THE PATHOPHYSIOLOGY OF ADDICTION

Richard Ries MD

Professor and Director
Addictions Division
University of Washington
Dept of Psychiatry and Behavioral Sciences
Seattle, WA.
rries@uw.edu

And thanks to CNS Productions for use of their Uppers Downers All-Arounders PPts
GENERAL DISCLOSURES

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RIES CONFLICT OF INTEREST STATEMENT

Richard Ries, MD has no financial relationships with an ACCME defined commercial interests.

But does grant funding around addiction and/or suicide from

- NIH (NIDA, NIAAA)
- SAMHSA
- Dept of Defense
- Washington State
Psychoactive Drugs

Uppers (stimulants)
Downers (depressants)
All Arounders (psycleodelics)
Other Drugs (inhalants, sports drugs, psychiatric drugs)
Compulsive Behaviors (e.g., gambling, eating disorders, Internet addiction)
Uppers (stimulants)

- Cocaine (hydrochloride, crack, freebase)
- Amphetamines (speed, meth, “ice”)
- Amphetamine congeners (Ritalin®, diet pills, e.g., fen-phen)
- Plant stimulants (khat, betel nut, yohimbe)
- Caffeine (coffee, tea, soft drinks, OTC meds)
- Nicotine (cigarettes, cigars, smokeless tobacco)
Downers (depressants)

Opiates/Opioids
- opium, codeine, morphine, heroin, methadone, Darvon®, codeine

Sedative-Hypnotics
- benzodiazepines, e.g., Xanax®, Valium®, barbiturates, e.g., Seconal®, others, e.g., Rohypnol®, Miltown®

Alcohol
- beer, wine, hard liquor

Others
- antihistamines, skeletal muscle relaxants, OTC downers, lookalike downers
All Arounders (psychedelics)

- LSD, psilocybin mushrooms, & other indole psychedelics
- Mescaline (peyote), ecstasy, & other phenylalkylamine psychedelics
- Belladonna, mandrake, & other anticholinergic psychedelics
- Ketamine, PCP, amanita mushrooms, nutmeg, mace, kava
- Marijuana (grass, hashish) & other cannabinols
## 2001 U.S. Drug Use in Past Month

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>48.3%</td>
<td>108.9 million</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>24.9%</td>
<td>60.4 million</td>
</tr>
<tr>
<td>Marijuana</td>
<td>5.4%</td>
<td>12.2 million</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>3.6%</td>
<td>8.1 million</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.7%</td>
<td>1.7 million</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.1%</td>
<td>123 thousand</td>
</tr>
</tbody>
</table>
Prevalence of Opioid Dependence

More than 1.3 million American adults were dependent on opioids in 2008

DRUG OVERDOSE DEATHS BY MAJOR DRUG TYPE, US, 1999-2010

NATIONAL OVERDOSE DEATHS
NUMBER OF DEATHS FROM PRESCRIPTION OPIOID PAIN RELIEVERS

Source: National Center for Health Statistics, CDC Wonder
Death Rates for Drug Overdose by State, 2010

Footnote: *10.9 is in two ranges due to rounding. HI is 10.88 while WI is 10.94
HOW DO DRUGS WORK?
Inhaling: 7 to 10 seconds
Intravenous (IV)  15 – 30 seconds
Intramuscular (IM)  3 – 5 minutes
Subcutaneous  3 – 5 minutes
Snorting or Mucosal Exposure: 3 to 5 minutes
Oral use (ingesting): 20 to 30 minutes
Contact or Transdermal: 1 to 2 days
WHAT ABOUT NEUROTRANSMITTERS?
Message Arrives

Nerve impulse

Presynaptic neuron

Vescicle with neurotransmitters

Reuptake port

Synaptic gap

Receptor site

Postsynaptic neuron
Cocaine Forces Neurotransmitter Release

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Heroin Inhibits Substance “P” Pain Message
Neurotransmitters

Acetylcholine  Substance “P”
Norepinephrine  Anandamide
Epinephrine  Glycine
Dopamine  Histamine
Endorphin  Nitric oxide
Enkephalin  Glutamic acid
Serotonin  Cortisone
GABA
Development of Amphetamine Tolerance Over Time

Desired effect

1st day  25th day  50th day  75th day  100th day

10 mg  100 mg  200 mg

d,l amphetamine ("crosstops")
Alcohol Tolerance and Withdrawal on Neurochemical Balance

Normal

Inhibition (GABA)  Excitation (Glutamate)

Acute Alcohol Intake

Alcohol  GABA  Glutamate

Chronic Intake/Dependence

Alcohol  Adaptation

GABA  Glutamate

Acute Withdrawal

Adaptation

GABA  Glutamate


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Levels of Use
Abstention
Experimental
Social/Recreational
Habitual
Abuse
Addiction
Addiction

• Practices addiction most of the time
• Continues use despite adverse consequences
• Denies there’s a problem
• After withdrawal has a strong tendency to relapse
• Has lost control
• Has altered brain chemistry
Uppers (stimulants)
Cocaine (hydrochloride, crack, freebase)
Amphetamines (speed, meth, “ice”)
Amphetamine congeners (Ritalin®, diet pills, e.g., fen-phen)
Plant stimulants (khat, betel nut, yohimbe)
Caffeine (coffee, tea, soft drinks, OTC meds)
Nicotine (cigarettes, cigars, chewing tobacco)
Initial Effects of Stimulants

Increased energy
Increased heart rate, blood pressure, breathing, & reflexes
Restlessness & excessive talking
Hypersensitivity
Dilated pupils
Little appetite or thirst
Overconfidence
Euphoria
Cocaine Absorption

Plasma Levels of Cocaine (nanograms per milliliter) vs. Minutes After Dose

- Intravenous
- Smoked
- Nasal
- Oral

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Smokable cocaine (freebase, crack, paste)
Crack pipes
Amphetamines

d,l amphetamine (e.g., benzedrine, “crosstops,” “black beauties,” “bennies”)

Methamphetamine (e.g., methedrine, “crank,” meth, “crystal”)

Dextroamphetamine (e.g., dexedrine, “dexies,” “beans,” “Christmas trees”)

Dextromethamphetamine (“ice,” “glass,” “batu,” “snot”)

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Methamphetamines
“Ice- a form of Meth”
Copyright, 2004, CNS Productions, Inc.
MDMA (ECSTASY)

• 3, 4-methylenedioxymethamphetamine
• Street terms: Adam, E, X, XTC, love drug, Molly
• A synthetic, psychoactive drug with both stimulant and hallucinogenic properties similar to methamphetamine and mescaline
• Adverse effects: enhanced physical activity, sweating, lack of coordination, mental confusion, jaw clenching, hyperthermia, and agitation

NIDA. (2010). *NIDA InfoFacts: MDMA (Ecstasy).*
WHAT IS “MOLLY”? 

1. Ecstasy pills with little MDMA and lots of caffeine, meth, assorted drugs? OR 
2. A pure crystalline form of MDMA, most often sold as a powder filled capsule? OR 
3. Methylone? Bath salts? 

- Reports of desired effects of euphoria, but also increased paranoia, agitated delirium, scary hallucinations, psychotic episodes, violent or destructive self-harm behavior, including death 
- Bottom line - Molly usually is not a pure form of MDMA, but may be a drug that can be very dangerous since its contents are unknown 

Synthetic Drugs

• “Spice,” “Bath Salts,” main names
• Chemically-based; not plant derived
• Complex chemistry
• Constantly changing to “stay legal”
• Need to prove “intended to use” to convict in some areas
FROM THE TERM “BATH SALTS” TO...

**Synthetic Cathinones**
- Mephedrone, methylone, 4-MEC
- Stimulants related to methcathinone, MDMA, amphetamines

**2C-Phenethylamines**
- Psychedelics related to mescaline
- Some were created in the past to imitate MDMA

**Tryptamines**
- 5-MeO-DMT & 4-AcO-DMT
- Psychedelics related to psilocin & bufotenin

**Piperazines**
- BZP & TFMPP
- Stimulants

And **Dissociatives** related to ketamine and PCP and **Opioids** related to morphine, fentanyl, and heroin.
Downers (depressants)

Opiates/Opioids

Opium, codeine, morphine, heroin

Vicodin®️, OxyContin®️

Heroin laced fentanyl

Sedative-Hypnotics

Benzodiazepines, e.g., Valium®️

Barbiturates, e.g., Seconal®️

Others, e.g., Rohypnol®️, Miltown®️

Alcohol

Beer, wine, hard liquor
Others Downers

Antihistamines

Skeletal muscle relaxants

Over-the-counter downers

Lookalike downers
## Opiates/Opioids

<table>
<thead>
<tr>
<th>From Opium</th>
<th>Semisynthetic</th>
<th>Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>opium</td>
<td>heroin</td>
<td>methadone</td>
</tr>
<tr>
<td>morphine</td>
<td>hydrocodone</td>
<td>propoxyphene</td>
</tr>
<tr>
<td></td>
<td>(Vicodin®)</td>
<td>(Darvon ®)</td>
</tr>
<tr>
<td>codeine</td>
<td>hydromorphone</td>
<td>meperidine</td>
</tr>
<tr>
<td></td>
<td>(Dilaudid ®)</td>
<td>(Demerol ®)</td>
</tr>
<tr>
<td>thebaine</td>
<td>oxycodone</td>
<td>fentanyl</td>
</tr>
<tr>
<td></td>
<td>(OxyContin ®)</td>
<td>(Sublimaze ®)</td>
</tr>
</tbody>
</table>
Effects: Opiates/Opioids
Pain suppression
Pinpoint pupils
Lowered heart rate, blood pressure, respiration
Constipation
Cough suppression
Lax muscle tone
Dryness of mouth
Euphoria
DRUG OVERDOSE DEATHS BY MAJOR DRUG TYPE, US, 1999-2010

Artificial Pain Suppression

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Black Tar Heroin
CHANGING HEROIN MARKET

• 1920’s to 90’s mostly Asian White
  – Low %
  – Concentrated in large Urban areas
• Later 90’s- now--Black Tar from Mexico
  – More concentrated,
  – Different Biz model- middle/smaller towns
  – Deliver via cell phone
• NOW and Future---Fentanyl/Su and Car-Fentanyl
  – 10-100 x stronger, synthetic, cheaper
  – More deadly, resists naloxone block
Methadone (Dolophine®)
Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)
Treatment Retention and Mortality Bup vs Placebo - all got “1-1 drug counseling”

- 75% retention
- 75% UTS negative
- 20% mortality in placebo group

Sedative-Hypnotics

Benzodiazepines
Xanax®, Valium®, Halcion®, Librium®, Rohypnol®, Klonopin®, Restoril®, Ativan®

Barbiturates
Seconal®, Nembutal®, Amytal®, phenobarbital

Others
Chloral hydrate, GHB, GBL, Placidyl®, etc.
Benzodiazepines

Very Long Acting
Halazepam (Paxipam®)
Prazepam (Centrax®)
Flurazepam (Dalmane®)

Intermediate Acting
Clonazepam (Klonipin®)
Chlordiazepoxide (Librium®)
Diazepam (Valium®)

Very Short Acting

Short Acting
Alprazolam (Xanax®)
Temazepam (Restoril®)
Oxazepam (Serax®)
Lorazepam (Ativan®)

Very Short Acting
Triazolam (Halcion®)
Effects of Benzodiazepines

Anxiety control (e.g., panic attack)
Relaxation
Drowsiness & sleep
Control seizures
Reduced muscular coordination
Dulled physical sensations

Use with Heroin/Opioids Triples
Lethality
Benzodiazepine Use in the United States
Mark Olfson, MD, MPH1,2; Marissa King, PhD3; Michael Schoenbaum, PhD4

Design, Setting, and Participants  A retrospective descriptive analysis of benzodiazepine prescriptions was performed with the 2008 LifeLink LRx Longitudinal Prescription database (IMS Health Inc), which includes approximately 60% of all retail pharmacies in the United States. Denominators were adjusted to generalize estimates to the US population.

Results
In 2008, approximately 5.2% adults 18 to 80 years used benzodiazepines.

The percentage increased with age from 2.6% (18-35 years) to 5.4% (36-50 years) to 7.4% (51-64 years) to 8.7% (65-80 years).

Benzodiazepine use was nearly twice as prevalent in women as men.

The proportion of benzodiazepine use that was long term increased with age from 14.7% (18-35 years) to 31.4% (65-80 years).
Effect of Anxiolytic and Hypnotic drug prescriptions on Mortality Hazards: retrospective cohort study.
Weich S1, Pearce HL, Croft P, Singh S, Crome I, Bashford J, Frisher M.

PARTICIPANTS:
34 727 patients aged 16 years and older first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001, and 69 418 patients with no prescriptions for such drugs (controls) matched by age, sex, and practice. Patients were followed-up for a mean of 7.6 years (range 0.1-13.4 years).

RESULTS:
The age adjusted hazard ratio for mortality = 3.46 (95% confidence interval 3.34 to 3.59) and 3.32 (3.19 to 3.45) after adjusting for other potential confounders.

Dose-response associations with mortality found for all three classes of study drugs (benzodiazepines, Z drugs (zaleplon, zolpidem, and zopiclone), and other drugs).
Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature.

Dodds TJ1,2.

DATA SOURCES:
A PubMed search of English-language publications from database inception until October 11, 2016,

A total of 17 studies were included in this review.

RESULTS:
Benzos ^ Suicide Risk ( OR’s = 3 to 5 x in most studies)

CONCLUSIONS:
Benzodiazepines appear to cause an overall increase in the risk of attempting or completing suicide.

Possible mechanisms of prosuicidal effects
# Part I - Drug Testing: Detection Period

## Range

<table>
<thead>
<tr>
<th>Substance</th>
<th>Detection Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol BAL/Breath</td>
<td>1/2 – 1 day</td>
</tr>
<tr>
<td>Alcohol EtG</td>
<td>1-4 days</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Barbiturates (most)</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>up to 30 days</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3-5 days, Cups don’t show- lor, clon, alprazolam</td>
</tr>
<tr>
<td>Cocaine</td>
<td>12 – 72 hours</td>
</tr>
<tr>
<td>Codeine</td>
<td>1 – 3 days</td>
</tr>
<tr>
<td>Darvond®</td>
<td>6 – 48 hours</td>
</tr>
</tbody>
</table>
COMPARISON OF CLONAZEPAM COMPLIANCE BY MEASUREMENT OF URINARY CONCENTRATION BY IMMUNOASSAY AND LC-MS/MS IN PAIN MANAGEMENT POPULATION.


- Samples from 180 patients taking clonazepam met these medication criteria
- Positivity rates were 21% (38 samples) by immunoassay (cups).
- The positivity rate was 70% (126 samples) if the LC-MS/MS cutoff was set at 200 ng/mL. (chromatography)
- Positivity rate was 87% (157 samples) if the LC-MS/MS was set at 40 ng/mL.
## Part II - Drug Testing: Detection Period Range - Urine Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilaudid</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Heroin</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Marijuana - Single use</td>
<td>1 – 3 days</td>
</tr>
<tr>
<td>Casual use - 4 joints/wk</td>
<td>5 – 7 days</td>
</tr>
<tr>
<td>Daily use</td>
<td>10 – 15 days</td>
</tr>
<tr>
<td>Chronic heavy use</td>
<td>1 – 2 months</td>
</tr>
<tr>
<td>Methadone</td>
<td>2 – 5 days</td>
</tr>
<tr>
<td>PCP - Casual use</td>
<td>2 – 7 days</td>
</tr>
<tr>
<td>Chronic use</td>
<td>up to 30 days</td>
</tr>
</tbody>
</table>
Treatment for **Stimulant Addiction**

Withdrawal  1-5 days  
Sedatives, antipsych.  
/sleep nutrition  
Initial- Intensive Oupt  groups or Inpt  
Longer-term Recovery  
1-1, grps, AA, CA,  NA,  COD?  
Meds ???  COD meds?  
Hep C/HIV Screen
Medical Treatments for Opioid Addiction

Naloxone (short acting antag: for OD)
Naltrexone (longer acting antag: helps decrease craving and use)
Methadone (full synth opioid decreases use/craving/crime)
Clonidine (Decrease WD Sx )
Buprenorphine (Partial opioid blocks use/OD/craving)
Current Issues in Addiction Treatment
1. Heroin epidemic and OPIOID OD’s
2. Health Care Reform ??
3. Expanding use of Medications for treatment
4. Developing New Meds for Addictions
5. Developing more treatment resources
6. Coerced treatment /voluntary treatment ?
7. Abstinence-oriented vs. harm reduction ?
8. Integration into Primary Care
9. And don’t forget the Anonymous programs