - prescription drug monitoring program (PDMP) data
  - monitoring instruments
  - monitoring intervals
  - pill counts
  - abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse
  - comparative effectiveness of treatment strategies for managing patients with addiction
- Uniformly recommended
- No studies except the risk prediction tools

Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

No data, no problem?

"As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials."

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ : British Medical Journal. 2003;327(7429):1459-1461.

Communication is Key

Remember, nothing happens in a vacuum.

Understanding the
WHY
is as important is determining the
WHAT

Pill Counts

Pill Counts

Widely recommended, but little guidance for how to go about it.

Best practices

- Schedule randomly, mid-fill
  - More than once a year, esp. if early refill requests arise
- Know what the pills look like
- Know what the count *should* be first
  - Requires review of the last few months
- Always have two people in the room
- Never take medications out of the presence of the patient
- Document everything

Pill Counts

What is the benefit/harm?

Potential Benefit
- Identifies potential over or under use
- Identifies potential diversion
- Chance to check in with treatment plan

Potential Harm
- May convey lack of trust

Urine Drug Screens (UDS)

Urine Drug Screens

Should be simple, but...

Best Practices
- Know the difference between IG testing and GC/MS
- Know your metabolites
- Always ask when the last dose was taken prior to getting urine & document it
- As with pill counts, do mid-fill
- If they cannot produce urine, reschedule within 3 days
  - Most drugs remain in urine that long

Urine Drug Screens

What is the benefit/harm?

Potential Benefit
- Confirms what should be there
- Identifies what should not be there
- Chance to check in with treatment plan

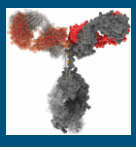
Potential Harm
- May convey lack of trust

Urine Drug Screens - IG vs GC/MS

Immunoglobulin (IG) Testing
- Initial Screen
- Immunoassay
- Qualitative
- Cheap
- ↑sensitivity ↓specificity
- Very prone to cross reactivity
  - Which depends on type of machine
- Higher concentrations required

Gas chromatography mass spectrometry (GC/MS)
- Confirmatory Screen
- Molecularly Identified
- Quantitative
- Not as cheap
- ↑sensitivity ↑specificity
- Nearly no cross reactivity
  - Exception: D&L isomer of methamphetamine
- Lower concentrations detected

Immunoglobulin UDS



UDS-IG Pearls

Is what you see what you get with IG tests?

Nope…

Potentially inappropriate positives
- Metabolic Conversions
- Non-illicit Exposures
- Cross reactivity

Potentially inappropriate negatives
- Limited test specificity
- Substance absent from urine
  - Pharmacologic induction
  - Genetic Polymorphism
- Diluted urine
- Specimen Manipulation

UDS-IG Common Substances Detected

Table 3. List of analytes commonly detected by commercial immunoassays[a].

Assay	Analytes
Amphetamines	Amphetamine, ephedrine, methamphetamine, methylenedioxyamphetamine, methylenedioxymethamphetamine, phentermine, phenylpropanolamine, pseudoephedrine
Barbiturates	Amobarbital, butabarbital, butalbital, pentobarbital, phenobarbital, secobarbital, thiopental
Benzodiazepines	Alprazolam, α-hydroxyalprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, midazolam, nordiazepam, oxazepam, temazepam, triazolam, α-hydroxytriazolam
Cannabinoids	Δ⁹-tetrahydrocannabinol, 11-hydroxy-Δ⁹-tetrahydrocannabinol, 11-nor-Δ⁹-tetrahydrocannabinol-9-carboxylic acid
Cocaine	Benzoylecgonine, cocaine, cocaethylene, ecgonine, ecgonine methyl ester
Methadone	l-α-acetyl-methadol, methadone
Methaqualone	Hydroxymethaqualone, methaqualone
Opiates	Codeine, dihydrocodeine, hydrocodone, hydromorphone, morphine, morphine-glucuronide
Phencyclidine	Phencyclidine, phencyclidine analogs
Propoxyphene	Norpropoxyphene, propoxyphene

[a]This list is not all-inclusive. Refer to assay package inserts for a complete list of analytes commonly detected by commercial immunoassays.
Data from [95].

Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. Bioanalysis. 2009;1(5):937–952. doi: 10.4155/bio.09.81.

UDS-IG Common Cross Reactions

Drug	Method	Interference	Ref.
Opiates	EMIT II, AxSYM FPIA, CEDIA, Roche Abuscreen OnLine reagents, Beckman opiate reagents	[+] Quinolones	[58]
	EMIT	[-] Tolmetin	[59]
	Syva RapidTest Genix RapidTech	[+] Rifampin	[59]
	EMIT II	[+] Ofloxacin	[60]
THC	EMIT	[+] Efavirenz	[61]
	EMIT	[+] Ibuprofen, naproxyn	[62]
	GC–MS	[-] Ibuprofen	[63]
	EMIT	[-] Tolmetin	[61]
	EMIT	[+] Pantoprazole	[92]
Cocaine	EMIT, EMIT II	[-] Salicylates	[6,2,65]
	GC–MS	[-] Fluconazole	[29,30]

Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. Bioanalysis.2009;1(5):937–952. doi: 10.4155/bio.09.81.

UDS-IG Common Cross Reactions

Amphetamines	EMIT II	[+] Benzphetamine, phenmetrazine, phentermine, ephedrine, mephentermine	[66]
	FPIA	[+] Mephentermine, phenmetrazine, phentermine, phenylpropanolamine, tyramine	[66]
	EMIT	[-] Tolmetin	[59]
	FPIA, GC–MS	[+] Selegiline	[67]
	EMIT	[+] Phentermine	[68]
	EMIT II	[+] Trazodone	[69]
	CEDIA, EMIT II	[+] Bupropion	[70,71]
	FPIA	[+] Fluorescein	[13]
	EMIT	[+] Ciprofloxacin, mefanamic acid, metronidazole, tolmetin	[13]
	EMIT II Plus	[+] Phenothiazines	[72,73]
	Bio-Quant amphetamine ELISA	[+] Phentermine, phenylethylamine	[74]
	Bio-Quant methamphetamine ELISA	[+] Ephedrine, pseudoephedrine	[74]
	EMIT II Plus	[+] Pseudoephedrine	[75]
	Biosite Triage	[-] Chlorpromazine metabolites	[76]

Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. Bioanalysis.2009;1(5):937–952. doi: 10.4155/bio.09.81.

UDS-IG Common Cross Reactions

Benzodiazepines	EMIT d.a.u. FPIA CEDIA	[+] Oxaprozin	[77]
	FPIA	[+] Fenoprofen, flurbiprofen, indomethacin, ketoprofen, tolmetin	[57,78]
Methadone	Integra Methadone II	[+] Quetiapine	[79,80]
	Integra Methadone II	[+] Cyamemazine, levomepromazine, possible olanzapine	[81]
Buprenorphine	CEDIA	[+] Morphine, [+] methadone, [+] codeine, [+] dihydrocodeine	[82–84]

CEDIA: Cloned Enzyme Donor Immunoassay (Microgenics Corporation); EMIT: Enzyme-Multiplied Immunoassay Technique (Dade Behring Incorporated); FPIA: Fluorescence polarization immunoassay; Positive [+] indicates an interference resulting in false positive results; negative [-] indicates interference resulting in false-negative results.

Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. Bioanalysis.2009;1(5):937–952. doi: 10.4155/bio.09.81.

UDS-IG Common Cross Reactions

Wait! What about poppy seeds!?

Other Sources

- Poppy seeds → + opiates
  - In clinical setting with low threshold
- Coca tea → cocaine
  - Tea not sold in US
- Cannabinoids + with:
  - Dronabinol (Marinol®)
  - THC/cannabidiol UK (Sativex®)
- Cannabinoids NOT + with:
  - Nabilone (Cesamet®)

Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. Bioanalysis.2009;1(5):937–952. doi: 10.4155/bio.09.81.

GC/MS UDS

UDS-GC/MS Pearls

Is what you see what you get with GC/MS tests?

Yes! (mostly)

Potentially inappropriate positives
- Methamphetamine

Potentially inappropriate negatives
- Substance absent from urine
  - Pharmacologic induction
  - Genetic polymorphism
- Diluted urine
- Specimen manipulation

UDS-GC/MS Pearls

The trouble with methamphetamine… isomerism.

- Methamphetamine has two forms; dextro (d) and levo (l)
  - CNS activity (l) < (d)
- Some medications produce one or both! We need further tests.

UDS-GC/MS Pearls

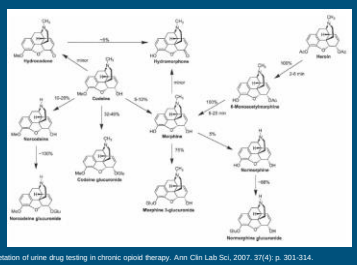
Table 1[2,3,5,6]

Drug (Active agent)	Metabolizes to:	AMP/MAMP Ratio
Illicit Methamphetamine (*d*-methamphetamine)	*d*-amphetamine and may contain small amounts of *l*-amphetamine	0.04 – 0.37
Didrex[a,c] (benzphetamine)	*d*-amphetamine and *d*-methamphetamine	0.53 – 11.17
Desoxyn[a,c] (*d*-methamphetamine)	*d*-amphetamine	0.1 – 2.6
Eldepryl[b], **Emsam**[b] **Zelapar**[b] (selegiline)	*l*-amphetamine and *l*-methamphetamine	0.28 – 0.36
Vicks® Nasal Inhaler *(OTC)* (*l*-methamphetamine)	*l*-amphetamine (conversion is relatively slow).	0.0 – 0.12

[a]Schedule III controlled substance [b]Schedule II controlled substance

Urine Drug Screen

Know your metabolites!



Reisfield G.M., Salazar E., Bertholf R.L., Rational use and interpretation of urine drug testing in chronic opioid therapy. Ann Clin Lab Sci, 2007. 37(4): p. 301-314.

UDS - Know your metabolites!

Opioids		Benzodiazepines	
Heroin	Morphine	Clorazepate	Oxazepam
Morphine	Hydrocodone	Chlordiazepoxide	Oxazepam
Codeine	Morphine, Hydrocodone	Diazepam	Temazepam, Oxazepam
Hydrocodone	Hydromorphone		
Oxycodone	Oxymorphone		

*List limited to metabolites that are themselves parent drugs.

Example Results

Buprenorphine	A POS-501.361	A POS-323.227	A POS-163.994	A POS-314.684	A POS-445.175
Norbuprenorphine	A POS-582.187	A POS-354.153	A POS-236.750	A POS-1000.361	A POS-1048.007
Synthetic Opioids					
Fentanyl	NEG	NEG	NEG	NEG	NEG
Norfentanyl	NEG	NEG	NEG	NEG	NEG
Methadone	NEG	NEG	NEG	NEG	NEG
EDDP (Methadone metabolite)	NEG	NEG	NEG	NEG	NEG
Tramadol	NEG	NEG	NEG	NEG	NEG
O-desmethyl-tramadol	NEG	NEG	NEG	NEG	NEG
N-desmethy-tramadol	NEG	NEG	NEG	NEG	NEG
Tapentadol	NEG	NEG	NEG	NEG	NEG
Meperidine	NEG	NEG	NEG	NEG	NEG
Normeperidine	NEG	NEG	NEG	NEG	NEG
Benzodiazepines					
Alpha-Hydroxyalprazolam	NEG	NEG	NEG	NEG	NEG
7-Amino-Cloazepam	NEG	NEG	NEG	NEG	NEG
Lorazepam	NEG	NEG	NEG	NEG	NEG
Nordiazepam	NEG	NEG	A POS-63.815	A POS-305.053	A POS-1187.860
Temazepam	NEG	A POS-112.523	A POS-275.033	A POS-1916.087	A POS-4868.612
Oxazepam	A POS-61.090	A POS-600.301	A POS-706.255	A POS-3072.922	A POS-5968.670

Controlled Prescription Drug Monitoring

Alaska State Prescription Drug Monitoring

No one is an island.

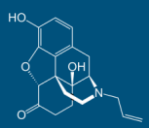
- AKPDMP reports the last two years of controlled medication history
  - Watch for alternate name spellings
  - Flags for risk behavior (# pharmacies and # prescribers)
  - Starting to include out-of-state fills
- Recommended use
  - Prior to dispensing at every fill of a controlled medication (CII and III)
  - When researching controlled medication history

Alaska State Prescription Drug Monitoring

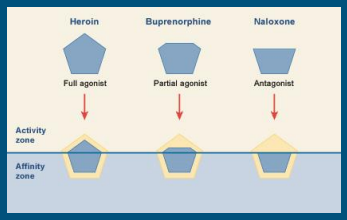
Not just for pharmacists anymore?

- AK Senate Bill 74
  - Licensed prescribers of controlled substances
    - Must have AKPDMP access
    - For Schedule II and III
      - Must check AKPDMP prior to prescribing unless
        - Inpatient
        - ED
        - 48 hours post-op
        - Script < 3 days

Intranasal Naloxone



Naloxone: Mechanism of Action



Adapted from Jones, H. E. (2004). 'Practical considerations for the clinical use of buprenorphine'. Science & Practice Perspectives 2, no. 2, pp. 4-20.

Naloxone Intranasal Kit

The CDC recommends providing naloxone intranasal spray in the following situations:

- History of overdose
- History of substance use disorder
- Prescribed opioid dose ≥50 MME/day
- Co-prescribed a benzodiazepine

https://www.cdc.gov/drugoverdose/pdf/guidelines_factsheet-a.pdf

Alaskan Law and Naloxone

- SB 23: This act was approved in March of 2016
  - Pharmacist can dispense opioid overdose drug (intranasal naloxone) without a prescription
  - Training required - follow board rules
    - C.f. Board of Pharmacy Regulation re: Standards for Independent Dispensing by a Pharmacist of an Opioid Overdose Drug (12 AAC 52.994)
- Provides immunity to those prescribing, providing, or administering opioid overdose drugs to a person

The Alaska State Legislature Senate Bill 23

Opioid Addiction Treatment

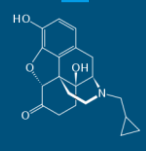
How to stay safe and functional.

Naltrexone

Buprenorphine +/- Naloxone

Transitions of Care

Naltrexone



Naltrexone

Purpose of use in addiction treatment: reversibly blocks or attenuates the effects of opioids

Naltrexone prescribing

For opioid addiction, naltrexone is only to be prescribed after a person has gone through opioid withdrawal.

Prescribing regimens:

Oral: Initial 25 mg; if no withdrawal signs occur, administer 50 mg/day thereafter

IM: 380 mg IM once every 4 weeks

Best prescribed and administered 7-10 days after the last dose of opioid.

Naltrexone vs. Naloxone

Naltrexone
Oral Bioavailability: Variable (5-40%)
Half-life:
- Oral: 4 hours (active metabolite 13 hours)
- IM: 5-10 days

Duration of action:
- Oral: 24-72 hours (dose dependent)
- IM: 4 weeks

Purpose: Opioid antagonism to prevent action of opioid agonists on the mu opioid receptor.

Naloxone
Oral Bioavailability: Poor
Half-Life:
- IM, IV, or SC: 0.5-1.5 hours,
- Intranasal: ~2 hours

Duration of action:
- 30-90 minutes

Purpose: Acute opioid antagonism to reverse effects of opioid overdose.

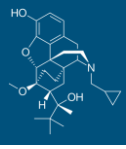
Naltrexone for Alcohol Addiction?

Alcohol: Alcohol is a complex substance, affecting a number of chemical systems in the brain. Among other effects, it is suspected that, when an alcoholic drinks, the brain's opioid system releases endorphins triggering reinforcement that entices the person to drink more. Naltrexone blocks opioid receptors in the brain (it is an antagonist), and this has been proposed as stemming the endorphin-mediated reinforcing effects of drinking alcohol.

Opioids: Naltrexone is a direct acting opioid antagonist. This medication binds with opioid receptors and blocks the effects of opioid medications.

Leavitt, Stewart. Evidence for the efficacy of naltrexone in alcohol dependence (alcoholism). Addiction treatment forum: Naltrexone clinical update. 2002. Accessed December 2016

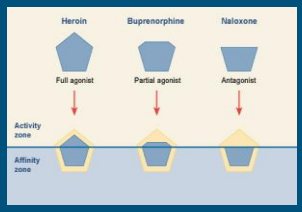
Buprenorphine



Buprenorphine

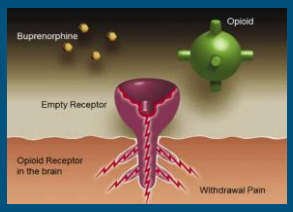
Mechanism of Action:

- Analgesic effect via binding to mu opiate receptors in CNS
- Partial mu agonist and partial kappa antagonist
- Analgesic effects plateau at high doses.
- Partial agonism attenuates certain opioid risks.



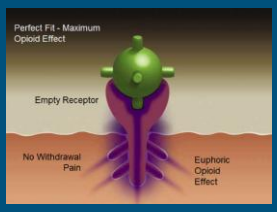
Buprenorphine

Buprenorphine and its purpose in opioid withdrawal



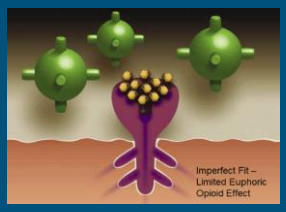
Buprenorphine

Opioid agonism to the mu opioid receptor



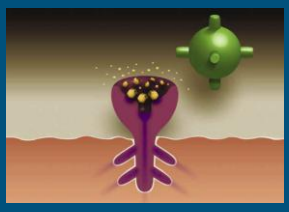
Buprenorphine

Partial agonism of the mu opioid receptor



Buprenorphine

Prevention of withdrawal only lasts so long



Buprenorphine Dosing

Initial induction based on Clinical Opiate Withdrawal Scale

- Buprenorphine/naloxone dosing:
  - Sublingual film: Up to 16 mg buprenorphine/ 4 mg naloxone daily
  - Sublingual tab: Up to 11.4 mg buprenorphine/ 2.9 mg naloxone daily
- Buprenorphine dosing:
  - Sublingual tab: Up to 16 mg/day
  - Buprenorphine/naloxone recommended of buprenorphine alone for unsupervised or maintenance therapy

Perioperative Management

What about the poor anaesthesiologists?

What happens when someone on high-dose buprenorphine for addiction needs anesthesia?

Buprenorphine and Anesthesia

Just the facts...

- Buprenorphine has 1000 times the receptor affinity at the mu receptor than morphine
  - Problem with peri- and postoperative pain management and anesthesia
- Half-life ranges from 20-73 hours
  - Enterohepatic cycling
- Duration of action depends on dose
  - < 4 mg -- 6-12 hours
  - > 16 mg -- 24-72 hours

Possible Options

- Stay on buprenorphine
  - Use greater doses of opioid for analgesia perioperatively (risky)
  - TID buprenorphine post-op for a time
- Transition to full opioid
  - Taper buprenorphine 14 days pre-op (stop days prior)
  - Start full agonist, continue thru and taper post-op
  - TID buprenorphine post-op for a time
- Methadone
  - For high risk persons

Stern, Elizabeth E., "Buprenorphine And The Anesthesia Considerations: A Literature Review" (2015). Nurse Anesthesia Capstones. Paper 2. http://dune.une.edu/na_capstones/2

Withdrawal Support

Withdrawal Support

People rarely die from opioid withdrawal… but that doesn't mean it's pleasant. We can help!

Signs/symptoms of Opiate Withdrawal

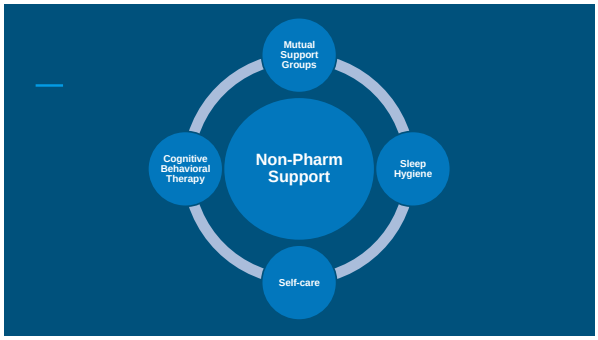
- Anxiety
- Depression
- Sleep Disturbance
- Fatigue
- Dysphoria
- Irritability

Acute withdrawal 4-10 days, but some symptoms can last weeks to months!

Substance Abuse Treatment Advisory, SAMHSA: July 2010; vol 9, Issue 1

Pharmacologic Withdrawal Support

Sympathetic Outflow	• Clonidine
Sleep	• Melatonin • Rozerem
Nutrition	• Vitamin supplementation (Zinc, Calcium, Magnesium, etc..)
Diarrhea	• Loperamide
Anxiety and emotional distress	• Quetiapine • Hydroxyzine



Post-Test

1) Which method of urine drug testing is the most prone to false positives?

a. Immunoglobulin Testing

2) What criteria does the CDC recommend for naloxone prescribing?

a. History of overdose, history of substance abuse, MME >50, concurrent benzodiazepine prescription

3) Of morphine, buprenorphine and naltrexone, place these in order of affinity at the mu opioid receptor.

a. Buprenorphine > naltrexone > morphine

4) What is the purpose of hydroxyzine in opioid withdrawal?

a. Hydroxyzine is an antihistamine that can help reduce symptoms of anxiety related to opioid withdrawal as well as reducing the effects of nausea and vomiting.

Questions?