Anesthetics;
Drugs of Abuse & Withdrawal

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Much Thanks To…

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Overview

Anesthetics
- Local
- Inhalational
- NM Blockers & Malignant Hyperthermia

Drugs of Abuse (Pearls)

Withdrawal
History

1904-Procaine (short Duration of Action)
1925 (dibucaine) & 1928 (tetracaine) → potent, long acting
1943-lidocaine
1956-mepivacaine, 1959-prilocaine
Structure

2 Distinct Groups

1) Amino Esters

2) Amino Amides
Local Anesthetics

Toxic Reactions
- Few & iatrogenic
- Blood vessel administration or toxic dose

**AMIDES** have largely replaced **ESTERS**
- Increased stability
- Relative absence of hypersensitivity reactions
  - **ESTER** hydrolysis = **PABA** (cross sensitivity)
  - **AMIDES** = Multidose preps → methylparabens
- Chemically related to PABA with **rare** allergic reactions
Local Anesthetics
Mode of Action

- Reversible & Predictable Binding
- Within membrane-bound sodium channels of conducting tissue (cytoplasmic side of membrane)
  → Failure to form/propagate action potentials
    (Small-diameter fibers carrying pain/temp sensation)

Pain fibers - higher firing rate & longer AP → ↑ susceptible to local anesthetics

Sodium Channel (3 States)
- Closed (resting or hyperpolarized)
- Open
- Inactivated
### ONSET OF ACTION

↓ pKa (uncharged)

### HIGHER POTENCY

Higher lipophilicity

Intermediate chain length

Higher protein binding

3-7 carbon equiv’s

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**TABLE 64-1. Pharmacologic Properties of Local Anesthetics**

<table>
<thead>
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<th>Protein Binding (%)</th>
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<th>Duration of Action</th>
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<td>Intermediate</td>
<td>Long</td>
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Local Anesthetics Pharmacokinetics

- Local vs. Systemic dispositions
- **Lipophilic** = crosses membranes! (BBB, placenta)
- Distribution depends on tissue perfusion
- Lungs = uptake; buffers systemic toxicity?
  - Saturable kinetics (lung uptake is exceeded → Toxicity)
- Peripheral vasodilation (except cocaine)
Local Anesthetics

Pharmacokinetics

Metabolism

AMI NO ESTER S  PABA

Plasma Cholinesterase

AMI NO AMIDES Metabolites unrelated to PABA

Slower via Liver

Factors that may $\uparrow$ Tox
$\downarrow$ plasma cholinesterase
$\downarrow$ Liver blood flow (CHF)
Local Anesthetics
Clinical manifestations

Direct cytotoxicity (nerve cells)
- Excessive concentrations or Bad formulations
- Uncommon

Transient neurologic symptoms
- Spinal anesthesia with lidocaine (intrathecal or infusion)
- Mech = Unknown (NOT Na channel blockade)

Skeletal muscle changes
- IM injections (highly potent, longer acting agents)
  - Reversible (2 weeks)
Local Anesthetics

Systemic Toxicity

- Allergic reactions (Amino Esters -- PABA) - Rare
- Methemoglobinemia
  - Reported with lidocaine, tetracaine, prilocaine
  - Topical/oropharyngeal benzocaine

**OXIDIZING AGENTS**

aniline

phenylhydroxylamine & nitrobenzene

Vasovagal Reactions Reported
Local Anesthetics
Systemic Toxicity

- Correlates with [plasma]
  - Dose, Rate, Site
  - Vasoconstrictor?
  - Potency
  - Metabolism (rate)

**Brain & Heart - #1 Targets**
- Rich perfusion
- Moderate tissue-blood partition coefficients
- Lack of diffusion limitations
- Cells that rely on voltage-gated Na channels
**Local Anesthetics  Systemic Toxicity**

**CNS Excitation:** block inhibitory pathways in amygdala → ↑ excitatory activity. Both Inhibitory & Excitatory neurons blocked as concentration ↑ → CNS ↓

**Bupivacaine:**
Large IV bolus = May only see brady, CNS depression & respiratory arrest!

- Convulsions
- Disorientation
- Muscular twitching
- Visual and auditory disorientation
- Lightheadedness
- Numbness of tongue

Cardiac arrest
Respiratory arrest
Local Anesthetics
Systemic Toxicity

CNS Effects Determinants
- Potency & Dose
- Rate of injection
- Drug interactions
- Acid-base status
  - Acidemia $\rightarrow$ ↓ protein binding $\rightarrow$ ↑ free drug
  - Hypercarbia
Local Anesthetics
Systemic Toxicity

Bupivacaine significantly more Cardiotoxic

CC/CNS ([Cardio collapse/CNS Tox])
- Lidocaine = 7 (CNS tox more evident)
- Bupivacaine = 3.7
Local Anesthetics
Systemic Toxicity

• **Lidocaine**
  – Na channel blockade greater if pt is tachycardic
  – Quickly dissociates at diastolic potentials
    • Rapid recovery

• **Bupivacaine**
  – Rapid binding & Slow dissociation
  – S is less cardiotoxic vs. R
  – Uncouples & inhibits Complex I of respiratory chain
  – Inhibits carnitine-acylcarnitine translocase
  – Blocks GABAergic neurons
  – May ↓ Ca++ release from SR → ↓ Contractility
Local Anesthetics
Management

CNS

• DC administration
• Supportive care (CV monitoring)
• **Benzos, Barbs** (Thiopental, Propofol)
• NM blocking agents (EEG monitoring)
• HD not effective (HP for lidocaine?)
Local Anesthetics Management

CV

• **Recognize!**  (CNS effects may preoccupy)
• Correct physiologic derangements
  – Hypoxemia, acidemia, hyperkalemia
• Maximize Oxygenation
• Support Ventilation/Circulation
• Hypotension (adrenergic agonists)
• Bradycardia (atropine)
Local Anesthetics Management

cv

• Dysrhythmias
  – Often refractory to standard care
• Pacing, Bypass
• Lidocaine for bupivacaine? (relatively less toxic)
• Prolonged CPR/Resuscitation efforts
• Na Bicarbonate? (To prevent acidosis)
• Insulin? (same magical reasons as elsewhere)
Lipid Infusion Resuscitation for Local Anesthetic Toxicity

Guy Weinberg, M.D., Department of Anesthesiology, University of Illinois at Chicago, Chicago, Illinois. guyw@uic.edu

http://lipidrescue.squarespace.com/welcome/
Pretreatment or Resuscitation with a Lipid Infusion Shifts the Dose-Response to Bupivacaine-induced Asystole in Rats

Weinberg, Guy L. MD; VadeBoncouer, Timothy MD; Ramaraju, Gopal A. MD; Garcia-Amaro, Marcelo F. MD; Cwik, Michael J. PhD

Issue: Volume 88(4), April 1998, pp 1071-1075

Began as a chance observation in the lab. This was a “confirmation” study.
Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest

Meg A. Rosenblatt, M.D.,* Mark Abel, M.D.,† Gregory W. Fischer, M.D.,† Chad J. Itzkovich, M.D.,‡ James B. Eisenkraft, M.D.§

Dr. Rosenblatt and her team are to be thoroughly congratulated for saving this patient’s life. While proving the clinical efficacy of lipid rescue, they have also validated a contemporary model of academic anesthesiology. There are limits to the information one can draw from a single case, but in the scenario where prospective clinical trials are impossible, we can take heart from this reported experience. A once feared complication of regional anesthesia may have just become slightly less fearsome.

Guy Weinberg, M.D., Department of Anesthesiology, University of Illinois at Chicago, Chicago, Illinois. guyw@uic.edu
Inhalational Anesthetics

• Ether
  – Paracelsus – put hens “to sleep” – The 1st description
  – 1735 used for “headaches & fits”
  – 1864 Mass Gen. Hospital dental procedure - Public Demo
  – Oliver Wendell Holmes (anesthesia = without feeling)

• Nitrous Oxide

• Chloroform
  – Replaced ether as choice for OB (1840s)

• Volatile Anesthetics (Fluroxene, Halothane, Methoxyflurane)
  – 1840’s – 1940’s = combustibility and direct organ toxicity
Inhalational Anesthetics

Improved Clinical Properties

Isoflurane

Desflurane

Enflurane

Difenflurane
Inhalational Anesthetics

Pathophysiology

Unique Receptor = Improbable
(Because there are so many agents → anesthesia)

- Function modulated from within cells
- Interact with many ion channels (target?)
- Side effects = effects in nonneural tissue (cardiac)
Inhalational Anesthetics
Pathophysiology

Goal = Reversible changes in neuro function
• Loss of perception and reaction to pain
• Unawareness of immediate events
• Loss of memory of events

Mechanism = Uncertain
• Physical-chemical behavior within hydrophobic regions of biological membrane lipids & proteins
Inhalational Anesthetics
Pharmacokinetics

Potency – Physiochemical Properties

• **Meyer-Overton lipid solubility theory**
  – Potency correlates directly with relative lipid solubility

• **Volume expansion theory**
  – High pressures (100-200 atm) reverse anesth. effects
  – Suggests that drugs cause anesthesia by ↑ membrane volume at normal atm pressure
Inhalational Anesthetics
Pharmacokinetics

Factors that influence absorption & distribution

• **Solubility** in blood
• **Solubility** in tissue
• **Blood flow** through lungs
• **Blood flow** distribution to various organs
• **Mass** of the tissue

**GOAL:**
Develop & Maintain satisfactory partial pressure in the Brain!
Inhalational Anesthetics
Pharmacokinetics

• Linked to pharmacodynamics
• Strive to achieve & maintain desired [alveolar]

**Minimum alveolar concentration (MAC)**

• Potency
• The [alveolar] at 1 atm that prevents movement in 50% of subjects in response to a painful stimulus
Inhalational Anesthetics

NITROUS OXIDE

Advantages

• Mild odor
• Absence of airway irritation
• Rapid induction & emergence
• Potent
• Minimal respiratory & circulatory effects
• Safe
Inhalational Anesthetics

NITROUS OXIDE

- Abuse Potential
- Asphyxia - Death/Brain damage from asphyxia (2°)
- Impurities – Nitric oxide, nitrogen dioxide
- Barotrauma
  - 35x more soluble in blood than Nitrogen
  - Pressure in air-containing spaces (bowel, ears, chest)
Nitrous oxide myelopathy in an abuser of whipped cream bulbs

Helmut Butzkueven MBBS, John O. King MD, FRACP

Neurology Registrar. Senior Neurologist. The Royal Melbourne Hospital
Melbourne, Victoria, Australia

Summary A 23 year old man presented with a severe posterior column myelopathy related to prolonged nitrous oxide abuse obtained from whipped cream bulbs. The site of pathology was identified by magnetic resonance imaging (MRI) and somatosensory evoked potentials. The mechanism of toxicity involves inactivation of vitamin B₁₂ dependent enzymes. Appropriate treatment with methionine and vitamin B₁₂ was instituted quickly with good neurological outcome. There are major concerns regarding the availability of nitrous oxide in supermarkets. © 2000 Harcourt Publishers Ltd

40–60 whipped cream bulbs per day during the last 6 months
NO $\rightarrow$ oxidizes cobalt in B12 $\rightarrow$ Inactive form

Methionine & THF both required for DNA & myelin synthesis!!!
Inhalational Anesthetics

NITROUS OXIDE

Hematologic Effects

• BONE MARROW SUPPRESSION
• Occurs in all patients
• Recovery generally occurs (4 days)
• PERNICIOUS ANEMIA-Like
  – This has ↓ B12 Absorption due to absence of Intrinsic Factor (vs NO – active B12 can’t be made by the body)
Inhalational Anesthetics

NITROUS OXIDE

Neurologic Effects

- Only after chronic exposure
- Is a disabling polyneuropathy
- Subacute Combined Degeneration of Spinal Cord
- Sensorimotor polyneuropathy
- Posterior & Lateral cord involvement
- Numbness & paresthesias in extremeties
- Weakness & truncal ataxia
Inhalational Anesthetics

NITROUS OXIDE

Management

• Removal of source
• B12
  – Helps best if brief exposure
  – Won’t help chronically exposed patients?
• Folinic acid 30 mg IV
  – May reverse BM abnormalities
• Methionine Supplementation
  – Experimentally (Primates) reduced demyelination
Inhalational Anesthetics

HALOTHANE
HALOTHANE HEPATITIS

(1) Mild Dysfunction
– 20% of exposed patients
– Asymptomatic
– Modestly ↑ transaminases within days
– Complete recovery
HALOTHANE

(2) Life-Threatening Hepatitis

- 1 in 10,000 patients
- Fatal hepatic necrosis in 1 of 35,000 patients
- A diagnosis of exclusion
- Increased risk
  - Multiple exposures
  - Obesity (fat reservoir, prolonged release)
  - Female
  - Age (middle age)
  - Ethnicity (Mexican)
Inhalational Anesthetics

HALOTHANE

HALOTHANE HEPATITIS

20% oxidative metabolism via CYP – trifluoroacetic acid

Volatile Metabolites:

Free Radicals
or
Haptens
Inhalational Anesthetics

- Enflurane – weakly associated
- Immune form of hepatitis (all but sevoflurane)

Isoflurane, Desflurane
Low Hepatotoxic Potential
Inhalational Anesthetics

HALOTHANE ABUSE

Ingestion
- AGE, depressed CNS, low BP, shallow breathing, bradycardia & extrasystoles, & **Acute Lung Injury**
- Coma resolves in 72 hours
- Sweet fruity odor of breath

Intravenous
- Coma, hypotension, **Acute Lung Injury**

Inhalation
- Most reported cases = hospital personnel
Inhalational Anesthetics

NEPHROTOXICITY

**Methoxyflurane** (intro 1962)
- Vasopressin-resistant polyuric renal insufficiency
- Nephrogenic DI
- Polyuria = negative fluid balance
- High Na, Osmolality, BUN
- Lasted 10-20 days (up to > 1 year)
- Tox = **Inorganic Fluoride (F)** released during biotransformation of methoxyflurane
  - F inhibits adenylate cyclase (ADH interference)?
Currently Used Anesthetics

- Halothane, Isoflurane, Enflurane, Desflurane, Sevo.
- **Enflurane & Sevoflurane** biotransform by deF
  - 5% of sevoflurane is metabolized
  - Transient decrease in urine-concentrating ability
  - Rarely clinically relevant
- Pre-existing RI = risk of renal dysfunction?
Inhalational Anesthetics

Anesthetic-Related CO Poisoning
Desflurane, Enflurane, Isoflurane

• Contain a difluoromethoxy moiety
  – Can be degraded to **Carbon Monoxide**

• CO production
  – *Inversely propor. to H2O content of CO2 absorbents*
  – Soda lime and Baralyme = CO2 absorbents
  – May dry with high gas-inflow rates
  – *Worst = first case Mon. after weekend of drying*

• COHb up to 36% (**no** M&M reported)
Anesthesia Is GOOD!!!
NEUROMUSCULAR BLOCKADE
Neuromuscular Blockers

History

**Curare**: Sir Walter Raleigh (Guyana 1595)
- 1898: King’s American Dispensatory
  - “**Curare** is a frightfully poisonous extract, prepared by the savages of South America”
- **Curare** pivotal in mech. of NM transmission
  - Claude Bernard frog studies
    - “**curare** must act on the terminal plates of motor nerves”
- 1878: **Curare** 1st clinical use (tetanus & Sz)
- Malicious use of NM Blockers! (Swango...)
Neuromuscular Blockers

Purpose

Reversibly inhibits transmission at the skeletal NMJ
- All = 1 +charged quaternary ammonium moiety $\rightarrow$ binds to the postsynaptic nicotinic (nAch) receptor at the NMJ
  $\rightarrow$ ↓ activation by Ach

nAch receptor

Ligand-gated ion channel
4 different protein subunits
Pentameric structure
Excitation-Contraction coupling in skeletal muscle

*Calcium Release Unit*
the intimate association of DHPR, RYR-1, & SR
Neuromuscular Blockers

Modulation of postsynaptic Ach receptor

Depolarizing (phase I block)

- **Succinylcholine** (the only one clinically)
- 2 molecules bind to each α site of nAch receptor
- Prolonged open state of ion channel!
- Fasciculations!!

- Succ not hydrolyzed efficiently by true AchE
- Voltage-gated Na channel in peri-junctional region
  - Prolonged inactive state → desensitization block
  
  → Muscle = *temporarily refractory* to presyn Ach release (phase I block)
Neuromuscular Blockers
Modulation of postsynaptic Ach receptor

Nondepolarizing (phase II block)

- Competitively inhibit effects of Ach
- *Prevent muscle depolarization!*
- One molecule of NDNMB binds to $\alpha$ site
  - Competitively inhibits normal channel activation

- **DO NOT** block voltage-gated Na channels on mus mem
  - So…Direct electrical stimulation of muscle contraction = possible
- Also block nAch receptors on prejunctional nerves
  - Inhibits Ach-stimulated Ach production & release
Neuromuscular Blockers
Pharmacokinetics

Highly water soluble (won’t cross BBB)
Speed of onset - 1/ molar potency
   (The > affinity for receptor, the fewer molecules/Kg tissue required)

In general: small, fast contracting muscles
   • Most susceptible (e.g. extraocular vs. large slow)
   • *Respiratory Sparing Effect*
Recovery fastest for diaphragm and IC muscles
Neuromuscular Blockers Complications

**Patient Awareness**
- NMBs do not affect consciousness
- Pupillary light reflex preserved in healthy patients

**Histamine Release**
- Nonimmunologic dose- and rate-related release
- Tubocurarine > atracurium & mivacurium > Succ
- NO release w/ pan, roc, vec

**Anaphylaxis**
- 60% anaphylactoid rxns during anesthesia – NMBs
- Of the NMBs, Rocuronium 43%, Succ 23%
  (Pancuronium = least)
Neuromuscular Blockers Complications

**Control of Respiration**
Subparalyzing doses
- Blunt hypoxic ventilatory response (HVR)
- But not the ventilatory response to hypercapnia

**Autonomic Side Effects**
Tubocurarine
- Blocks nAch rec at PNS ganglia → Tachycardia
- At SNS ganglia → ↓ sympathetic response
- Histamine release

→ HYPOTENSION!
Neuromuscular Blockers Complications

**Autonomic Side Effects**

- Muscarinic receptors mostly unaffected
- Pancuronium
  - Blocks PNS transmission at Cardiac M Recs (Atropine-like effect)
  - Block of presynaptic M receptors at SNS terminals
  - ? Indirect NE-releasing effect at postgang fibers

→ Dose- and injection rate-related increase in Heart Rate, BP, CO, and Sympathetic Tone
Neuromuscular Blockers
Complications

**Autonomic Side Effects**

*Succinylcholine*
- Rarely: Dysrhythmias - bradycardia, junct & vent rhythms
- Due to Stimulation of **Cardiac M Receptors**
- May be prevented with atropine (15-20 mcg/kg IV)

*Bradycardia*
- May be severe in children with large/repeated doses
Neuromuscular Blockers Interactions

**Potentiate** duration or effect of NDNMB
- Respiratory acidosis, hypoK, hypoCa, hyperMg, hypoP, hypothermia, shock, liver or kidney failure

**Resistance** (mild) to effect of NDNMB
- Acute sepsis & inflammatory states
Neuromuscular Blockers

Succinylcholine TOX

1) **Prolonged Effect**
   - Decreased plasma cholinesterase (or abnormal activity)
   - OP or Carbamate Poisoning
   - Hepatic Dz, Malnutrition, Pregnancy
   - Phase II block (large doses over short period – 8mg/kg)
Neuromuscular Blockers

“Normal or RI Patients” 1 mg/kg raises [K] approximately 0.5 mEq/L

Succinylcholine TOX

2) Hyperkalemia

Exaggerated with myopathy or proliferation of extrajunctional Ach rec

Susceptibility after neuro injury begins in 4-7 days!

Denervation
- Head or SC injury, CVA, neuropathy
- Muscle pathology
- Trauma, compartment syndrome, muscular dystrophy

Assume cardiac arrest after Sucks is due to hyperkalemia
Neuromuscular Blockers

Succinylcholine TOX

3) **Rhabdomyolysis**
   - Especially at risk = underlying myopathy
   - Ex: Kids with Duchenne muscular dystrophy

   - Life-threatening hyper K?
     - Mortality is highest with rhabdomyolysis (30%)
Succinylcholine TOX

4) **Muscle Spasms**

- Masseter Muscle Rigidity (MMR)
  - *Pediatric Patients:* 0.3-1% (Succ + Halothane)

- Trismus, myoclonus, chest wall rigidity
  - Can’t be aborted by NDNMB (indep of neural activity)
Neuromuscular Blockers

Succinylcholine TOX Also Volatile Anesthetics!

5) Malignant Hyperthermia
   - Inherited hypermetabolic condition
   - 1:20,000 children, 1:50,000 adults
   - Duchenne MD, central core Dz, King-Denborough syndrome, osteogenesis imperfecta, myotonia

MH-triggering agents (within 12 hours)
   - Interact with an abnormal RYR-1 channel (mostly)
   - Prolonged open state
   - Rapid efflux of calcium from SR (accelerated)
   - Hypermetabolic – pCO2, temp, tone, lactate (all ↑)
Malignant Hyperthermia

Signs and Symptoms of MH (First 30 Min)

- Tachycardia 90%
- Hypercarbia 80%
- Rigidity 80%
- Hypertension 75%
- Hyperthermia 70%

May be a late sign

Earliest signs = EARLY & RAPID INCREASED CO2 production and arterial, venous end tidal CO2
Malignant Hyperthermia Management

• Aggressive Supportive Care
  volume, cooling, hyper K…

DANTROLENE

• Prior Mortality Rate = 70% (now < 5%!!!)
• Partially blocks Calcium release from SR
• Dose = 2-3 mg/Kg
• Maintence dosing for any reoccurrence (25%)  IV q 4-6 hrs for 24-48 hours
Neuromuscular Blockers

NDNMBs TOX

• Persistent Weakness
  – Administration longer than 48 hours
  – Critical illness associated (multifactorial)
• 2.5-3.5 – fold increase in ICU mortality & ICU stay
Neuromuscular Blockers

Unique Toxicity

- **Metocurine** – contains iodine, hypersensitivity and shellfish allergy
- **Rapacuronium** – fatal bronchospasm, withdrawn.
Drugs of Abuse/Withdrawal

Tolerance

• Physiologic process: increasing drug concentrations required
• Shift in dose-response curve to the right
• Receptor modulation (opioids), metab (barbs), or both (EtOH)
• “Cross Tolerance” Key to treating W/D

Dependence

• Implies that cessation leads to withdrawal

Withdrawal

• Physiologic (autonomic instability, NV/D, hyperactivity, etc.)
Hallucinogens

- Lysergamides
  - LSD
  - Ergine
- Indolalkylamines / Typtamine
  - Psilocin & Psilocybin
  - Dimethyltryptamine (DMT)
  - 5-Methoxy-DMT
  - Bufotenine
- Phenylethylamines
  - Mescaline
  - MDMA (Ecstasy)
  - Methcathinone (Khat, Jeff)
  - Methamphetamine
- Tetrahydrocannabinoids
  - Marijuana
  - Hashish
- Belladonna Alkaloids
  - Jimsonweed
  - Deadly nightshade
- Miscellaneous
  - Salvia divinorum
  - Ketamine
  - Phencyclidine (PCP)
Hallucinogens

- Many flavors
- Common action - CNS serotonin receptors (5-HT)
- Affects many psychological & physiologic processes (Mood, personality, affect, appetite, motor function, sexual activity, temperature regulation, pain perception)
- > 14 known 5-HT receptor subtypes; Each with different effects & degrees of effect by different structures
- Other neurotransmitters also
Drugs of Abuse/Withdrawal

Amphetamines

Primary mechanism of Tox
- release of catecholamines (DA, NE) from presynaptic terminals
  & block reuptake by competitive inhibition

Methyl additions = ↑ CNS & duration

Now = Serotonergic
Dopamine Release due to Amphetamines

- **Low Dose** – Released from cyto by exchange diffusion at dopa uptake transporter site in membrane
- **Moderate Dose** – Amphetamines diffuse into presyn terminal → affect NT transporter on vesicular membrane → releasing dopa into cyto → Dopa undergoes reverse transport at Dopa Uptake Receptor → ↑ Dopa in synapse
- **High Dose** – amphetamines diffuse into the vesicle → alkalinizes vesicles → ↑ Dopa release from vesicles → ↑ Membrane Reverse Transport → ↑ Dopa in Synapse
Drugs of Abuse/Withdrawal

Amphetamines

Methamphetamine

- CNS effect more substantial (chemistry!)
- Prolonged half-life (19-34 hours)

- Primary ingredient = ephedrine
  - Hydrogenated to Methamphetamine

- Meth Lab Tox
  Lead, HCl acid, HCl gas, anhydrous ammonia, red phosphorus, iodine
Drugs of Abuse/Withdrawal

Amphetamines

3,4-Methylenedioxyamphetamine (MDMA)

• Entactogen (means touching within)
  – Euphoria, expands consciousness, Inner peace
  – Desire to socialize, heightened sexuality
• One-tenth the CNS stimulant effect

• Serotonergic (5-HT chemistry!)
• Hyponatremia
  – *Hypovolemic* (dancing/sweating), *Euvolemic* (SIADH), *Hypervolemic* (water drinking)
• Long-term neuropsychiatric effects
Other Phenylethylamines

Mescaline

Goldfranks Toxicology 2006

2CB, Nexus, Bromo

Substitution at the para position of the phenyl ring → ↑ hallucinogenic or 5HT effects.

Myristicin is also phenylethylamine based

2CT-7, Blue Mystic
Peyote & Mescaline

- A spineless cactus
- *Lophophora williamsii*
- Disk-shaped buttons are cut from the roots, on the top of the cactus and dried
- Peyote buttons - round, fleshy tops of the cactus that have been sliced off and dried.
Peyote & Mescaline

- Bitter-tasting buttons
  - Eaten whole
  - Dried crushed into a powder

- 6-12 buttons (270-540 mg of mescaline) typical
- Equivalent to roughly 5 grams of dried peyote
- Legal use in the US - Native American Church religious ceremonies & treatment of physical and psychological ailments.
- Used for centuries for the psychedelic effects experienced when it is ingested
Peyote
Mescaline

• Contains a large spectrum of phenethylamines ... the principal of which is mescaline

• Clinical
  – Visual hallucinations and radically altered states of consciousness
  – Usually pleasurable and illuminating
  – Occasional - Anxiety or revulsion
  – Not physically addictive
  – N/V & Diaphoresis often precede hallucinations
  – Effects lasting for up to 12 hours
Indolalkylamines (Tryptamines)

- Serotonin
- Lysergic Acid Diethylamide (LSD)
- Psilocybin
- Bufotenine
Lysergamides

- LSD is the synthetic one
- Natural lysergamides
  - Morning glory (Ipomoea)
    - These seeds have
    - 200-300 seeds - hallucinogenic
  - Hawaiian baby wood rose (Argyreia nervosa)
• A dried grain spike of rye grass infected with ergot (Claviceps purpurea). Some of the grains have been replaced by a dark, compact, fungal mass called a sclerotium (superficially resemble rat droppings).
• The sclerotia contain
  • vasoconstricting ergotamine alkaloids
  • lysergic acid alkaloids which are the precursor for LSD 25.
The morning glory seeds contain a lysergic acid alkaloid called ergine (d-lysergic acid amide, the "natural" LSD). The more potent synthetic LSD is d-lysergic acid diethylamide.
Psilocybin

- Found in Psilocybe, Panaelous, Concocybe genera
- Grow in Pacific Northwest and southern US; often in pastures
- In the GI tract, is metabolized to Psilocin (active hallucinogen)
- Effects same as LSD but duration is shorter; ~ 4 hours
Toads and Hallucinations
The Bufo genus

- All species have parotid glands on their backs that activate various xenobiotics (dopamine, epinephrine, serotonin)
- Many species → bufotenine
- Only *B. alvarius* → 5-MeO-DMT
Other Hallucinogen Flavors

- PCP
- Ketamine

Piperidine
PCP

- Developed in 1950s
- Dissociative anesthetic
- Never approved for human use
  Bad agitation as
  awoke from
  anesthesia)

- Brain Effects
  - Disrupts NMDA receptor for glutamate
  - Glutamate receptors…
    - Perception of pain
    - Cognition - including learning and memory
    - Emotion
  - Dopamine action altered
    - Neurotransmitter
      Euphoria and "rush" due to excessive and low
Ketamine

• Dissociative anesthetic
• Made in 1963 to replace PCP
• Current Use - Anesthesia and veterinary medicine.
• “Street” K mostly diverted from veterinarians' offices.
• Manufactured Liquid.
• Illicit ketamine – Evaporization powder Snorted or compressed into pills.
• Versus PCP - Much potency & Duration.
Cocaine Derivation and Types

Leaf → Mechanical Hydrocarbon

Cocaine HCl Salt in Solution

Cocaine Alkaloid (benzoylmethylecgonine)

Extracted into Aqueous Phase
Evaporated → white powder (cocaine hydrochloride)

• Decomposes if heated
• Insufflated
• Applied to other mucous membrane
• Dissolved in water

Hydrocarbon Solvent (Ether) extracts cocaine base

Free-Base Liquid

Dissolve in HCl → Evaporated w/ Heating

tobacco or marijuana cigarette is dipped… dried…

Crack

Smoked

Injected or Ingested
Cocaine Metabolism

N-Demethylation

Non-Enzymatic Hydrolysis

Cholinesterase

Norcocaine

Benzoylcegonine

Ecgonine Methyl Ester

Goldfranks Toxicology 2006
Robert Hoffman Cocaine Chapter
Mechanism

Cocaine blocks the Pre-Synaptic reuptake of biogenic amines

- Serotonin
  - Addiction
  - Reward
  - Seizures
- Dopamine
  - Locomotor Effects
- Neuronal Norepinephrine
  - Hypertension
- Adrenal Epinephrine
  - Tachycardia

Cocaine → ↑ Cerebral Excitatory amino acids

Sedation → ↓ CNS & peripheral effects of biogenic amines

Psychomotor agitation
Hyperthermia
Seizures
An important consideration for Treatment
Cocaine Withdrawal

- Emotional component = YES
  • Intense craving

- Physical component = DEBATABLE
  • **Washed-Out Syndrome**
    - Catecholamine Depletion
    - Lethargy & Adynamic
SON, WE FOUND BLOOD IN YOUR ALCOHOL STREAM!
<table>
<thead>
<tr>
<th>Ethanol (MW)</th>
<th>Af odorless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific gravity: 0.7930 (≈0.8) g/mL</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution (Vd): 0.0 L/kg</td>
<td></td>
</tr>
</tbody>
</table>

Serum ethanol concentration (mg/dL) =

\[
\text{C} (\text{mg}) / \text{Vd} (\text{L/kg}) \times \text{body weight (kg)} \times 10
\]

\[
\text{mmol/l} = \text{mg/MW} = \text{mg/ml} / 4.6
\]

For a 70-kg individual:

**Dose of ethanol**

- 10 mL/kg of 10% (20 proof)
- 5 mL/kg of 10% (20 proof)
- 2.5 mL/kg of 10% (20 proof)
- 250 mL (5 "shots") of 40% (80 proof)
- 30 mL (1 "shot") of 40% (80 proof)

**Blood ethanol concentration**

167 mg/dL (36.30 mmol/L)

50 mg/dL (11.87 mmol/L)

25 mg/dL (5.87 mmol/L)

143 mg/dL (31.05 mmol/L)

**Blood concentration consistent with legal intoxication**: 10.87–17.39 mmol/L (50–80 mg/dL or 0.05–0.08 g/dL [%])

**Average reduction in blood ethanol level (elimination phase)**

- Nontolerant adult: 3.26–4.35 mmol/L/h (15–20 mg/dL/h, 40–50 mg/kg/h)
- Tolerant adult: 6.52–8.70 mmol/L/h (30–40 mg/dL/h, 175 mg/kg/h)
No specific Receptor
Gluconeogenesis is Inhibited
Pyruvate is reduced to lactate
Oxaloacetate is reduced to malate

PREVENTS… flow of metabolites in the direction of gluconeogenesis
Ethanol
EtOH induced hypoglycemia due to high redox ratio!

Malnourished & Children
Highest Risk!
Ethanol

Also cofactor for $\alpha$-KGD (Krebs) & transketolase (PPP) & important for neuronal conduction

Figure A22-1. Thiamine links anaerobic glycolysis to the Krebs cycle. Anaerobic glycolysis only yields 2 moles of ATP as each mole of glucose is metabolized to 2 moles of pyruvate. To obtain the 36 additional ATP equivalents that can be derived as the Krebs cycle converts pyruvate to CO$_2$ and H$_2$O, pyruvate must first be combined with CoA to form acetyl-CoA and CO$_2$. This process is dependent on the thiamine-requiring enzyme system known as pyruvate dehydrogenase complex.
Figure 75-3. Mechanism of alcoholic ketoacidosis. TCA cycle = tricarboxylic acid cycle. (Modified, with permission, from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders in Endocrine Metabolic Disorders. Emerg Med Clin North Am 1989;7:952.)
Disulfiram Reactions

Accumulation of Acetaldehyde = histamine release?.... symptomatology
Also inhibits DA beta-hydroxylase (NE synthesis), via chelation of Cu
50% inhib of CYP 2E1, induces 2B1 & 2A1
Withdrawal Pathophysiology

Inside Cell ® Negative (Hyperpolarized)

Cell Firing
Threshold Potential

Resting Potential

New Resting Potential

Action Potential

Membrane Potential (mV)

Time (ms)

1 2 3 4
Suddenly Remove EtOH\(^\text{®}\) In-Cell Cl-

Disinhibited

Threshold Potential

New Resting Potential

Original Resting Potential

Resting Potential

Time (ms)

1  2  3  4

Membrane Potential

-30 mV

-70 mV

-90 mV

Chronic EtOH Effects

Action Potential

Tolerance! (Cell D)
Ethanol/Sedative Hypnotic Withdrawal

**MILD**
- Tremor
- Tachycardia
- HTN
- Diaphoresis
- Anxiety

**Delirium Tremens**
- 24 hrs after
- Lasts 3-5 days
- Altered sensorium
- May=hallucinate (visual or tactile), Sz’s, psycomotor agitation.
- Autonom Instable

**Seizures “rum fits”**
- 6-48 hours after
- Single, Generalized, Brief, short postictal

**Alcoholic Hallucinos.**
- Visual or auditory
- Persecutory
- Within a few hours
- Independently?
- Clear Mentation
- Disturbing
Drugs of Abuse/Withdrawal

Gamma-Hydroxybutyric Acid
Drugs of Abuse/Withdrawal

GHB Withdrawal

- Potentially severe & life-threatening
- Rapid development (within hours of use)
- Agitation, disorientation, hallucinations, HTN, tachycardia, hyperthermia, tremor, Sz
- Consistent with sedative-hypnotic W/D
  - Treatment the same
Drugs of Abuse/Withdrawal

Inhalants
Drugs of Abuse/Withdrawal

Inhalants

<table>
<thead>
<tr>
<th>Inhalant</th>
<th>Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glues/glue removers</td>
<td>Toluene, x-hexane, benzene, xylenes, trichloroethane, trichloroethylene, tetrachloroethylene, ethyl acetate, methyl ethyl ketone, methyl chloride, ketones, butane, propane, isobutane, propylene, chlorofluorocarbons, silicone.</td>
</tr>
<tr>
<td>Spray paint</td>
<td>Toluene, methylene chloride, methanol, n-hexanes, and aromatic hydrocarbons, ethanol, methanol, methylene chloride, xylene, propanes.</td>
</tr>
<tr>
<td>Hair spray, deodorants, as</td>
<td>Toluene, methylene chloride, methanol, n-hexanes, and aromatic hydrocarbons, ethanol, methanol, methylene chloride, xylene, propanes.</td>
</tr>
<tr>
<td>Toothpaste</td>
<td>Tetrachloroethylene, methylene chloride, trichloroethylene, chloroform.</td>
</tr>
<tr>
<td>Dental floss</td>
<td>Tetrachloroethylene, trichloroethylene, xylene, n-hexane, Acetone, ethanol, isobutyl alcohol, ethyl naphtha.</td>
</tr>
<tr>
<td>Lipstick, varnishes, &quot;Tarps&quot;</td>
<td>Tetrachloroethylene, trichloroethylene, xylene, n-hexane, Acetone, ethanol, isobutyl alcohol, ethyl naphtha.</td>
</tr>
<tr>
<td>Rags, cleaners</td>
<td>Tetrachloroethylene, trichloroethylene, xylene, n-hexane, Acetone, ethanol, isobutyl alcohol, ethyl naphtha.</td>
</tr>
<tr>
<td>Wrapped cream, &quot;whippings&quot;</td>
<td>Tetrachloroethylene, trichloroethylene, xylene, n-hexane, Acetone, ethanol, isobutyl alcohol, ethyl naphtha.</td>
</tr>
</tbody>
</table>
Slip em a Mickey!
Drugs of Abuse/Withdrawal

Cannabinoids

W/D?
- Tremor
- Sweaty
- Fever
- Nausea
- Irritable
- Restless
- Sleepless
- Nervous

Metabolites may be detected in the urine of chronic users for several weeks.
Drugs of Abuse/Withdrawal

Nicotine

– Tertiary amine, colorless, bitter, H2O soluble
– Weakly alkaline (pKa=8.0-8.5)
– **Solanaceae** family of plants
  • *Nicotiana tabacum*
  • *N. rustica* (higher concentration, Turkish tobacco)
– Lobeline
  • *Lobelia inflata* (Indian tobacco)
– Cystisine (mescal beans)
– Coniine
  • Lethal alkaloid in poison hemlock
Drugs of Abuse/Withdrawal

- Often biphasic; with nicotinic stimulation early; followed by “loss of stimulation” due to receptor fatigue
- Note can have both sympathetic and parasympathetic signs and symptoms
- Vomiting is #1 most common; occurs early.
- Death due to CV collapse and respiratory depression
Drugs of Abuse/Withdrawal
Nicotine Withdrawal

**Subjective**
- Anger/aggression/hostility
- Anxiety
- Blurred vision
- Confusion
- Constipation
- Craving for cigarettes
- Drowsiness
- Gastrointestinal upset
- Headache
- Hunger
- Impaired concentration
- Irritability/impatience
- Moodiness
- Restlessness
- Sleep disturbance

**Objective**
- Decreased arousal pattern on EEG
- Decreased blood pressure
- Decreased heart rate
- Diminished psychomotor performance
- Impaired short-term memory
- Reduced plasma catecholamines
- Weight gain

**Cartoon Text:**
Yeah, I finally quit smoking. What? Moody? No, not really... well, maybe just a little.
<table>
<thead>
<tr>
<th>Cardiorenal</th>
<th>Systemic vasoconstriction</th>
<th>Orthostatic hypotension</th>
<th>Bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>(Purpura, Petechiae)</td>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Reduced ACTH, insulin</td>
<td>Reduced glucocorticoids</td>
<td>Reduced motility</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Reduced gastric, acid, biliary</td>
<td>Increased small bowel transit</td>
<td>Increased anal sphincter tone</td>
</tr>
<tr>
<td>Heparin</td>
<td>Scleroderma</td>
<td>Analgesia</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Analgesia</td>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>Otitis media</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory depression</td>
<td>Bronchoconstriction</td>
<td>Acute lung injury</td>
</tr>
</tbody>
</table>
Drugs of Abuse/Withdrawal

Opioids

- 2D6 polymorphisms affect clinical effects
- Heroin – better BBB penetration bc of more hydrocarbon groups →the “Rush”
- 6-MAM
  - Not natural; confirms heroin presence
  - More potent than morphine
Drugs of Abuse/Withdrawal

Opioids

Heroin (3,6-diacetylmorphine)
- Hydrochloride salt
  - White or beige powder (insufflation)
  - H2O soluble = IV administration
- Heroin base
  - More prevalent form
  - Brown or black
  - Relatively insoluble in H2O
  - Insufflation
  - Chasing the dragon
    - Spongiform leukoencephalopathy
Dextromethorphan

- D-isomer of codeine analog levorphanol
- No analgesic, respiratory, or CNS effects at therapeutic doses
- Dextrophan is active metabolite
- Serotonin release
- Affects NMDA receptor at PCP site (Hallucinations)
- Sigma receptor effects
- Toxicity: Hyperexcitable, lethargy, ataxia, diaphoresis, HTN, nystagmus, dystonia, seizures; occasionally opioid-like

Does Narcan work? Variable
Meperidine

- Meperidine  Nor-meperidine
  T½  3-4 hrs   15-30 hrs
- Serotonin due to reuptake of the NT & release
- Toxicity: twitches, tremors, myoclonus; seizures

MAOIs potentiated:
  Agitation  Irritability
  Hyperpyrexia  Tachycardia
  Hypertension

The unique drug reaction compared to other opioids?
Tramadol

• Analog of codeine
• Analgesia:
  – Mu-agonism is 10% of codeine
  – NE and serotonin reuptake pain modulation

Toxicity - lethargy, tachycardia, agitation, seizures, hypertension.

• Narcan reverses sedation and some of the analgesia; but...its use has seizures
• Physical dependence has occurred
Drugs of Abuse/Withdrawal

Opioids

Averse Effects

- Acute lung injury
- Seizures (*tramadol, propoxyphene, meperidine*)
- Na channel blockade (*propoxyphene*)
- Decreased BP (histamine release)
- Rigid Chest (*fentanyl*)
- Myoclonus (*fentanyl, meperidine*)
Drugs of Abuse/Withdrawal

Opioid Withdrawal

- Uncomfortable
- Generally not life-threatening
- Heroin W/D = 4 – 8 hours
- Methadone W/D = 36 – 72 hours
- Psychological
  - Craving
  - Dysphoria
  - Anxiety
  - Insomnia
- Physiologic
  - Tachycardia
  - Tachypnea
  - Diaphoresis
  - Tearing
  - Yawning
  - Rhinorrhea
  - Myalgias
  - Piloerection
  - Delirium
  - Seizures
  - CV collapse
  - Hyperpyrexia
  - Not: Yawning, Rhinorrhea
  - N/V/D

Not:
- N/V/D
**TABLE 30-1 Vital Signs and Mental Status Changes in Withdrawal**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>OPIOIDS</th>
<th>SEDATIVE-HYPNOTICS*</th>
<th>ALCOHOL</th>
<th>COCAINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*Includes benzodiazepines, barbiturates, and γ-hydroxybutyrate/γ-butyrolactone.
You are getting sleepy...