Psychopharmacology

Part 2

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PART 2

- Mesolimbic Reward Circuits
- Substance Abuse Disorders
- Depressants
- Stimulants
• Final common pathway of reward
• “pleasure center of the brain”
• Dopamine is the “pleasure neurotransmitter”
Fig. 1

Acetylcholine

Nicotine

Tyr-o-o-o-000-

Anandamide
Reward: DA mesolimbic pathway

nucleus accumbens

VTA

Adopted from Essential Psychopharmacology 3rd edition Steven Stahl
Natural Ways to Trigger Mesolimbic DA

- Intellectual accomplishments
- Athletic accomplishments
- Enjoying a concert
- “Natural Highs”
- Brain’s OWN
  - Morphine/Herion (endorphins)
  - Marijauna (anandamide)
  - Nicotine (acetylcholine)
  - Cocaine or Amphetamine (Dopamine)
"I'm going out to get some endorphins."
Delivers normal reinforcement to adaptive behaviors

Numerous drug of abuse bypass brain’s own neurotransmitters and directly stimulate the reward system receptors

Adopted from Essential Psychopharmacology 3rd edition Steven Stahl
FRONTAL LOBE VERSUS THE LIMBIC SYSTEM

Anatomical Structures Involved in Regulation of Food Intake

- Dorsomedial PFC
- Plane of Cross Section
- Ventromedial PFC
- Orbitofrontal Cortex

Cross Section of the Brain

- Prefrontal Cortex
- Cingulate Cortex
- Striatum
- Insular Cortex
- Amygdala
- Hippocampus
- Hypothalamus
- Brainstem

Limbic and Paralimbic Structures
Repeated Exposure to Drugs of Abuse Triggers Drug Seeking Behavior

RESULT: Instructs the spiny neurons to take action impulsively, right away, automatically, obligatorily and without thought. These changes in the reactive system highjack the entire reward circuitry when addiction develops.

The Amygdala is the site of emotional learning (fear, fear extinction). Proximity to another structure makes the Amygdala remember not just pleasure but environmental cues assoc. with pleasurable or non pleasurable in withdrawal memory.
Competitive with Reactive System From Prefrontal Cortex

RESULT: Maintained

The O PFC regulates impulses, analyze situations, keeps flexibility of choice, rationality to take action.
Pharmacology:

- Ethanol is the allosteric modulator of g-aminobutyric acid A (GABAA) receptors.
  - Thus acutely, alcohol renders its central effects (e.g., anxiolytic, sedative, anticonvulsant, and motor coordination impairment) - GABAA receptors primarily in the cerebral cortex, medial septal neurons, and hippocampal neurons.
  - In addition, alcohol acutely has a direct inhibitory effect on N-methyl-D-aspartate (NMDA) receptors, thus reducing excitatory glutamatergic transmission.
  - It also disinhibits GABA-mediated dopaminergic-projections to the ventral tegmental area (VTA), leading to increases in extracellular dopamine (DA) in the nucleus accumbens (NA), which are likely responsible for the initially pleasurable effects of alcohol and for the impulse to drink more.

• Pharmacokinetics: metabolized to formaldehyde in the liver by aldehyde dehydrogenase.

• Effects: in addition to pharmacology
  – Alcohol consumption-related problems are the third leading cause of death in the United States
  – May lead to withdrawal seizures or delirium tremens (DTs), either of which may be fatal without adequate treatment.
  – Although alcoholism is present in 20% to 50% of hospitalized patients, it is diagnosed only about 5% of the time.
  – A poll of physicians affiliated to the American Medical Association revealed that 71% of them believed they were too ambivalent or not competent to properly treat alcoholic patients.
Tolerance and Dependence:
- The development of alcohol tolerance with chronic ethanol use is a **neuroadaptive process** (to reduce the acute effects of alcohol and provide homeostasis).
- Adaptive suppression of GABA activity, mediated by internalization and downregulation of GABAA-BZ receptor complexes.
- Chronic alcohol consumption also leads to increased synaptic glutamate (GLU) release, as well as increased NMDA.
- In addition, chronic ethanol exposure leads to overactivity of noradrenergic neurons in the CNS and the peripheral nervous system likely
  - via desensitization of a2 receptors or lack of a2 agonist activity and excessive norepinephrine (NE) production as the excess extracellular DA is converted into NE via DA-b-hydroxylase.

Toxicology

There is no antidote for alcohol intoxication. Treatment is supportive and symptomatic, it includes:

- Assessment of respiratory status and determination on whether intubation for airway protection is required
- Metabolic assessment; including electrolyte, glucose, and fluid status
- Before glucose is administered, consider supplementation with thiamine, to prevent Wernicke-Korsakoff syndrome
- Toxicology assessment, to determine whether other substances may contribute to the patient’s condition; the presence of other CNS-depressant agents (eg, BZs, barbiturates, opioids) may increase the risk for respiratory depression, need for intubation, delirium, and withdrawal syndromes
- The overall management of acute intoxication depends on the patient’s degree of habituation, the total amount of alcohol ingested, and the presence of other ingested substances
Withdrawal (tremors or shakes)
- Tremors begin on the first day, peaking about 16 to 24 hours (in 90% of cases) after a relative or absolute abstinence from alcohol.
- At times the onset may be as late as 10 days after the last drink.
- Tremors, nervousness, irritability, nausea, and vomiting are the earliest and most common signs.
- Tremors are usually generalized, coarse, and of fast frequency (about 5–7 cycles/s) and they worsen with motor activity or emotional stress.
• Withdrawal (tremors or shakes)

- In uncomplicated cases, withdrawal usually subsides in 5 to 7 days even without treatment.
- Symptoms (eg, anorexia, nausea, vomiting, psychological tension, general malaise, hypertension, autonomic hyperactivity, tachycardia, diaphoresis, orthostatic hypotension, irritability, vivid dreams, and insomnia) may last up to 14 days.
- Extrapyramidal symptoms may occur during alcohol withdrawal after several weeks of continuous drinking or after an intensive brief binge of a day’s duration, even in a patient not previously or currently treated with antipsychotics.
• Withdrawal (Seizures)
  – Withdrawal seizures begin on the first day, peaking about 12 to 48 hours (95% occurring within 7–38 hours) after a relative or absolute abstinence from alcohol.
  – Grand mal seizures arise in up to 25% of patients with an AWS and are characterized by generalized seizures.
  – Several metabolic abnormalities are associated with their occurrence, including low serum Mg, respiratory alkalosis, hypoglycemia, and increased intracellular sodium.
• Withdrawal (Hallucinations)
  – Hallucinosis often begins on the first day, peaking about 48 to 96 hours after a relative or absolute abstinence from alcohol.
  – Alcoholic hallucinations usually consist of primarily auditory (or less frequently visual) misperceptions.
  – Hallucinations may persist after other withdrawal symptoms resolve.
• **Withdrawal (DTs)**
  
  – DTs usually appear 1 to 3 days after a relative or absolute abstinence from alcohol.
  
  – The peak intensity usually occurs on the fourth to fifth day after abstinence.
  
  – It occurs in up to 10% of alcoholics hospitalized for detoxification.
  
  – Its mortality is high: about 1% in treated cases and up to 15% when left untreated.
  
  – Confusion and fluctuating consciousness and hallucinations
  
  – Usually coincident with other medical conditions such as cardiac disease, pyrexia, dehydration, electrolyte abnormalities.
ETHYL ALCOHOL, ETHANOL, ETOH

- Specific measures:
  Correct and monitor fluid balances, electrolytes, and vital signs.

Vitamin supplementation:
  Thiamine 100 mg intravenously/intramuscularly/by mouth × 3 to 5 days
  Folate 1 mg by mouth daily
  Multivitamin, 1 tab by mouth daily
  B complex vitamin 2 tabs by mouth daily
  Vitamin K 5 to 10 mg subcutaneously × 1 (if international normalized ratio [INR] is >1.3)

Monitor:
  Vital signs every 2 hours
  Blood glucose level
  Fluid balance
  Electrolytes (especially Mg^{++}, Na^+, K^+)

- Behavioral management:
  Frequent and appropriate reality orientation
  Adequate maintenance of sleep/wake cycle; keep patients in a tranquil, well-lit space during daytime; lights off at night
  Restraints may be needed for combative/agitated patients
  Sitters may be required for patients who are confused or in restraints

Other supportive medications: beta blockers, alpha blockers, seizure meds, benzodiazepines.
**Dependence:**

- **Disulfiram**, an aldehyde dehydrogenase inhibitor, causes the classic antabuse reaction
  - (ie, palpitations, flushing, hypotension, tachycardia, headache, nausea, and vomiting) when patients treated with disulfiram drink alcohol, caused by a fast accumulation of acetaldehyde (aversive technique).
  - Open-label studies have suggested that disulfiram may be superior to acamprosate and naltrexone in preventing alcohol abuse relapse. Severe adverse psychiatric and medical reactions (eg, myocardial infarction, congestive heart failure, respiratory depression, and convulsions), including death, have been associated with its use.


Dependence:

- **Acamprosate**: a structural analogue of GABA and GLU, is believed to interact with these neurotransmitter systems in the CNS to attenuate glutamatergic excitation that occurs with abstinence and thus to reduce alcohol craving. Despite initially encouraging results, the data are mixed regarding its efficacy.

- **Naltrexone**: an opiate receptor antagonist, blocks the reinforcing effects of alcohol by preventing the stimulation of opioid receptors and the reduction of DA release in the VTA. Some large studies have contradicted their efficacy for alcohol dependence.
Dependence:
- Long term effects
  - Destruction of nerve cells producing permanent brain syndrome called Korsakoff’s syndrome (dementia)
  - Cognitive deficits even without dementia
  - Pancreatitis and chronic gastritis
  - Liver damage
  - Increased risk of breast CA in women
  - Other cancers
- Intoxication involves potentiation in GABA function and antagonism of NMDA type glutamate function.
• **Treatment for Dependence and Abuse:**
  - **Goals of pharmacotherapy**
    - Reversal of acute effect of EtOH
    - Treatment and prevention of withdrawal symptoms and complications.
    - Maintenance of abstinence and prevention of relapse
    - Treatment of co-existing psychiatric disorders
  - **Intoxication:** no medication used, just supportive care.
  - **Withdrawal:**
    - long acting benzodiazepines (lorazepam in elders, diazepam or chlordiazepoxide)
    - Clonidine (inconsistent when compared to benzo)
    - Atenolol (superior to placebo but not lots of evidence)
    - Anticonvulsants: acute withdrawal and long term maintenance
    - Antipsychotics: alleviates delirium, hallucinations but lowers seizure threshold
INHALANTS

• Types:
  – Anesthetics, industrial or household solvents, office supply solvents, Commercial gases, household products, propellants and Aliphatic nitrites or organic solvents.

• Toxicity: death is rare during acute intoxication but due to anoxia, cardiac arrest, aspiration, or trauma.
  – Serious complications of long term use: liver, kidney failure, dementia, loss of cognition or high cognitive functions, gait impairment, fetal solvent syndrome.

• Treatment: supportive, oxygen
• Pharmacology: reduce the electrical and metabolic action of the brain with decreased whole brain glucose metabolism.
  – Glutamate and GABA modulated

• Pharmacokinetics: very long or short half life
  – T1/2 short ones are lipid soluble thus fast to induce sleep, and long T1/2 ones are slow to induce sleep with long hangover
• Effects:
  – Not analgesic
  – Anxiolysis
  – Alter sleep patterns, suppress dreaming and REM
  – Depress memory and cognition for hours or days

• Tolerance and Dependence: easily develop tolerance and dependence.

• Toxicology: drowsiness, supportive treatment of OD.
• Thiopental (Pentothal)
• Methohexital (Brevital)
• Propofol (Diprovan)
• Etomidate (Amidate)
Propofol

- Designed to use as a hypnotic for induction and maintenance of general anaesthesia for MECHANICALLY VENTILATED patients.
- Euphoria and Amnesia properties lend it to be a drug of abuse.
- 30-60 minute half life, highly protein bound excreted by the kidney, half dose adj for frail
- MJ found to have been given 25mg w lidocaine plus lorazepam before death
• GABA receptor:
  – Benzodiazepines are pro GABAergic

• Pharmacokinetics:
  – Long acting: active metabolites
  – Short acting: no active metabolites
    • Versed (midazolam)
    • Serax (oxazepam)
    • Restoril (temazepam)
    • Halcion (triazolam)
    • Xanax (alprazolam)
BENZODIAZEPINES

• **Effects**
  – Thought to reset the threshold of the amygdala to be more responsive to GABA.
  – People with panic disorder have a global decrease in benzodiazepine binding in the orbitofrontal cortex and insula.
  – Antiepileptic action on GABA receptors in cerebellum and hippocampus
  – Muscle relaxant effects: spinal cord, cerebellum and brain stem action

• **Toxicity**
  – Mental confusion
  – Amnesia
  – Actions on cerebral cortex and hippocampus

• **Tolerance and Dependence:**
  – GABA effects on the ventral tegumentum and nucleus accumbens
SECOND GENERATION ANXIOLYTICS

• Zolpidem (Ambien)
  – Pharmacokinetics:
    • Relatively shorter acting but long acting versions
  – Pharmacodynamics:
    • "partial agonists" at GABA receptor

– Effects and Toxicity:
  • Sleep behaviors
  • Similar toxicity to first generation
  • Nausea and vomiting at high doses
  • Higher mortality rate with ALL sleep aids
Pharmacology:
- Anxiety can at least in part be due to defects in neurotransmission of serotonin.
- There are 15 subtypes of 5HT
  - 5HT1A are high density in the hippocampus, amygdala
  - Mice bred without 5HT1A receptors = increased fear

Special Class:
- Buspar (buspirone)
  - 5HT1A agonist
  - Anxiolysis without significant sedation
  - Minimal amnesia or confusion, or psychomotor impairment
  - Doesn’t potentiate EtOH effects
  - Little prediction for abuse
  - Some antidepressant effect
  - Doesn’t promote onset of sleep
Ketamine

• NMDA receptor
  – NMDA receptor is excitatory for glutamate which is released with noxious peripheral stimuli causing neuropathic pain, reduced functionality of opioid receptors.
  – Activation of the NMDA receptor can result in lower opioid receptor sensitivity.

• NMDA receptor antagonism
  – might play a role in neurodegenerative and psychotic disorders, like Alzheimer's disease and schizophrenia
  – Indirectly disinhibits glutamatergic and cholinergic projections to the cerebral cortex
  – these compounds cause adverse behavioral (psychotomimetic) effects and can produce neurotoxicity characterized by neuronal vacuolization, induction of heat-shock protein, neuronal/axonal degeneration and regional brain cell death
Table 1. NMDA Antagonists for Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analgesic Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>IM: 2-4 mg/kg IV: 0.2-0.75 mg/kg Continuous IV infusion: 2-7 mcg/kg/min</td>
<td>CNS effects: hallucinations, confusion, dreamlike state, irrational behavior</td>
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<td></td>
<td></td>
<td>Other effects: Respiratory depression, increased CSF pressure, hypertension,</td>
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<tr>
<td></td>
<td></td>
<td>tachycardia, tremor, nystagmus, myocardial depression</td>
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<tr>
<td>Methadone</td>
<td>Opioid-naïve: Initial oral dose, 2.5-10 mg q8-12h (interval may range from 4-12</td>
<td>CNS depression, respiratory depression, QTc prolongation, constipation, nausea</td>
</tr>
<tr>
<td></td>
<td>h as analgesic duration is short during initial therapy, although it increases</td>
<td>and vomiting, dizziness, disorientation</td>
</tr>
<tr>
<td></td>
<td>with prolonged therapy) Opioid-tolerant: Oral morphine to oral methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>conversion is variable</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>PO: 10-30 mg/day</td>
<td>Hypertension, dizziness, drowsiness, confusion, anxiety, hallucinations,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cataract</td>
</tr>
<tr>
<td>Amantadine</td>
<td>IV: 200 mg infused over 3 h PO: 100-200 mg/day</td>
<td>Orthostatic hypotension, dry mouth, drowsiness, agitation, confusion,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hallucinations, dyskinesia</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>PO: 45-400 mg/day</td>
<td>Light-headedness, drowsiness, confusion, nervousness, visual disturbances,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>serotonin syndrome</td>
</tr>
</tbody>
</table>

*CNS: central nervous system; CSF: cerebrospinal fluid; IM: intramuscular; min: minute; NMDA: N-methyl-D-aspartate.*

*Source: References 5, 7, 12.*
Dextromethorphan - DXM

**DXM Plateaus**

Abusers describe the DXM experience as occurring on four different plateaus. Abusers ingest increasing amounts of DXM (based on their weight) to reach each succeeding plateau. Abusers report the following effects occurring in each plateau:

**First Plateau:** Mild inebriation.

**Second Plateau:** An effect similar to alcohol intoxication and, occasionally, mild hallucinations. The abuser’s speech can become slurred, and short-term memory may be temporarily impaired.

**Third Plateau:** An altered state of consciousness. The abuser’s senses, particularly vision, can become impaired.

**Fourth Plateau:** Mind and body dissociation or an "out-of-body" experience. The abuser can lose some or all contact with his or her senses. The effects at this plateau are comparable to the effects caused by ketamine or PCP (phencyclidine).
Dextromethorphan- DXM

- Inexpensive
- Easy to obtain
- Combined w guaifenesin
- Internet: powdered form
- Tablets, capsules, liquids
- 140 cough and cold meds
- DEA could qualify CS act
- Texas and ND tried to prohibit sale to minors
• Cocaine

• Amphetamines

• Other behavioral Stimulants
• Background:
  – Used to be used to treat depression
  – Local anesthesia
  – Active alkaloid of cocoa

• Pharmacokinetics:
  – Absorbed from all sites of application
  – 30-90 minute half life
  – Quickly eliminated from blood, 8 hours or more from brain
  – When combined with EtOH intake, metabolized by a common enzyme (ethyl ester of benzoylecgonine). The metabolite blocks DA reuptake and also causes euphoria.

• Pharmacology: potentiates DA, NE and 5HT levels
• Effects short term:
  – Increased alertness
  – Motor hyperactivity
  – Tachycardia
  – Vasoconstriction
  – Hypertension
  – Bronchodilation
  – Increased body temperature
  – Pupil dilation
  – Increased glucose availability
  – Shift blood from organs to muscle

• Toxic and psychotic effects, long term and high dose use:
  – Paranoid psychosis
  – Hypervigilence, sleep deprivation
  – Impulsive and compulsive behavior
  – Acute toxicity: 1-2 mg/kg body weight
  – Chronic cocaine use leads to virtually every psychiatric syndrome
• Treatment of dependency:
  – Typically cocaine dependent individuals are young, dependent on at least three drugs, male, coexisting psychopathology, EtOH dependence, associated with violent premature deaths.
  – Anti withdrawal drugs: methylphenidate
  – Anti craving agents (none with success, ecopipan D1D2 blocker)
  – Treatment of comorbid psychological disorders
AMPHETAMINES AND OTHER BEHAVIORAL STIMULANTS

• Background:
  • Simpathomimetics
  • Used for weight loss
  • ADHD
  • alertness

• Pharmacology:
  • NE
  • DA
  • Increase BP, HR, etc..
AMPHETAMINES AND OTHER BEHAVIORAL STIMULANTS

• Dependence and Tolerance:
  – Amphetamines
  – Withdrawal syndrome: weight gain, decreased energy, increased sleep.
  – Some people experience depression or psychotic episodes upon withdrawal
    • Treat with AD or antipsychotic

• ICE (Free based methamphetamine)
  – Pharmacokinetics: free based, concentrated methamphetamine.
    • Long half life (12 hours)
  – Effects: like stimulants
  – Toxicity: persistent psychiatric, cardiovascular, metabolic and neuromuscular changes.
AMPHEMATINES AND OTHER BEHAVIORAL STIMULANTS

• Non Amphetamine Behavioral Stimulants:
  – Methyphenidate(Concerta, Ritalin)
  – Pemoline (Cylert)
  – Subutramine (Meridia- off market)
  – Modafinil
  – Racemic Amphetamine (Addrall)
Caffeine

• Easy to get
• World’s most popular psychoactive drug
• In plant species, caffeine acts as a pesticide
  • Caffeine paralyzes and kills some insects feeding upon the plant
  • Soil around coffee plants: insecticide and inhibits seed germination of other near plants

<table>
<thead>
<tr>
<th>Energy drink</th>
<th>Size*</th>
<th>Caffeine**</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Hour Energy</td>
<td>2 oz. (60 mL)</td>
<td>207 mg</td>
</tr>
<tr>
<td>AMP, regular or sugar-free</td>
<td>8 oz. (240 mL)</td>
<td>72-74 mg</td>
</tr>
<tr>
<td>Cran-Energy</td>
<td>8 oz. (240 mL)</td>
<td>70 mg</td>
</tr>
<tr>
<td>Full Throttle</td>
<td>8 oz. (240 mL)</td>
<td>70-72 mg</td>
</tr>
<tr>
<td>Monster</td>
<td>8 oz. (240 mL)</td>
<td>80 mg</td>
</tr>
<tr>
<td>Red Bull</td>
<td>8.4 oz. (250 mL)</td>
<td>76-80 mg</td>
</tr>
<tr>
<td>Rockstar, regular or sugar-free</td>
<td>8 oz. (240 mL)</td>
<td>79-80 mg</td>
</tr>
<tr>
<td>Vault, regular or sugar-free</td>
<td>8 oz. (240 mL)</td>
<td>47 mg</td>
</tr>
</tbody>
</table>


*Sizes are listed in fluid ounces (oz.) and milliliters (mL).
**Caffeine is listed in milligrams (mg).
Caffeine

• Hidden sources
  – Yerba mate
  – Guarana
  – Ilex guayusa
  – Headache tablets

• Pharmacology-Toxicology
  – Stimulant, tolerance, addictiveness, mental clarity
  – Both water and lipid soluble
  – LD=80 cups of coffee, typically V Fib
  – 2 Grams OD hospitaliiztion
Main symptoms of Caffeine overdose

**Central**
- Irritability
- Anxiety
- Restlessness
- Confusion
- Delirium
- Headache
- Insomnia

**Visual**
- Seeing flashes

**Ears**
- Ringing

**Skin**
- Increased sensitivity to touch or pain

**Muscular**
- Seizures
- Trembling
- Twitching
- Overextension

**Heart**
- Rapid heartbeat
- Irregular rhythm

**Respiratory**
- Rapid breathing

**Urinary**
- Frequent urination

**Systemic**
- Dehydration
- Fever

**Gastric**
- Abdominal pain
- Nausea
- Vomiting (possibly with blood)
Caffeine

• Metabolism and Elimination
  – Varies widely amongst individuals
  – Liver function
  – Concurrent medications
    • Oral contraceptives can double half life
    • Fluvoxamine (Luvox®) can reduce clearance by 90% and extend half life by 10 fold
    • Fluoroquinolone antibiotics reduce clearance
  – European research looked at 47K subjects for genetic variants of metabolism: faster metabolizers consume more
Caffeine Restriction in Sweden

Decrease in the number of intentional caffeine related intoxications after OTC single purchase restriction from 250 to 30mg in 2004

1993-2009:
83,580 autopsy toxicology reports

20 cases of caffeine contribution to fatal outcome

65% before 2004
Caffeine was noncontributory from 2007-2009
Treatment of nicotine addiction: varenicline (Chantix) nicotinic partial agonist. Patches too.

*it’s the pulse of nicotine (puff) that causes euphoria which drives addiction, the meds create consistant low level just enough to reduce craving, but avoid withdrawal.
THE END PART 2

• Questions?

• Comments?

• Share Ideas?