

Forensic Toxicology:
An Update on OTC and Illicit Drugs



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Objectives

- 1-Discuss laboratory methods for detecting drugs post-mortem
- 2-Describe newer illicit drugs symptoms and signs of intoxication and laboratory detection
- 3-Describe over the counter drug toxicity as it relates to medical examiners

Clinical vs. Forensic Toxicology

- Clinical:
 - emergency screening (e.g. overdose)
 - therapeutic drug monitoring (TDM) (limited menu of drugs)



Testing only done if likely to affect the management and course of clinical treatment.

Forensic Toxicology

Broad based screening and measurement for legal purpose

- Postmortem (ME/Coroner)
- Criminal (MVA; assault)
- Workplace drug testing
- Sports (human & animal)

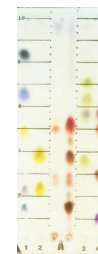


Why?

- Cause of death?
- Contribution to death?
- Cause Impairment?
- Explain Behavior?
- Footnote: Drug or alcohol caused deaths almost never show specific signs at autopsy.

How?

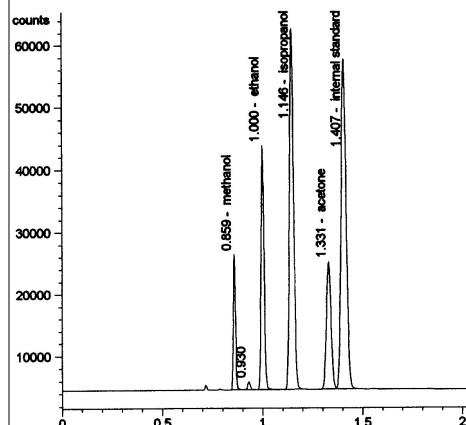
- Immunoassay
- TLC
- GC
- HPLC
- **GC/MS—85% of drug identification**
- LC/MS
- (AA; ICP-MS)



What are the (Analytical) Problems?

- 1. Endogenous substances
 - cholesterol, fats, proteins
 - putrefactive amines
- 2. Enormous range of drug concentrations
 - therapeutic concentrations range over at least 100,000 fold
 - can vary >1000x even for single class of drugs
- 3. Some drugs cannot be readily detected
 - Analytical conditions may not be appropriate
 - Drug/poison may be new or very unusual

“Forensic” Alcohol



Forensic

VS.



Clinical

Intoxication?

- A young man appeared intoxicated on a trans-Canada Greyhound bus
- Police met the bus; escorted the man to hospital at 2.30 am
- Examined; released to police & placed in cells to “sober-up”
- Found with agonal breathing 7 am; died shortly after
- Blood alcohol “0”; acetone 170 mg/100mL
- Blood glucose 1930; vitreous 1224 mg/100mL

Postmortem Fermentation

Blood ON ITS OWN is UNRELIABLE as a specimen for assessing the presence of alcohol at the time of death.



Blood

Vitreous

Postmortem Fermentation

- 86 y.o. lady died suddenly from heart disease; autopsy ordered and blood taken for routine toxicology
- Blood alcohol 320 mg/100 ml
 - Urine 0; bile 20 mg/100 ml
- No evidence of alcohol abuse
- No alcohol in morgue
- Meds in blood and urine correlated
 - Warfarin & digoxin; also blood typing

Carbon Monoxide Deaths

Some are obvious...



Carbon monoxide binds to hemoglobin 200x stronger than oxygen!

Carbon Monoxide Deaths

Some sources are less obvious...



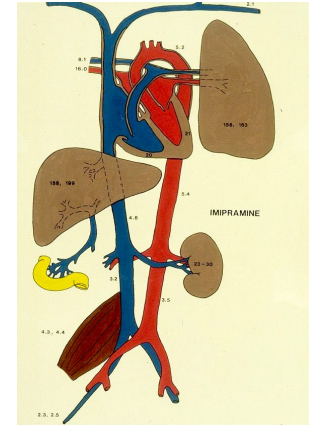
Postmortem Redistribution

> False Premise

- Blood levels of drugs after autopsy reflect those at the time of death

> Reality

- Many drug levels increase after death; some 2–10 fold
- Many mechanisms
- Some drug levels decrease after death (e.g. cocaine)



Other Interpretation Issues

- Combined Drug Deaths
 - additive or synergistic toxicity
- Tolerance
 - need to increase dose for same effect
- Genetically Impaired Metabolism
 - 7-10% Caucasians are slow metabolizers
- Drug-Drug Interactions
 - can cause synergistic or fatal toxicity

Other Interpretation Issues

- Drug Accumulation
 - caused by decreased metabolism or clearance
- Medical Artifacts
 - intravenous lines; incomplete distribution
- Delayed deaths
 - drug toxicity causes physiological damage; drugs levels may fall to near zero before death occurs

Toxicity

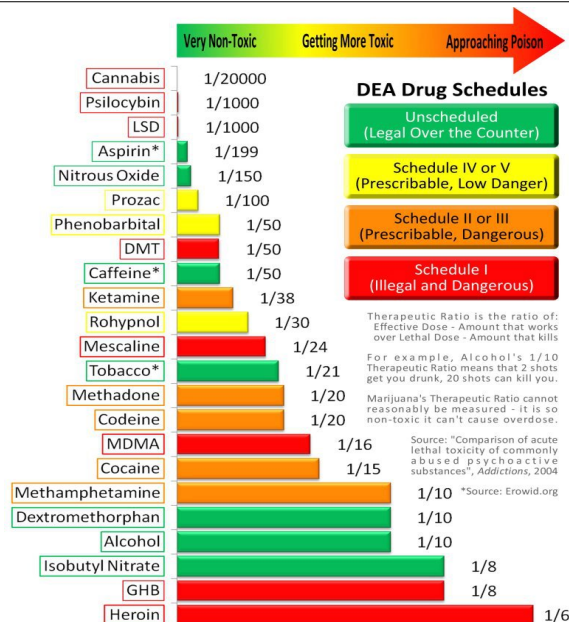
- LD_{50} – refers to amount of substance that would kill 50% of test population within 4 hrs.
- Typically represented as (mg subst. / kg weight)

LD_{50} information

<1 mg/kg = taste to drop ~500 mg/kg = ounce
 ~50 mg/kg = teaspoon ~5000 mg/kg = pint

Sugar - LD_{50} =29700 Caffeine - LD_{50} =192
 Ethanol - LD_{50} =7060 Nicotine - LD_{50} =48
 Salt - LD_{50} =3000 Cyanide - LD_{50} =6.4

Botulinum toxin - LD_{50} =0.00005



Roles of the Toxicologist

- Must identify one of thousands of drugs and poisons
- Must find nanogram to microgram quantities dissipated throughout the entire body
- Not always looking for exact chemicals, but metabolites of desired chemicals (ex. heroin → morphine within seconds)

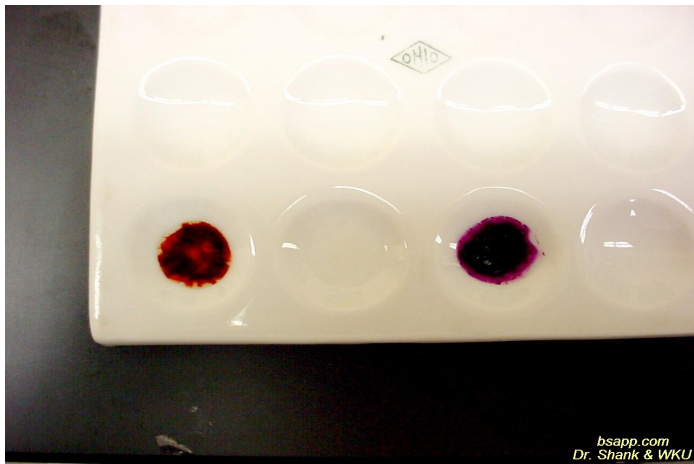
Toxicology Procedures

- Presumptive/Screening
 - quick test to narrow down possibilities
 - spot/color tests
- Confirmation
 - determines exact identity
 - thin-layer/gas chromatography, IR spectroscopy, mass spectrometry

Presumptive/Screening

- **Marquis Test:**
 - Turns purple in the presence of opiates
 - Turns orange-brown in presence of amphetamines
- **Scott Test:**
 - Turns blue in the presence of cocaine
- **Duquenois-Levine:**
 - Turns purple in the presence of tetrahydrocannabinol

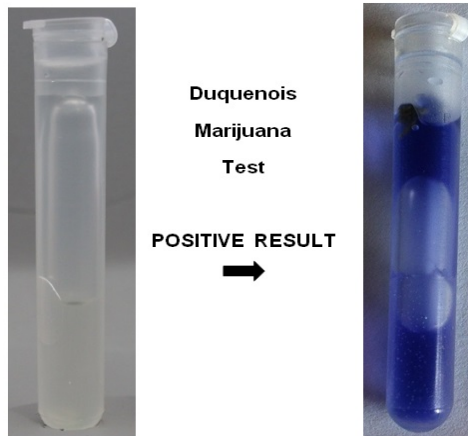
Marquis Test



Scott Test



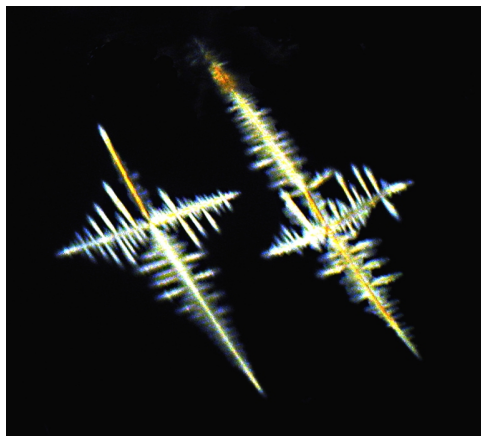
Duquenois-Levine



Confirmatory Tests

- **Microcrystalline Tests:** Identifies drug by using chemicals that react to produce characteristic crystals
- **Chromatography:** Separates drugs and gives tentative ID
- **Mass Spectrometry:** Chemical “fingerprint” – no two drugs fragment the same
- **IR Spectroscopy:** IR light is absorbed by different chemicals

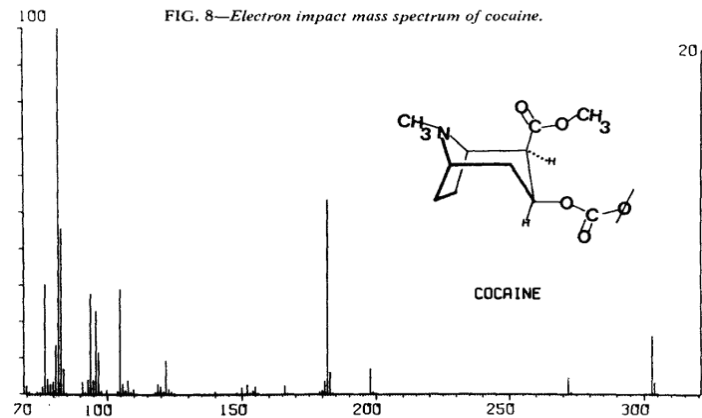
Microcrystalline Tests



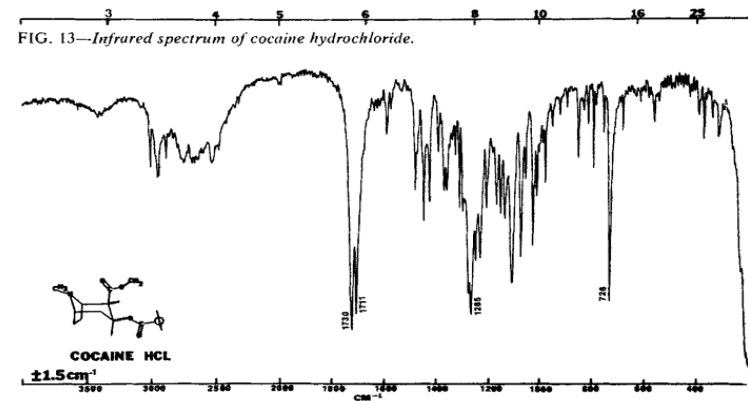
Chromatography



Mass Spectrometry



IR Spectroscopy



Testing Samples

- Divided into 2 samples
 - 1st sample is for screening test
 - 2nd sample is for confirmatory test
 - Only done for samples that test positive during screening

Testing Samples

- Blood
 - 10 mL whole blood, anticoagulant, preservative
 - More expensive, but more accurate, can detect hours to days usage
- Urine
 - Samples always given under direct supervision
 - Easy, cheap, can detect hours to days usage

Testing Samples

- Hair samples
 - Collected from scalp or body
 - Can detect days to months usage
- Saliva
 - Can detect hours to ~2 days usage
- Vitreous humor
 - Only used post-mortem
 - Resists putrefaction, can detect usage after embalming

Initial Approach to ODs

- Try to determine type of exposure
 - Acute
 - Chronic
 - Acute-on-chronic

Diagnosis of Toxic Agent

- Personal history is often unreliable. Question patient, family members, witnesses to the exposure for identity of agent
- Retrieval of the container from which the exposure came from is important, Try to ascertain the exact agent, quantity and time of exposure if able
- Past medical history is often a clue to ingestants
- Don't forget OTC medications, herbals, etc as possible ingestants
- Medications of other household members can be helpful

Evaluation of Patient

- Certain groupings of symptoms called “toxidromes” can lead you to the agent:
 - Ex. A patient breathing 6 times/minute with a significantly high pCO₂, pinpoint pupils, and obtundation is probably some sort of opioid OD

Table 2. Common Toxidromes.

Type of Agent	Physical Findings	Potential Antidotes
Stimulant (e.g., cocaine)	Tachycardia, restlessness, excessive speech and excessive motor activity, tremor	Benzodiazepines
Sedative hypnotic (e.g., ethanol)	Sedation, confusion, delirium, hallucinations, coma, slurred speech, ataxia	Supportive therapy
Opiate (e.g., heroin)	Altered mental status, miosis, unresponsiveness, slow respiratory rate, hypothermia	Naloxone
Anticholinergic agent (e.g., belladonna, diphenhydramine), "dry"*	Fever, ileus, flushing, tachycardia, urinary retention, dry skin, blurred vision, mydriasis, psychosis	Physostigmine
Cholinergic agent (e.g., organophosphate pesticide, sarin gas), "wet"	Salivation, lacrimation, urination, defecation, gastrointestinal distress (diarrhea), emesis (referred to as SLUDGE), and bronchorrhea	Atropine Pralidoxime

* The toxidrome of anticholinergic agents may be remembered as "hot as a hare, dry as a bone, red as a beet, mad as a hatter."

<http://content.nejm.org/content/vol355/issue6/images/large/13t2.jpeg>. Accessed 8/20/07

Laboratory Markers in OD

- ABGs, Electrolytes, LFTs, urine toxicology, blood alcohol levels in nearly all patients.
- Serum osmolality can be an early marker of different alcohol toxicity—it should be checked in all suspected ODs
- Serum ASA and APAP in all patients.
- Selected quantitative levels of specific agents if necessary (e.g. theophylline levels if that's the suspected OD)

History of meth

- Amphetamine created in Germany in 1887
- Used widely during WWII by the Nazi and Japanese armies
- Japanese kamikaze pilots were documented to be high on meth
- Major challenge in postwar Japan
- Biker gangs in California after WWII began to distribute meth

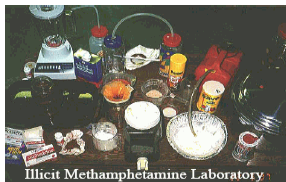
Today, A World Wide Problem

- Cocaine: 10 million regular users
- Heroin: 15 million regular users
- Meth: 42 million regular users

Source: World Health Organization. Cited by Richard Rawson (UCLA Integrated Substance Abuse Programs, and Pacific South West Addiction Technology Transfer Center), "Meth: A Focus on Women and Children," Women and Children in Recovery Conference of the Indiana Family and Social Services Administration, Division of Mental Health and Addiction, IN Government Building, April 7, 2005

Components for Making Meth

- Precursor (pseudoephedrine)
- Reagent: e.g., water reactive metal (lithium, sodium, red phosphorous, iodine, sodium hydroxide)
- Solvent (acetone, alcohol, benzene, camp fuel, chloroform, ethanol, ether, methanol, mineral spirits, paint/lacquer thinner, toluene, xylene)
- Glassware and hardware



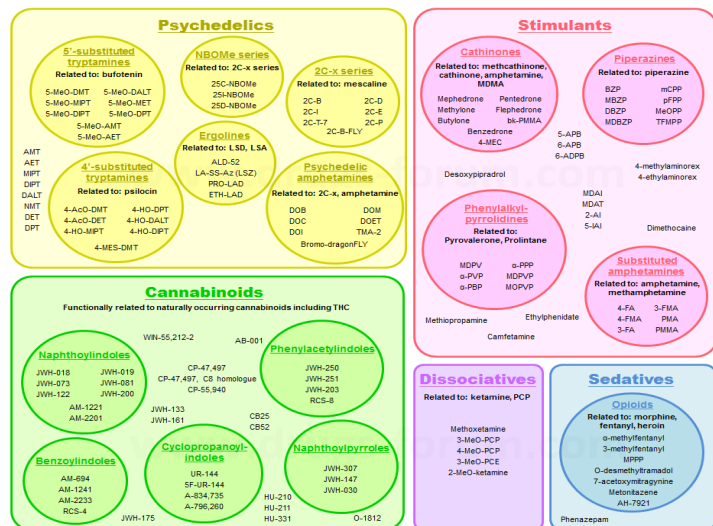
Source: DEA.

Forensic Toxicology of Meth

- Postmortem blood concentrations have been described to range from 1.4 to 13 mg/L in abusers who died of traumatic injury by violent means
- Deaths resulting from overdose have been shown with methamphetamine concentrations ranging from 0.09 to 18 mg/L, with an average of 1.0 mg/L
- Blood/plasma ratio for methamphetamine is ~0.6–0.7
- T_{1/2} 7-34 hours
- Postmortem blood concentrations are ~1.5 times greater than antemortem concentrations.

McIntyre IM, et al. *Journal of Analytical Toxicology*, 2013; 37, 386–389

“Designer” Psychoactive Substances



SOURCE: <http://www.drugs-forum.com>, updated 2013.

Synthetic Cannabinoids

- Wide variety of herbal mixtures
- Marketed as “safe” alternatives to marijuana
- Brand names include: “Spice,” “K2,” fake weed, “Yucatan Fire,” “Skunk,” “Moon Rocks,” herbal incense, “Crazy Clown,” “Herbal Madness”
- Labeled “not for human consumption”
- Contain dried, shredded plant material (inert) and chemical additives that are responsible for their effects.



material

43

SOURCE: NIDA. (2012). *NIDA DrugFacts: Spice (Synthetic Marijuana)*.

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SYMPTOMS OF SYNTHETIC MARIJUANA USE

SYMPTOMS OF SYNTHETIC MARIJUANA USE

OVERALL SYMPTOMS

- Increased Agitation
- Paranoid Delusions
- Depression
- Hallucinations
- Exaggerated Thoughts of Suicide
- Feeling of Impending Doom
- Panic Attacks
- Heart Attacks

Please Call 911 IMMEDIATELY if you suspect someone has used Synthetic Marijuana!

Many of these symptoms may be life threatening and may change suddenly.

"Glazed" expression, red eyes

Psychosis

Inability to Speak

Body Temperature Fluctuation, Inability to Feel Pain, Seizures

Increased Blood Pressure and Heart Rate, Heart Attack

Temporary Paralysis, Cramping

Kidney Failure

Vomiting

Graphic by To The Maximus Foundation. Please use with attribution.

What are the Undesired Effects?

- Insomnia
- somatic pain
- nausea
- seizures
- agitation
- vomiting
- internal restlessness
- tremors
- palpitations
- headaches
- death
- perceptual alterations
- illusions
- visual and auditory hallucinations
- paranoia
- aggression
- depersonalization
- dissociation
- anxiety
- depressed moods
- hypertension
- hyperventilation

"Now with EXTRA rat poison"

- "Synthetic Cannabis Laced With Poison Linked to Severe Bleeding, CDC Warns"
 - Batches of K2/Spice distributed in the Midwest laced with brodifacoum, a highly potent vitamin K antagonist anticoagulant similar to warfarin
 - Numerous reports of severe even fatal bleeding throughout the upper Midwest
 - Be aware of this connection—PT/INR will be elevated in patients without liver disease or on warfarin

<https://www.cdc.gov/nceh/hsb/chemicals/sc/default.html>> Accessed 5/30/18

Problem: Detection is difficult

Analyses of samples for presence of synthetic cannabinoids in 141 suspected cases.

Sample (total)	Any SC (%)	XLR-11 (%)	CID (%)	XLR-11 and CID (%)	Nicotine (%)	No SC definitively identified (%)
Drug (36)	22 (61)	18 (50)	13 (36)	11 (31)	5 (14)	14 (39)
Blood (12)	9 (75)	9* (75)	Not detected	Not detected	Not detected	3 (25)
Urine (31)	24 (77)	23* (74)	21 (68)	20 (65)	Not detected	7 (23)

CID, carboxamide indazole derivatives, SC, synthetic cannabinoids,

*Suspected metabolite of XLR-11 (UR-144 compounds)

WHY? HUNDREDS of potential compounds act as SC

Sud, P, et al. West J Emerg Med. 2018 May;19(3):567-572

Synthetic Cathinones

- Could be MDPV, 4-MMC, mephedrone, or methylene
- Sold on-line with little info on dosage, etc.
- Advertised as legal highs, legal meth, cocaine, or ecstasy
- Taken orally or by inhaling
- Serious side effects include tachycardia, hypertension, confusion or psychosis, nausea, convulsions
- Labeled “not for human consumption” to get around laws prohibiting sales or possession



SOURCE: Wood & Dargan. (2012). *Therapeutic Drug Monitoring*, 34, 363-367.

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Synthetic Cathinones are β -keto ('bk') Analogs of Amphetamine



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Emergency Room Visits Related to Synthetic Cannabis and Cathinones: DAWN, 2011

	% Male	% Under Age 21	% Sent to ICU or Sub. Abuse Treatment	% Discharged Home
Synthetic Cannabis	70%	55%	3%	78%
Synthetic Cathinones	76%	14%	12%	55%

SOURCE: OAS, SAMHSA-CSAT. (2013). Drug Abuse Warning Network, 2011 data.

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Recognizing Synthetic Cathinone Intoxication

- Present with severe sympathetic stimulation:
 - Tachycardia
 - Hypertension
 - Hyperthermia
 - Seizures
- Present with profoundly altered mental status:
 - Severe panic attacks
 - Agitation
 - Paranoia
 - Hallucinations
 - Suicidal behavior



SOURCE: NYS OASAS. (2012). *Clinical Guidance of Synthetic Drugs of Abuse*, draft document.

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Forensic Specimens

- NYC Coroners review over a 3 year period
 - buphedrone, mephedrone, methylone, ethylone, 4-methylcathinone, n-ethylcathinone, and methylenedioxypyrovalerone (MDPV) were detected in postmortem specimens
- Chromatography blood LOD, LOQ, and ULOL is 0.025, 0.10, and 1.5 mg/L
- 15 cases of death possibly (suicide) or probably related to bath salt abuse found levels from 0.3 to 4.8 mg/L

deRoux SJ, et al. J Forensic Sci. 2017 May;62(3):695-699

Kratom

- Structurally similar to some hallucinogens but no hallucinogenic activity or effects
- Acts on opioid receptors
- Not scheduled in U.S.
- Seems to be a stimulant in lower doses
 - Mitragynine
- Seems to be a sedative at higher doses
 - 7-hydroxymitragynine
- Often produces a mixed effect
- Onset of effects within 5 to 10 minutes of ingestion; effects last for several hours
- GC-MS selective ion mode analysis following solid-phase extraction. Concentrations were determined in the peripheral blood (0.23 mg/L), central blood (0.19 mg/L), liver (0.43 mg/kg), vitreous (<0.05 mg/L), urine (0.37 mg/L)
- Controversy concerning the “therapeutic range” of Kratom



SOURCE: Ken Dickenson, MS, RPh, Hon DSc, July 2013 (Emerging Drug Trends 2013: Beyond Synthetics and Bath Salts). 54

Krokodil

- Russian cheap replacement drug for heroin made from cooking down desomorphine with gasoline, paint thinner, alcohol, iodine, red phosphorous (match heads), etc.
- In Russia, lack of clean needles and methadone, high cost of heroin, poverty, high numbers of HIV+ individuals, etc.
- No confirmed cases of desomorphine in the U.S. since 2 were identified in 2004.
- Injuries that look like krokodil can be due to shared dirty needles, bacteria, toxic adulterants, gangrene, staph infection, MRSA.

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OTC Meds and Forensics: Loperamide

- Available OTC for diarrhea
 - Chemically similar to methadone
 - As opioids have become harder to obtain the number of ODs and deaths from loperamide has increased significantly
 - Numerous case reports and series
 - SX: VT/Torsades and other cardiotoxicity
 - Constipation, CNS depression, respiratory depression
 - Bowel obstruction

Loperamide Case

- A 33 year old Caucasian female with a history of prior opioid dependence presented to the emergency department (ED) with a chief complaint of acute onset of shortness of breath (SOB), generalized weakness, and tingling over her entire body.
- The SOB started one day prior to presenting to the ED, but the symptom quickly resolved. Later, the SOB began again and was associated with generalized weakness, tingling all over the entire body, dizziness, and diaphoresis. The patient called the Emergency Medical Services who subsequently found the patient in ventricular tachycardia (VT), which spontaneously converted back to sinus rhythm en route. The patient admitted that for the past year, she had been taking **70 pills of loperamide daily** to prevent opioid withdrawal symptoms secondary to stopping Lortab a few years prior to admission. The patient denied taking other medications or other medical problems.

Idris A, et al. American Journal of Emergency Medicine
(2018)

Forensic Testing

- Gold standard is liquid chromatography tandem mass spectrometry (LC–MS–MS)
 - Many labs do not perform
- New study found that gas chromatography mass spectrometry (GC/MS) can also be used
 - Study found fatal levels ranging between 130 to 1,400 ng/mL with a mean concentration of 583 ng/mL with a median between 374 and 440 ng/mL

Beck R, et al. Journal of Analytical Toxicology,
Volume 41, 2017, Pages 729–734

Diphenhydramine

- Now recognized as lethal in children and infants at lower doses than previously thought
- Patients may not be aware of its ubiquitous use in many cold/allergy preparations
- Use commonly as a sedative by parents who may think that its OTC status renders it “safe”
- Lay Media scrutiny higher

Diphenhydramine Forensics

- Review of published cases of deaths
- The mean age (and range) for adult cases was 36.9 years (18–60); pediatric cases, 7.38 years (1.25–17); and infant cases, 11.8 weeks (6–24), respectively
- Corresponding average blood DPH levels were adult, 14.72 mg/L (0.087–35.08); pediatric, 4.39 mg/L (0.069–12.10);, and infant, 1.35 mg/L (1.1–1.6)
- Symptoms: Seizures and arrhythmias

Kufner E, et al. American Journal of Forensic Medicine and
Pathology. 31(1):106, MAR 2010

Acetaminophen

Most commonly overdosed drug

Toxicity is complicated by other drugs taken with it

Toxicity signs and symptoms may not be apparent until too late.

Treated with IV or PO NAC

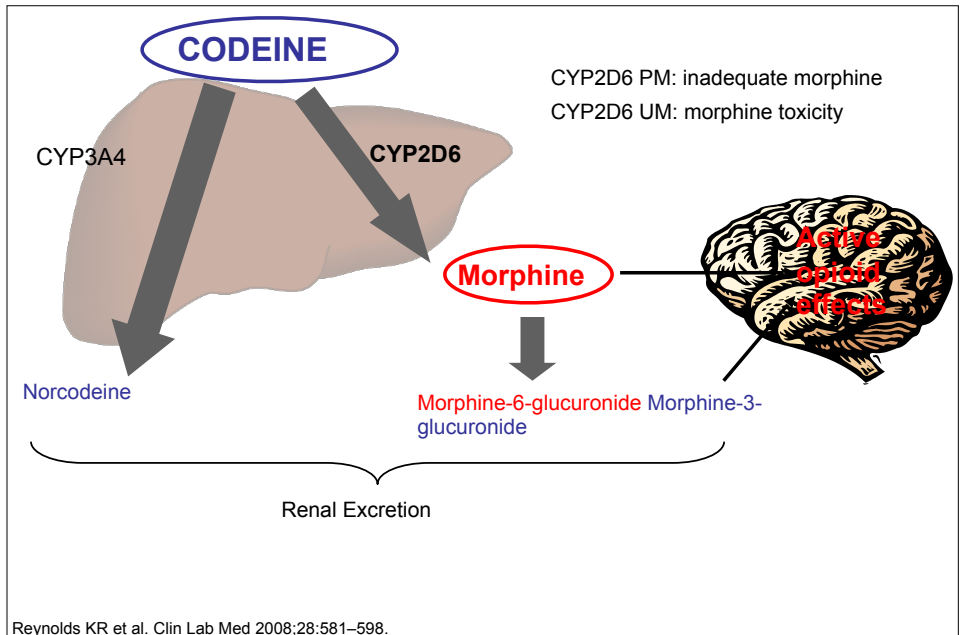
Time is of the essence in treating

APAP and NSAIDs

- APAP deaths have remained steady in U.S. = roughly 400 cases yearly
- Estimates of NSAIDs induced GIB at roughly 15,000 yearly in U.S. but fatalities much rarer
- Their therapeutic range in serum of ibuprofen is generally 10–50 $\mu\text{g/mL}$ and toxic effects are manifested from 200 $\mu\text{g/mL}$
- NSAIDs are routinely measured by liquid chromatography (LC)

Opioid Toxicity and Pharmacogenomics

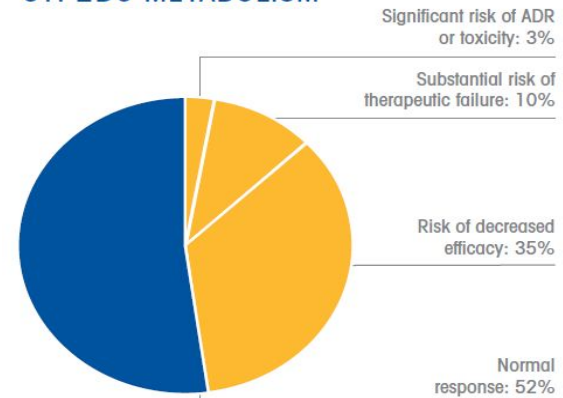
- The ability to metabolize some opioids is genetically determined
- Particularly with codeine some patients may have no effect while others may have severe exaggerated effects



Effects of CYP2D6

- Decreased drug metabolism = lack of efficacy
 - Poor pain control
 - Mis-interpretation of drug seeking behavior
- Ultra-rapid drug metabolism = possible side effects
 - Over-production of active compound
 - Mis-interpretation of over-compliance
 - Possible lower doses required

OPIOID RISK RATES IN CYP2D6 METABOLISM



Morphine Overdose from Codeine

8-15-12 FDA Drug Safety

Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death

- 3 deaths reported in children (2-5yo) who received codeine after undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea
- 3 deaths in children who were CYP2D6 UMs
- All children received typical codeine doses
- Morphine toxicity signs developed within 1-2 days after starting codeine
- Supratherapeutic post-mortem morphine concentrations in the 3 death cases

Forensic Implications

- What may be “normal” doses of codeine—especially in children may lead to exaggerated effects and even death
- Pharmacogenomic testing can be done post-mortem and may help explain such effects
- Codeine and morphine blood and tissue levels should be checked
- More on this in the future??

Conclusions

- New designer drugs of abuse and the inappropriate use of OTC medications may lead to injury or death
- The forensic clinician should be aware of trends in this area
- Working closely with your toxicology laboratory is critical
- Match antemortem symptoms to postmortem examination

Questions?

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