



Psychopharmacology

Part 2

Presented by Demetra Antimisiaris, PharmD, CGP, FASCP

Associate Professor

Department of Family Medicine and Geriatrics

Associate, U of L Department of Neurology

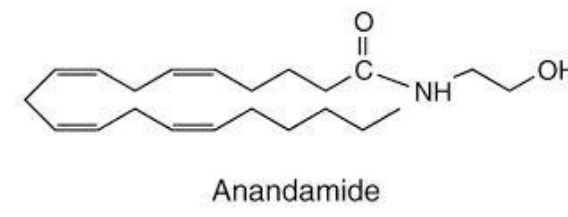
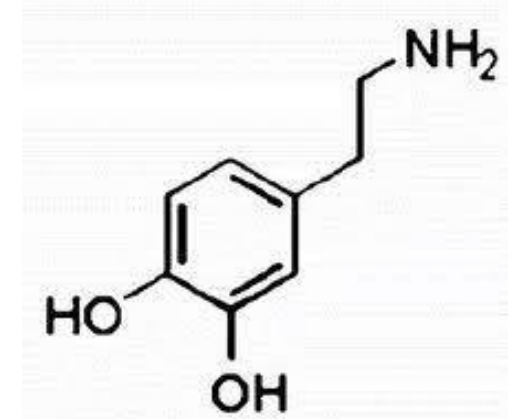
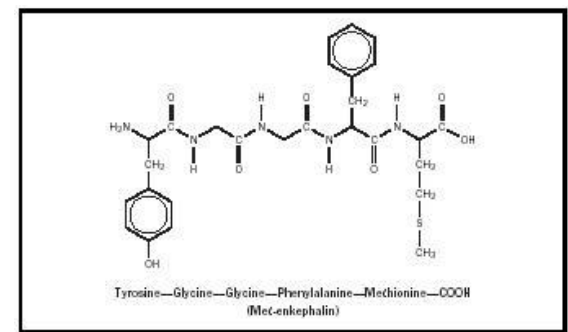
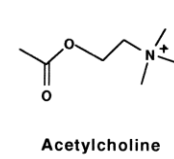
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PART 2

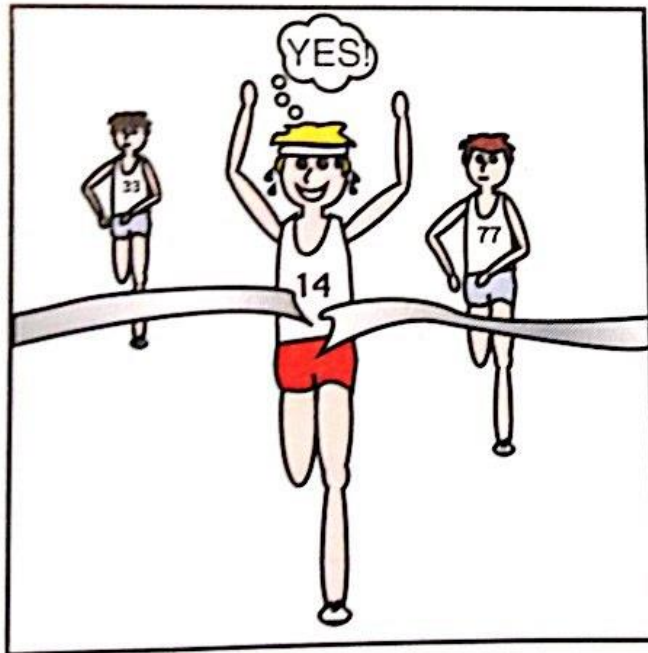
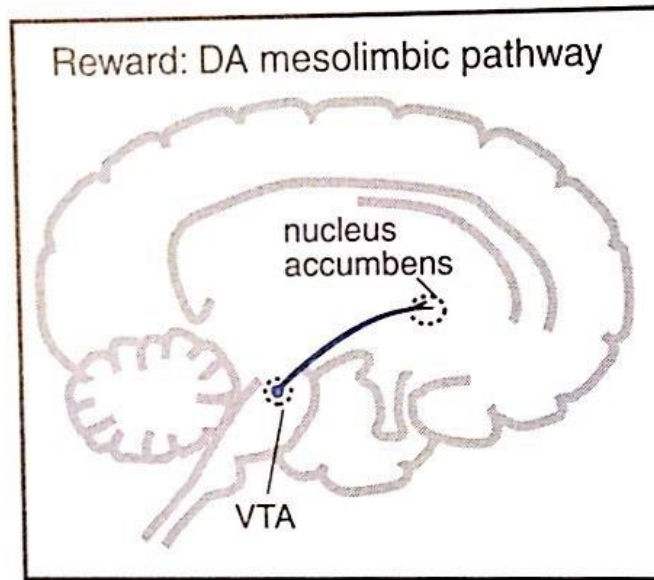
- Mesolimbic Reward Circuits
- Substance Abuse Disorders
- Depressants
- Stimulants

MESOLIMBIC DOPAMINE CIRCUIT

- Final common pathway of reward
- “pleasure center of the brain”
- Dopamine is the “pleasure neurotransmitter”

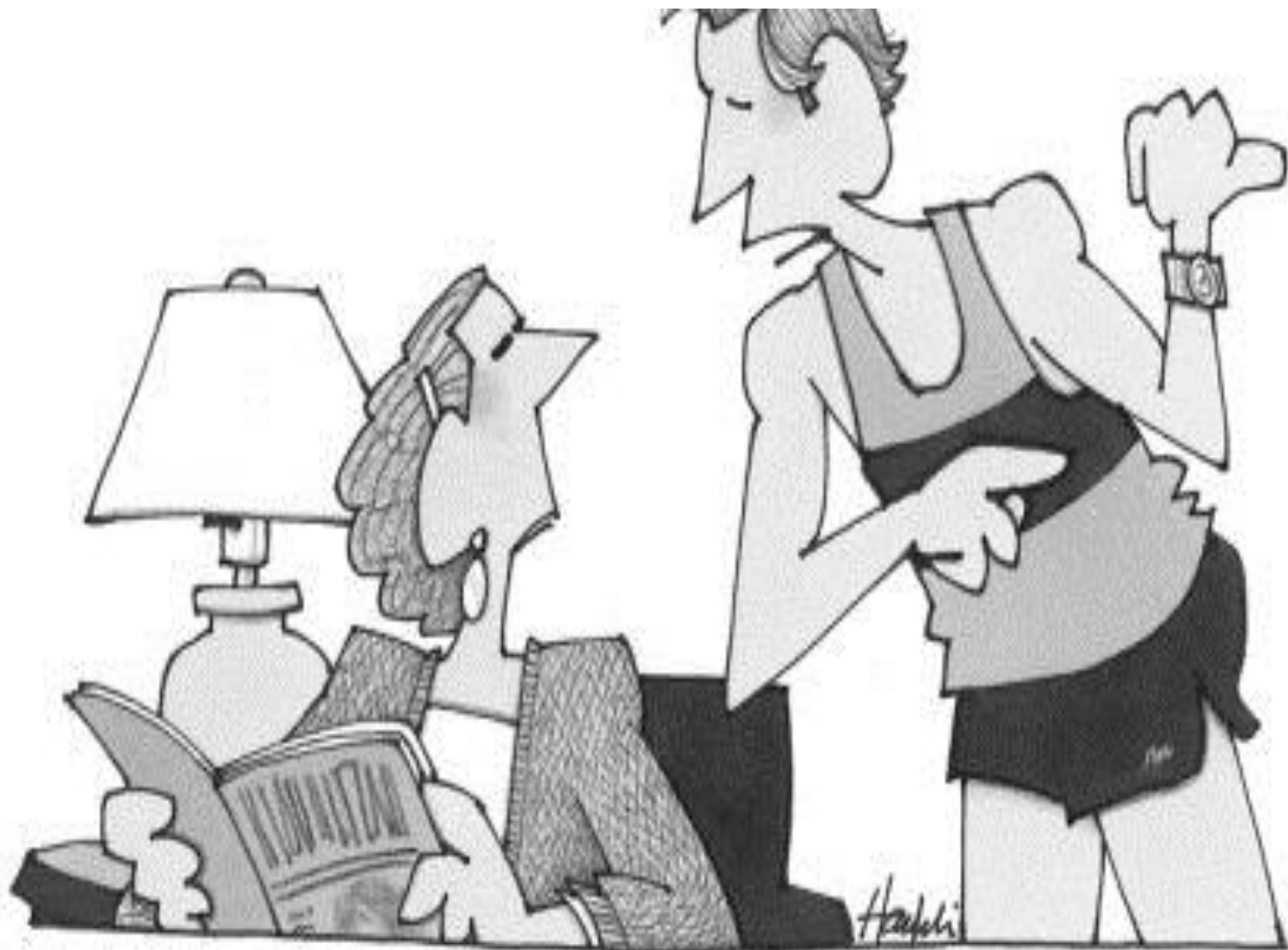


Adopted from
Essential
Psychopharma
cology 3rd
edition Steven
Stahl



Natural Ways to Trigger Mesolimbic DA

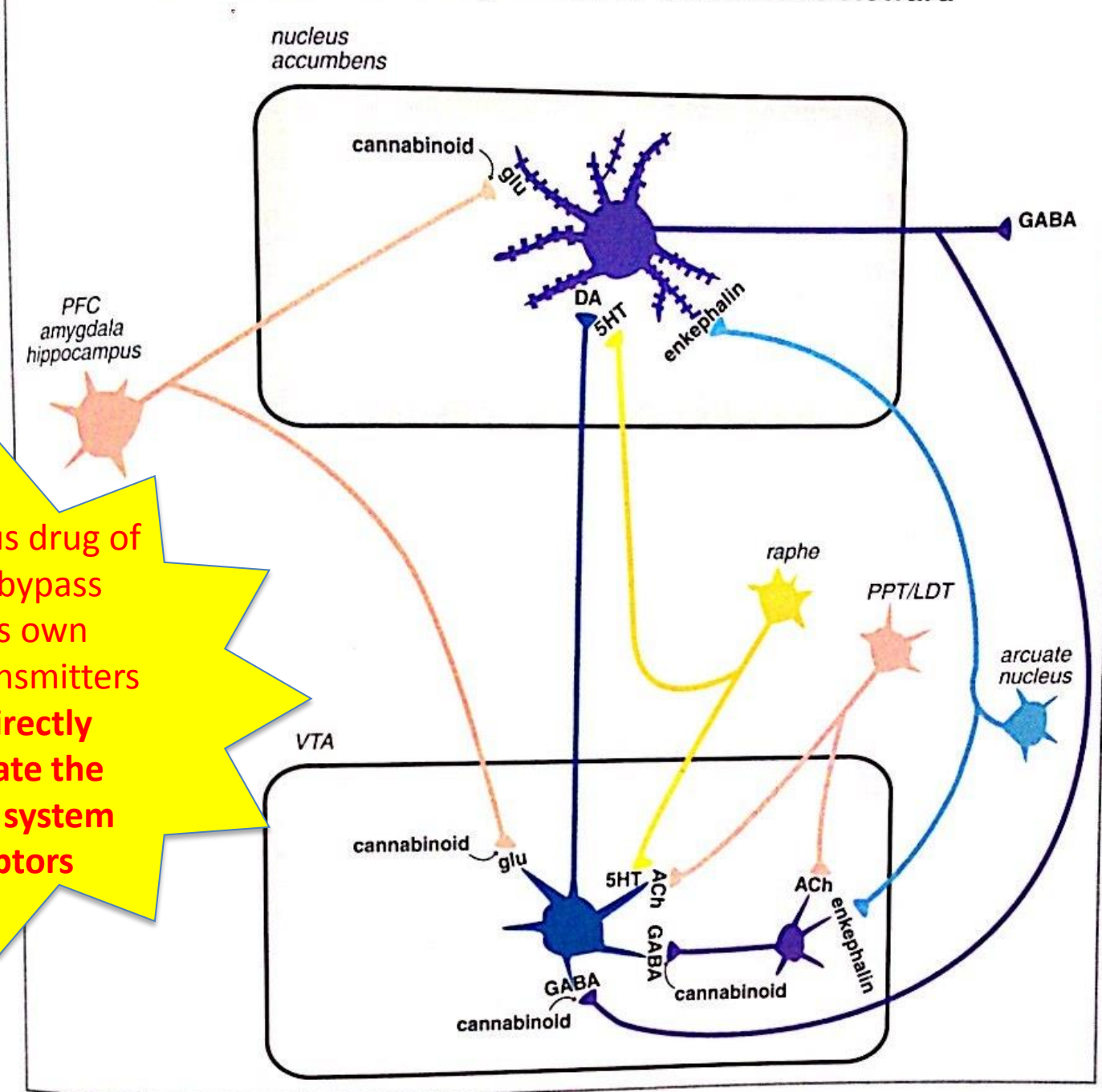
- Intellectual accomplishments
- Athletic accomplishments
- Enjoying a concert
- “Natural Highs”
- Brain’s OWN
 - Morphine/Herion (endorphins)
 - Marijauna (anandamide)
 - Nicotine (acetylcholine)
 - Cocaine or Amphetamine (Dopamine)



"I'm going out to get some endorphins."

Delivers normal reinforcement to adaptive behaviors

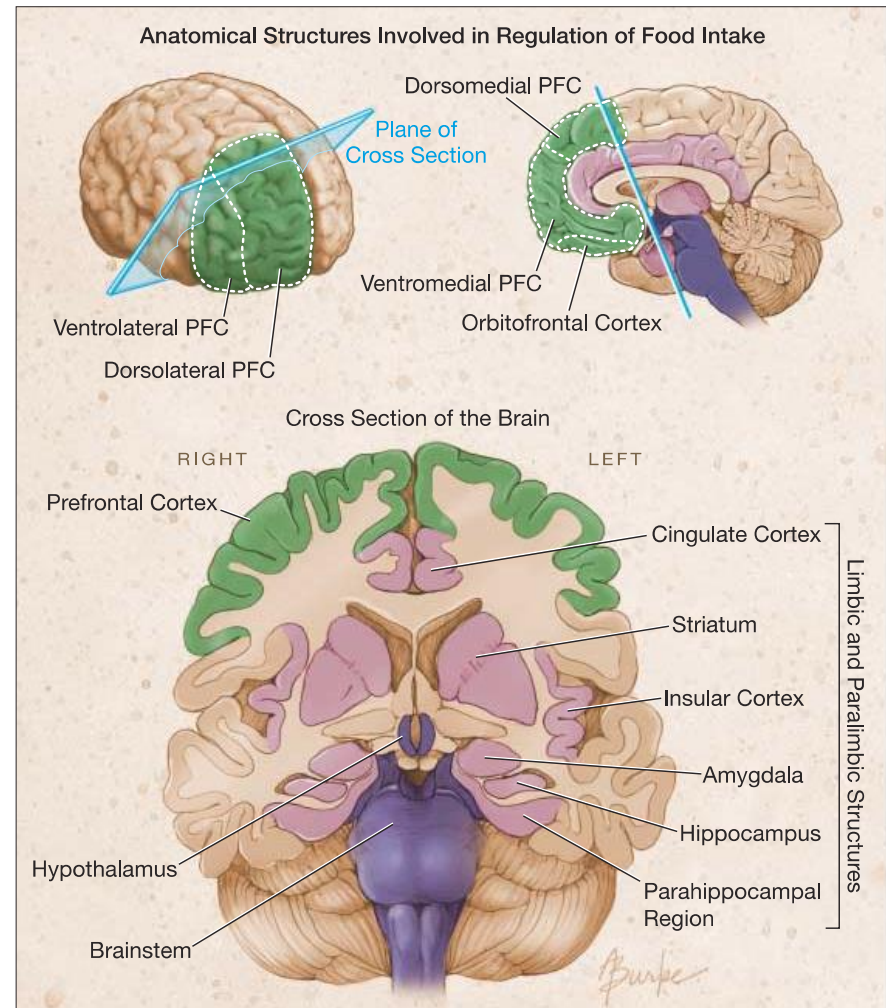
Neurotransmitter Regulation of Mesolimbic Reward



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

Adopted from *Essential Psychopharmacology 3rd edition* Steven Stahl

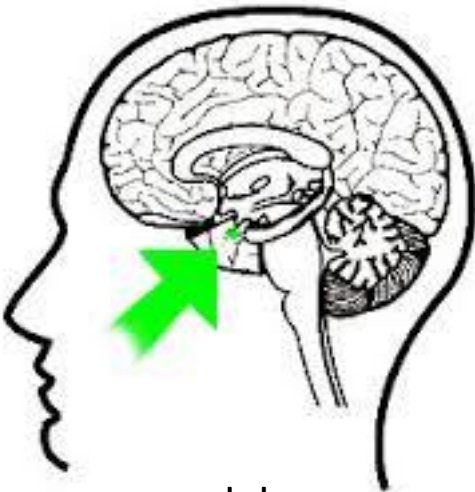
FRONTAL LOBE VERSUS THE LIMBIC SYSTEM



THE REACTIVE REWARD SYSTEM

**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 hijack the entire reward circuitry when addiction develops.



amygdala

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.

THE REFLECTIVE REWARD SYSTEM

**Competitive with
Reactive System
From Prefrontal
Cortex**

RESULT: Maintained



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

CNS DEPRESSANTS



ETHYL ALCOHOL, ETHANOL, ETOH

- Pharmacology:
 - Ethanol is the allosteric modulator of γ -aminobutyric acid A (GABA_A) receptors.
 - Thus acutely, alcohol renders its central effects (eg, anxiolytic, sedative, anticonvulsant, and motor coordination impairment) - GABA_A 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.

-Faingold CL, N'Gouemo P, Riaz A. Ethanol and neurotransmitter interactions— from molecular to integrative effects. *Prog Neurobiol* 1998;55(5):509–35.

-Tsai G, Coyle JT. The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. *Annu Rev Med* 1998;49:173–84.

-Di Chiara G, Imperato A. Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with trans-cerebral dialysis in freely moving rats. *Ann N Y Acad Sci* 1986;473:367–81.

ETHYL ALCOHOL, ETHANOL, ETOH

- 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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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 α_2 receptors or lack of α_2 agonist activity and excessive norepinephrine (NE) production as the excess extracellular DA is converted into NE via DA- β -hydroxylase.

Hawley RJ, Nemeroff CB, Bissette G, et al. Neurochemical correlates of sympathetic activation during severe alcohol withdrawal. *Alcohol Clin Exp Res* 1994; 18(6):1312–6.

Sjoquist B, Perdahl E, Winblad B. The effect of alcoholism on salsolinol and biogenic amines in human brain. *Drug Alcohol Depend* 1983;12(1):15–23.

Pohorecky LA. Influence of alcohol on peripheral neurotransmitter function. *Fed Proc* 1982;41(8):2452–5.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.
 - Extrapiramidal 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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **Withdrawal (Hallucinations)**
 - Hallucinoses 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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.

ETHYL ALCOHOL, ETHANOL, ETOH

- **Dependence:**

- Disulfiram, an aldehyde dehydrogenase inhibitor, causes the classic antabuse reaction
 - (ie, palpitations, flushing, hypo- tension, 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.

De Sousa A. An open randomized study comparing disulfiram and acampro- sate in the treatment of alcohol dependence. *Alcohol Alcohol* 2005;40(6): 545–8.

De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treat- ment of alcohol dependence. *Alcohol Alcohol* 2004;39(6):528–31.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.⁷³ Some large studies have contradicted their efficacy for alcohol dependence.

Campral (Acamprosate Calcium) Home Page. 2010. Available at: <http://www.prempharm.ca/Campral%20Product%20Monographs%20English.pdf>.

Littleton J. Acamprosate in alcohol dependence: how does it work? *Addiction* 1995;90(9):1179–88.

ETHYL ALCOHOL, ETHANOL, ETOH

- **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.

ETHYL ALCOHOL, ETHANOL, ETOH

- 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

BARBITURATES

- 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
 - T_{1/2} short ones are lipid soluble thus fast to induce sleep, and long T_{1/2} ones are slow to induce sleep with long hangover

BARBITURATES

- 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.

GENERAL ANESTHETICS

- Thiopental (Pentothal)
- Methohexital (Brevital)
- Propofol (Diprivan)
- Etomidate (Amidate)

Propafol

- 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

BENZODIAZEPINES

- 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 tegentum 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

SEROTONINERGIC DRUGS AS ANXIOLYTICS

- 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

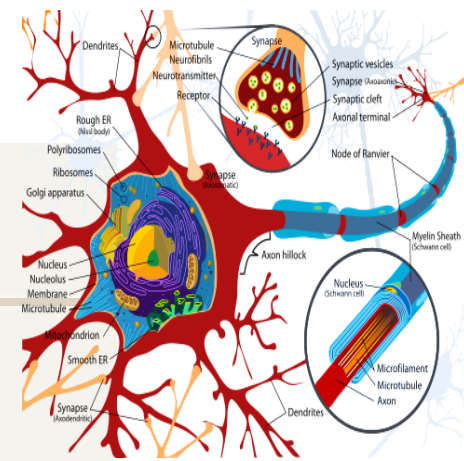
Ketamine

- 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

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

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



STIMIULANTS

- Cocaine
- Amphetamines
- Other behavioral Stimulants

COCAINE

- 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

COCAINE

- 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
 - Hypervigilance, sleep deprivation
 - Impulsive and compulsive behavior
 - Acute toxicity: 1-2 mg/kg body weight
 - Chronic cocaine use leads to virtually every psychiatric syndrome

COCAINE

- 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:
 - Sympathomimetics
 - 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.

AMPHETAMINES 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

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

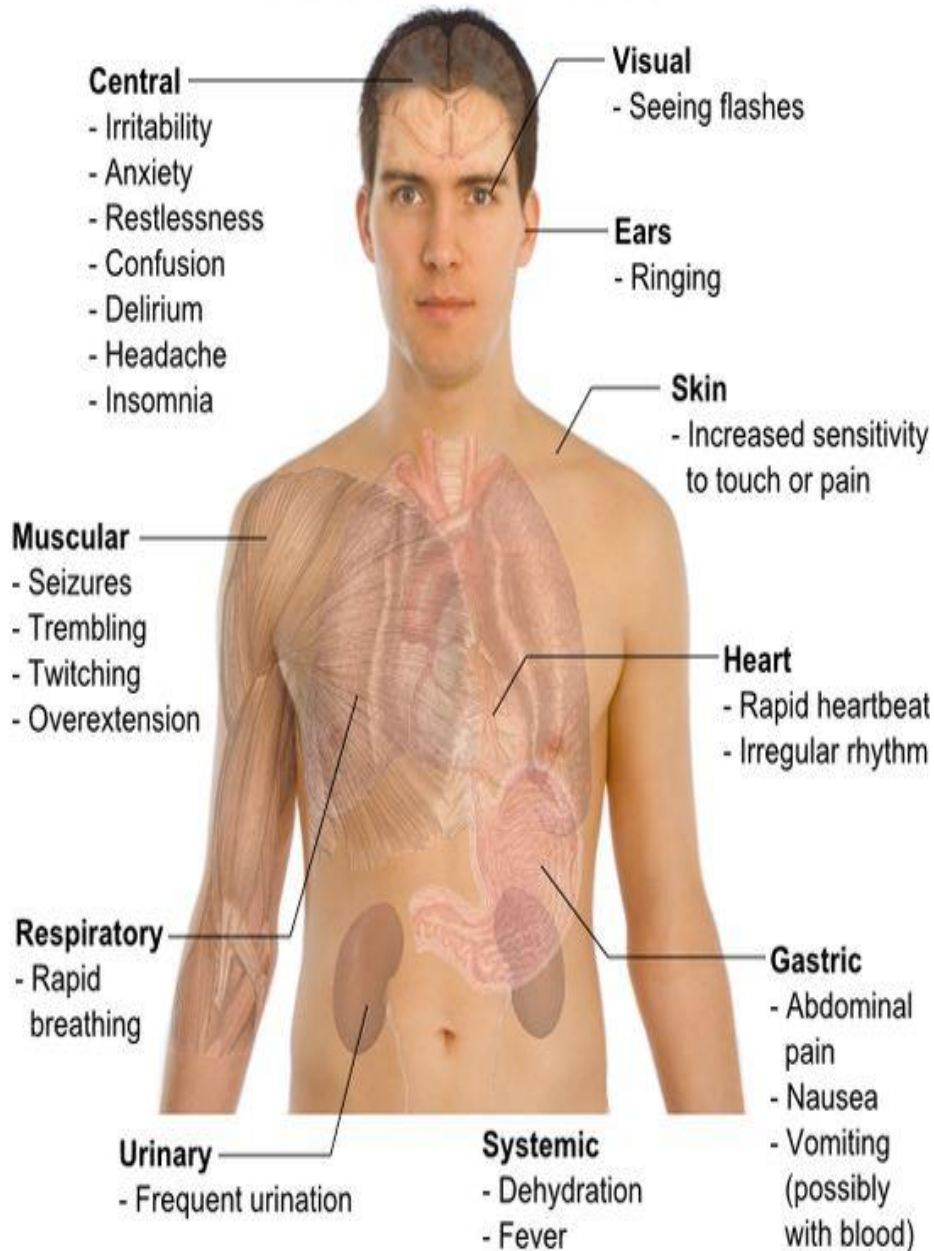
Adapted from Journal of Food Science, 2010; American Academy of Pediatrics, 2011; USDA National Nutrient Database for Standard Reference, Release 23, 2010; Consumer Reports, 2011; Mayo Clinic Proceedings, 2010
*Sizes are listed in fluid ounces (oz.) and milliliters (mL).

**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 hospitalization

Main symptoms of Caffeine overdose

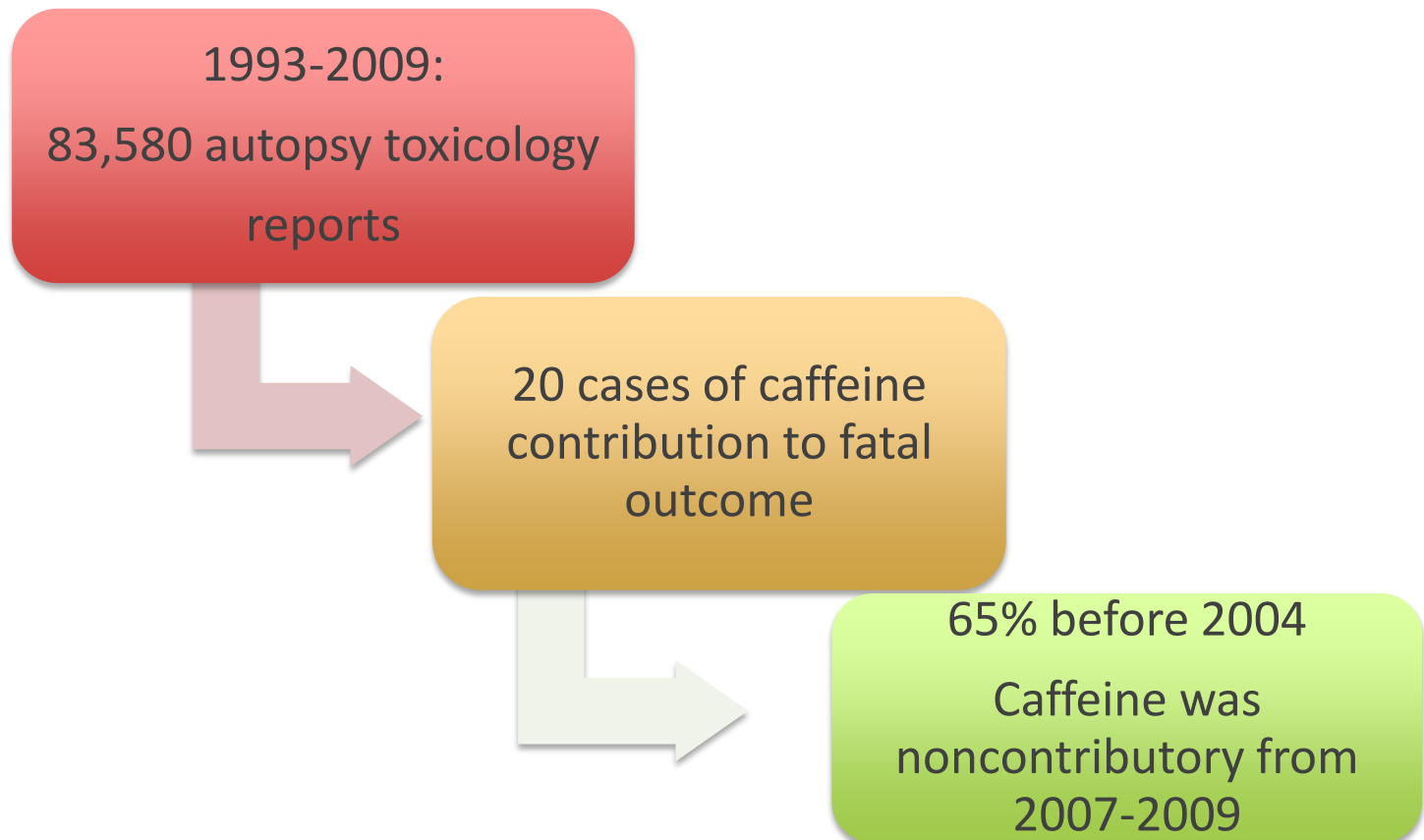


Caffeine

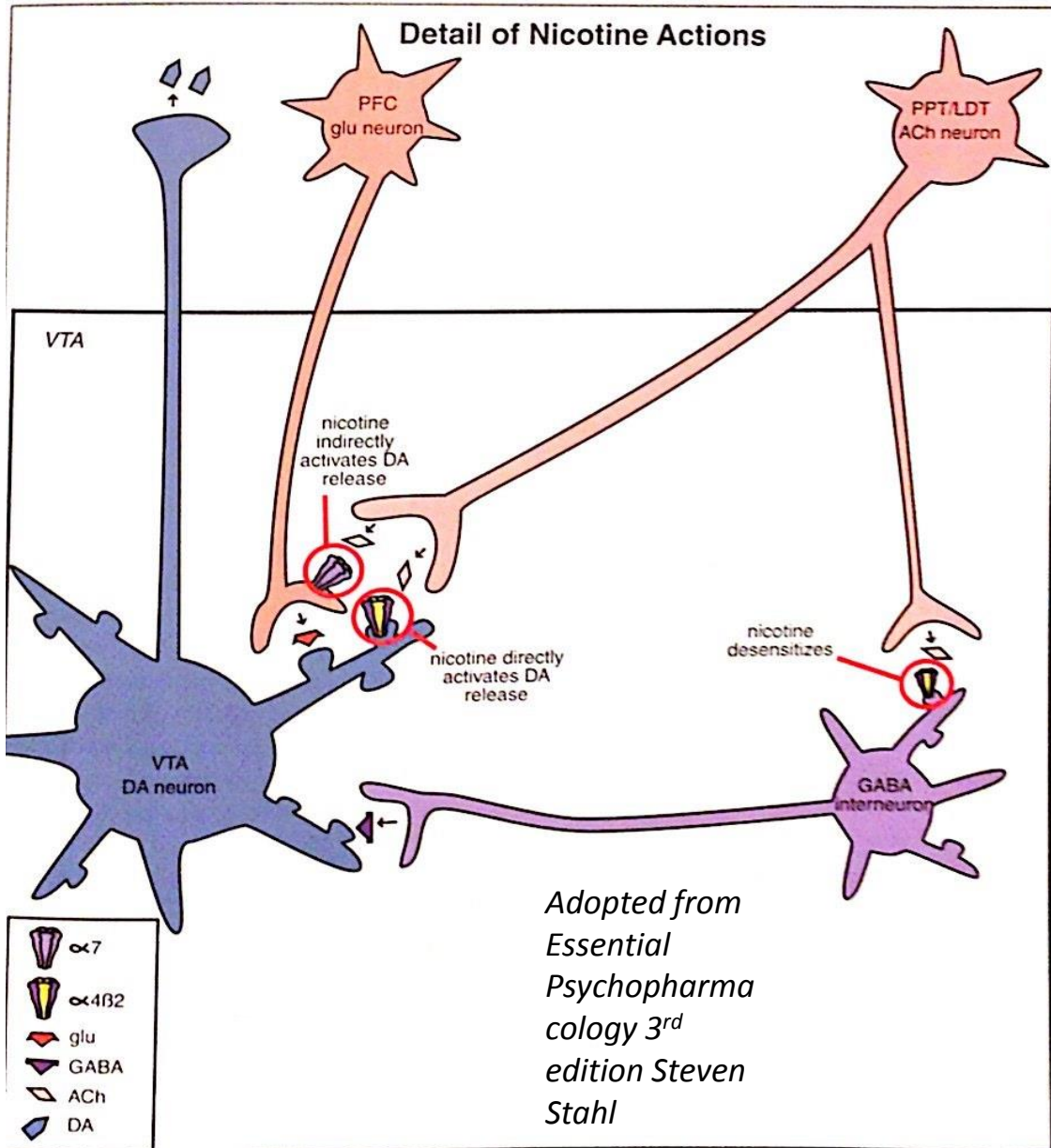
- Metabolism and Elimination
 - Varies widely amongst individuals
 - Liver function
 - Concurrent medications
 - Oral contraceptives can double half life
 - Fluvoxamine (Luvox[®]) can reduce clearance by 90% and extend half life by 10 fold
 - Fluoroquinolone antibiotics reduce clearance
 - European research 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



NICOTINE



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 consistent low level just enough to reduce craving, but avoid withdrawal.

THE END PART 2

- Questions?
- Comments?
- Share Ideas?