# Psych 2020 Notes

A drug is a chemical compound that may produce psychological, behavioural, and physiological effects

Psychoactive effects: Alterations in cognitive, behavioral and motor process

- Such as: euphoria, distortions of time perception, hallucinations, or increased libido

Drugs in categories

- Useful in some aspects but not exactly representative of similarities between drug effects
- Common categorizations:
    - Alcohol
    - Caffeine & minor stimulants
    - Nicotine
    - Cannabis
    - Hallucinogens,
    - Inhalants
    - Major stimulants
    - Sedative hypnotics
    - Opiates
    - Steroids

Surveys

- Governments perform surveys to gauge drug use in their jurisdictions
- Can be differentiated by age groups, categorizations of drugs, different aspects of drug use such as frequency, etc.

Statistics:

- 77% of Canadians aged 15+ consumed alcohol in the past year (83 for men, 73 for women)
- 20% of Canadians aged 15+ exceeded the low risk alcohol drinking guidelines for either long term or short term effects (2/day for women, 3/day for men)
- 13% of Canadians, 15+ identified as current smokers with 16% of males and 10% of females (highest in the 20-24 age range)
- 9% of Canadians aged 15+ report daily smoking
- 13% of Canadians 15+ have tried e-cigs, 30% of 20-24
- 12% of Canadians aged 15+ have used a cannabis product in the past year with the rate being higher in males (15%) than females (10%)
- 2% of Canadians aged 15+ reported past year use of at least one of the following drugs
    - cocaine, MDMA, amphetamine, hallucinogen, heroin, or other illegal opiates
- Past year medical use of opiates, stimulants or sedative-hypnotics was reported by 22% of Canadians
    - Use higher in females than males (25/18)
- Medical use of opiates at 13%, abuse at 2%
- Medical use of stimulants at 1%, abuse at 23%
- Medical use of sedative hypnotic was reported by 10%, abuse at 3%

- Non-medical use (NMU) of one of the above prescribed drugs was higher in those less than 25
- 3% of Canadians aged 15+ reported at least one harm (physical, mental, emotional, social) from NMU

Drug Names:

Drugs have four names that are used interchangeably

1. Chemical Name: Terms used to describe the type of molecule and the locations of chemical groups on the molecule
    a. Ex. 1,3,7 trimethylxantine is the chemical name for caffeine
    b. This name is not common in public use
2. Generic Name or Non-proprietary name: commonly used name for a drug; a name that can be used by any company marketing the drug
    a. Diazepam, triazolam, etc.
3. Trade name or proprietary name: given by a company and can only be used by that company
    a. Prozac, Halcion, Valium, etc.
    b. A drug may have several trade names once the original patent has expired
4. Street Name: derivatives of trade names or names in reference to some physical aspect of the drug
    a. Love drug, barrel acid, black beauties, etc.

Basic Processes when a drug is administered:

1. Drug is administered and absorbed (gets into the blood)
2. The drug is then distributed through the body via the circulatory system
3. The drug reaches its site of action
4. Exerts its effect
5. Leaves site of action
6. Drug is metabolized to an inactive form
7. Drug and its metabolites are eliminated from the body

- Administration, absorption, distribution, metabolism, elimination
    - Collectively known as Pharmacokinetics
    - Processes involved with the interaction of the drug with receptors are known as pharmacodynamics

Routes of administration

- The most common methods are:
    - Oral
        - Must pass through the stomach or small intestine into the bloodstream
            - Many drugs are destroyed in the acidic environment of the stomach
        - Drugs that are alkaline (basic), most drugs, become ionized in the stomach and cannot pass out into the bloodstream
        - Once drugs reach the more alkaline small intestine, they can be absorbed into the bloodstream If they pass through the intestine wall by simple passive diffusion from the area of higher concentration to the area of lower concentration

        - Drugs taken orally are routed to the liver where a substantial part may be metabolized (first pass metabolism) before the drug even has an opportunity to produce an effect
    - Mucous membranes – nose, eyes, vagina, rectum, skin
        - Eg. Cocaine through the nose
        - Nicotine patches
        - Chewing gum caffeine and nicotine, are absorbed through both mucus membranes in the mouth and the swallowing of saliva into the stomach
    - Inhalation – very effective method for administering drugs although this method can produce considerable lung damage
        - Inhaled drugs include nicotine, thc, and solvents such as glue and gasoline
        - Two common terms:
            - Huffing and bagging
        - Inhaled drugs reach the brain in about 5-8 seconds and is faster than if the drug is injected
    - Injection – largely dependent on the blood flow in the area of injection
        - The volume of blood is greater in the peritoneal cavity than in the muscles and is greater in the muscles than under the skin
        - Absorption is more rapid following intraperitoneal administration than following intramuscular, which is more rapid than subcutaneous
        - Mainlining is the term used for intravenous injections in the drug subculture
        - 'skin popping' is the term used to refer to subcutaneous injections of illicit drugs

Distribution of drugs

- drugs by injection (other than iv) or via pulmonary route enter circulation diffusing through pores in capillary walls
- those taken orally must be lipid soluble to be absorbed from the digestive system since there are no pores in the lining of the stomach or intestines
- drugs are absorbed from the site of administration into the circulation and is distributed throughout the body roughly proportionally to the blood flow in an area
- Several factors which affect the entry of a drug into the circulation and its ultimate arrival at the target site
    - Ionization
        - Most drugs are weak acids or weak bases
            - Weak acids readily ionize in alkaline environments and become less ionized in acidic environments
            - It is the opposite for basic drugs
        - Ionized molecules are not readily absorbed, thus the % of non-ionized molecules determines the rate of absorption
        - The lining of the digestive system has a ph that ranges from 1.5 (acidic) to 7 (neutral)
            - Gets less acidic further from the stomach

        - This makes it so the rate of gastric emptying has a profound influence on the onset of drug action
        - Ionized particles penetrate more poorly
    - Lipid solubility
        - These penetrate cell membranes more readily than non lipid soluble compounds
            - Ex. Heroin is more lipid soluble than morphine (although they're chemically similar) and thereby crosses the blood brain barrier more easily
    - Blood brain barrier
        - Not a physical barrier but the permeability characteristics of brain capillaries is restricted
        - This barrier reduces diffusion of water soluble and ionized molecules but does not impede lipid soluble or un-ionized molecules
        - Similar to absorption by the placenta
            - Fetuses absorb 75% of the mothers concentration within 5 minutes
    - Bonding
        - Drugs administer their affect by interacting with receptors at the target tissue
        - A bond forms between charged groups in the receptor molecule and oppositely charged groups on the drug
        - Most often a drugs effect is proportional to the fraction of receptors occupied
        - Binding is reversible, meaning the drug may become bound, then unbound, and this may continue until the drug is somehow deactivated
        - The same is true for neurotransmitters
    - Agonists
        - A drug that mimics the effect of a neurotransmitter
        - This may occur because the agonist binds to receptors, blocks reuptake or inhibits metabolic breakdown
    - Antagonists
        - Compounds which reduce the effects of a receptor agonist by binding to active receptors but producing no pharmacological action
        - Naloxone is an opiate receptor antagonist
        - Different agonist drugs exert different levels of agonistic activity
            - This is relevant since it is possible to reduce the agonistic activity of one drug by using another that will occupy the same receptors but exert a weaker agonistic action
            - There are a limited number of receptors to be occupied and if those receptors are occupied by a weak agonist then even if a stronger agonist is administered it cannot access the receptors

Dose Response Curve

- The responses exhibited from the administration of a drug are graded according to the amount of the drug given → the dose
    - Usually expressed in mg, or mg/kg on a weight of patient basis
        - This is done to ensure a similar reaction
- Dose response curve (DRC) is the most commonly used graphical presentation mode of drug effects
    - Vertical axis of a DRC typically shows the % of subject exhibiting the measured effect
    - Horizontal axis shows the dose
    - Allows the comparison of potency
- A more potent drug has a curve to the left of a less potent drug
    - There is often more than one drc for a drug as it depends on what response you are measuring
- ED50: the dose of the drug that is effective in producing a response in 50% if the subjects
- LD50: the dose which kills 50% of the subjects
- Therapeutic index: ratio of LD50/ED50
    - Higher the ratio, greater the difference, and the less likely the chance that lethal or toxic effects will occur
- The Margin of Safety: A more conservative measure of a drugs safety and is the ratio of the LD1/ED99
    - This will always be a smaller value than the TI

Phenomena

- Chronic drug use may result in a progressive attenuation of a drug effect → tolerance
    - Represented by a shift to the right in the dose response curve
- Some drug effects are progressively augmented over the course of repeated administration → sensitization
    - Depicted by a shift to the left in the DRC
- A change in responsiveness to one drug may transfer to other drugs → cross tolerance & cross sensitization
- Tolerance
    - Tolerance does not occur to the drug – it occurs to the drug's effects, developing at different rates to different drug effects
    - Tolerance of the drug's desired effects may occur quicker than to the drug's toxic effects
        - Increasing the dose to achieve the same desired affect may increase the risk of exhibiting toxic affects
        - The TI will decrease
    - This is a major issue with street drugs where potency may change from batch to batch or dealer to dealer
        - Overdosing is common in this case

Physical Dependence

- Said to have developed when a chronic user of a drug experiences withdrawal syndrome (a set of symptoms) upon cessation of administration
    - Ex. Caffeine headaches → have more coffee
- Leads to Negative Reinforcement
    - Engaging in some behavior terminates or prevents the occurrence of some unpleasant event
- Addiction
    - Not defined in the Diagnostic and Statistical Manual 5 (DSM V) although common in usage
    - Omitted 'because of its uncertain definition and its potentially negative connotation'
- Substance Use Disorder
    - Described as ranging from mild to moderate to severe
    - This is a diagnostic category in DSM V
    - When this is diagnosed the drug's name is put in place of 'substance'
    - DSM V recognizes 9 classes of drugs that qualify for substance use disorder designation:
        - Alcohol, cannabis, hallucinogens, inhalants, opioids, sedative-hypnotics & anxiolytics, stimulants, tobacco, other (steroids)
    - Essential feature of SUD is a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems
        - Often SUD results in an underlying change in brain circuits that may persist beyond detoxification
    - The American Psychiatric Association recognizes 3 different levels of substance use disorder based on the number of criteria a patient exhibits in each of 4 categories

DSM V Criteria for SUD:

1) Impaired control
    a. The individual may take the drug in larger amounts or over a longer period than was originally intended
    b. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful attempts to decrease of discontinue use
    c. May spend a great deal of time obtaining the substance, using the substance, or recovering from the effects of the substance
        i. In severe cases, virtually all the individual's daily activities revolve around the substance
    d. Craving occurs – Craving is queried by asking if there has ever been a time when they had such strong urges to take the drug, they could not think of anything else
2) Social impairment
    a. Failure to fulfill major role obligations at work, school, home, or elsewhere

    b. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the sub.
    c. Important social, occupational, or recreational activities may be given up or reduced
3) Risky Use
    a. Recurrent drug use in situations or under conditions where use is physically hazardous
    b. The individual continues substance use despite knowledge of having a persistent or recurrent physical or psychological problem associated with use
        i. The key issue is not the existence of the problem but rather the failure to abstain from use despite the recognition of the difficulties caused
4) Pharmacological Criteria
    a. Tolerance, marked by requiring an increasingly large dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed
    b. Withdrawal symptoms varying according to the drug
        i. Neither of the above is required to diagnose a SUD though

- Severity of the SUD is measured based on how many of the above criteria are met
    - Mild – 2-3
    - Moderate – 4-5
    - Severe – 6+

Substance-Induced Disorders

- Seen as distinct from SUD as per the DSM V
- Essential feature is a reversible substance-specific syndrome that is causing some level of problem and is due to recent ingestion of a substance
    - These include intoxication, withdrawal, etc.
- DSM V recognizes 10 classes of drugs that may produce SIDs, these being the 9 recognized as producing SUD, and Caffeine

Termination of Drug Action

- There are several routes of drug elimination
    - Skin, lungs, kidneys
    - A small amount may leave in sweat
- The most important route of elimination is via the urine after the drug has been metabolized in the liver
- The liver is a very important organ in this process because it is the major site of enzymatic breakdown of drugs
    - Usually results in metabolites, which are less lipid soluble (more water soluble), larger, carry a greater charge, and are inactive or less active than the original compound
    - This is important because they are *less* likely to be reabsorbed from the kidneys
- Renal reabsorption is pH dependant
    - Weak acids are more readily when tubular urine is alkaline because the weak acids become more ionized and are trapped in tubular urine
        - Conversely, weak bases are excreted more if urine is acidic

    - With that in mind, pH is managed to aid treatment of drug toxicity
        - Sodium acetate is a urinary alkalizer and sodium biphosphate is a urinary acidifier
    - Although this is a slow treatment and is not useful for acute overdose

Elimination Half Like ($t_{1/2}$)

- Refers to the time needed for half of a drug dose to be eliminated from the body
- Relevant to understanding the duration of a drug's effects and is important when considering which drug to use for certain medical conditions
- It takes 6 half-lives for most of a drug to be eliminated (98.4%) and for a person to be considered drug free
    - The half-life of Marijuana is 5 days at least

The Neuron and Neurotransmission

- Drugs affect neurotransmission
- The neuron is the functional unit of the nervous system
- An interneuronal synaptic junction consists of the presynaptic element and the postsynaptic receptor area
    - They are separated by a small space called the synapse
- An action potential arriving at an axon terminal can cause the release from the presynaptic element of substances known as the neurotransmitters
    - Neurotransmitter substances are stored in synaptic vesicles in the axon terminal of the presynaptic element
    - The arriving action potential causes these vesicles to attach to the presynaptic membrane and open, exuding the stored neurotransmitter
    - The exuded neurotransmitter crosses the synaptic cleft where it binds to receptor elements (transmembrane proteins)
    - There may also be receptors on the presynaptic element called auto-receptors, giving negative feedback, regulating the release of the neurotransmitters

Neurotransmitters

- Most drugs exert their action by affecting the synthesis, release, or reuptake of neurotransmitters
- General model of the synthesis and breakdown of neurotransmitter substances:
    - Precursor substances, which are most often amino acids available from diet, are the basic building blocks of neurotransmitters
    - Synthesizing agents are needed to build neurotransmitters from the precursor
        - Often more than one step may be involved in synthesis of a neurotransmitter, and usually the action of one of the synthesizing agents is the slowest or rate limiting step in neurotransmission
    - The neurotransmitter once synthesized must be transported to the presynaptic terminal and stored
    - The stored or newly synthesized neurotransmitter is released
    - Released neurotransmitters bind to postsynaptic receptors
    - The neurotransmitter becomes unbound at which pint it can bind again to the receptor to produce additional action, attach to transporter proteins and be

taken back up (reuptake) into the presynaptic element to be used again, or attach to proteins that catabolize or breakdown

- There are a very large number of potential neurotransmitters

# Alcohol

There are several types of alcohol

- Here alcohol is either Ethanol or Ethyl Alcohol
- Formed as a result of the conversion of sugars into cellular energy
    - Formula: $C_6H_{12}O_6 \rightarrow 2C_2H_5OH+2CO_2$
    - One molecule of glucose (or some other sugar) is acted upon by yeast, in the presence of heat, and the absence of oxygen, produces cellular energy and 2 molecules of ethanol ($C_2H_5OH$) and 2 molecules of carbon dioxide as waste
    - This process is called fermentation
    - Occurs naturally in any item that has sugars (such as fruits) or starches that can be converted to sugars (such as grains and potatoes)
- Alcohols are made commercially using tightly controlled processes

History of Alcohol Use

- The first alcohols were surly made by accident
- Archeology shows that beer jugs were used to make alcohol intentionally as long ago as 10000 BC
- Fermented honey, called Mead, is recognized as the first intentionally produced alcoholic drink
- Alcohol was a normal part of life in Egyptian, Chinese, Babylonian, and Indian societies from 5000 to 2000 BC
    - Moderation was the norm
    - Laws were aimed at production and sale of alcohol instead of on the drinking
- Wine was a regular part of Greek society by 2000 BC
    - Evidence of growing concern about abuse
    - The Cult of Dionysus was devoted to heavy drinking as it brought one closer to the gods
    - Plato and Aristotle spoke of the dangers of excessive drinking
- Drinking was commonplace in ancient Rome
    - First wine connoisseurs as they would import based on quality, discussing the merits of different vintage years, using specialty glasses, and trying to one up each other
    - Soldiers were promoted based on how much they drink
    - Several writers here suggested a view of chronic alcoholism as a disease, much like many today
        - Seneca (4BC-65AD)
            - Distinguished between moderate and heavy use
                - ‘loss of control’
        - Ulpain (170-228AD)

        - Addictive nature noted
- The highest natural form of alcohol is only 14% at which the yeast dies and stops the process
    - Thus ancient people discovered distillation to strengthen it
    - Dated around 700 to 800 AD although the Chinese had their own methods in 1000 BC
- Distillation
    - Alcoholic liquids are boiled
    - Alcohol, having a lower boiling point, steams off, condenses by cooling and is now a higher concentrated alcohol
        - Can be repeated several times
- Drinking in Europe
    - Was primarily wine and beer until the 1500s
    - Decline of the church, improved transport, and prosperity brought the rise of alcohol
    - More distilled beverages that are cheaper
    - Source of government revenue through taxation
        - Originally supported drinking
        - Today, used for revenue and control, Price elasticity of alcohol at -0.5% per % increase in price
- Gin in England
    - Potatoes and flavoured with juniper berry
        - 'madam Geneva'
    - 1720-1750, a jump in gin consumption called the Gin Epidemic
        - Legislative motions to curb gin sales but they cause the 'Gin Riots'
- Alcohol in the US
    - Colonizers brought alcohol with them
        - Widespread and often heavy
    - Large opposition to alcohol, mainly distilled spirits
        - Dr Benjamin Rush
            - Alcohol is a disease and abstinence is the only cure
            - Made the inebriometer to show the effects of different types of drinking
        - Lead to the temperance movement in Canada and US
            - American Society for the Promotion of Temperance
            - Started promoting moderation and eventually abstinence
        - Women's Christian Temperance Union formed in 1873
    - In 1875 a temperance national meeting lead to the Dominion Alliance for the Total Suppression of the Liquor Traffic
    - Culminated in the Volstead Act of 1919, total prohibition in US and Canada
        - Canada only was in effect from March 1918 to December 1919
        - Provinces had power to prohibit independently
    - Speakeasies popped up as places where illegal alcohol could be sold

Consumption in Modern Times

- Second most widely used psychoactive substance in the world
    - World Wide 15+ alcohol per capita consumption is estimated to be 6.1 litres of pure alcohol or 350 standard drinks per year
    - Top 2 are Portugal and Luxembourg at 1100 drinks/year
    - Canada is 45$^{th}$ at 450 Drinks/year
    - Lowest are the eastern Mediterranean and SE Asian regions at 80to90% abstinence
- Average first drink age is 12 in Canada and the US
    - Average age for consistent use is 16
- 80% of Canadians have drank in the last year
    - 20% of those dangerously
- SEE STATS ON P.16
- See AUDIT alcohol questionnaire on p 17

Canada

- Canadians spent about 20 billion on alcohol in 2014
    - 667 per person
- In social costs, alcohol costs 14.5 billion
- 15% of all healthcare expenditures are alcohol related while 10% of all deaths are
- 40% of traffic fatalities involve intoxication
- 50% of fall and fire deaths
- alcoholics die 15 years sooner
- 80% of alcoholic beverages are consumed by 30% of drinkers
    - 50% is consumed by 10% of drinks
- 10% of males and 5% of females meet the definition of alcohol use disorder

Characteristics of Alcoholic beverages and the Absorption of alcohol

Main types

- Beer
    - Average 5%
- Wine
    - Average 9% to 14%
    - Fortified wines are about 20%
- Distilled spirits
    - Average 40%
    - Absinthe may be up to 80%
    - Neutral grain spirits are 95%

Absorption

- Mainly taken by drinking however inhalation of the alcohol vapors can be done
    - AWOL (alcohol without liquid) is a mist that can be inhaled
        - Effects are more rapid
        - Could be dangerous as it does not have a first pass of metabolism before entering the brain
- Most alcohol is absorbed in the small intestine, some in the stomach
    - Alcohol is subject to metabolism in the stomach by alcohol dehydrogenase

- Absorption is impacted by several factors
    - The greater the concentration of alcohol up to 25% the more rapid its absorption
        - Higher peak concentrations
        - Moves to intestines more quickly
    - Other chemicals in alcoholic beverages slow absorption
        - Vodka and Gin are quicker than colored spirits like rye
    - Food in the stomach sloes absorption and can reduce peak blood alcohol concentrations by as much as 50%
        - Because of delayed gastric emptying, the stomach can metabolize more
    - Alcohol in carbonated beverages, like champagne, is more rapidly absorbed
        - Carbonation speeds gastric emptying
    - The more rapidly the beverage is ingested the higher the peak BAC
    - Lean body material disperses alcohol more than fat body material
    - More alcohol enters a female's bloodstream due to 50% less metabolism in the stomach
- Alcohol is metabolized by alcohol dehydrogenase to acetaldehyde
    - Acetaldehyde is then broken down by acetaldehyde dehydrogenase to acetic acid and ultimately to carbon dioxide and water
    - One standard drink contains 13.5 grams of alcohol (13500mg)
    - 5% escapes by lungs and sweat, high doses up to 15%, causing alcoholic's breath
- Typical measure of alcohol is the Blood alcohol curve (BAC) or the Blood alcohol level (BAL)
    - Shows the amount of alcohol in blood as a function of time since ingestion
    - Bell shaped curve
    - In Ontario, BAC of 0.05 or more defines legal impairment
        - See BAC calculators

Alcohol effects

- 90% of blood alcohol crosses the blood brain barrier
- Effects by volume at different BACs:
    - 0.03 or less: little effect, no loss of coordination, slight euphoria, increased sociability, slight stimulating effect on behavior
    - 0.03-0.06: relaxation, sensation of warmth, euphoria, beginning of behavioral, cognitive, and reasoning impairments
    - 0.06-0.09: noticeable behavioral impairment, reduced reaction times, impairment of attention, judgement, self control, perception, euphoria and dysphoria possible, increased irritability and aggressiveness
    - 0.09-0.12: substantial impairment of motor coordination, attention, judgement, slurred speech
    - 0.12-0.19: gross motor impairment, blurred vision, dysphoria, judgement and perception severely impaired, nausea
    - 0.20: stuporous, confused, disoriented, difficulty standing or walking, nausea and vomiting
    - 0.25: blackouts
    - 0.30: pass out

    - 0.35: coma is possible
    - 0.45+: death is possible

Behavioral ataxia and loss of motor coordination

- alcohol produces loss of coordination and general behavioural ataxia in humans and animals
    - inner ear impacted
- Finger-Finger Test
    - A mark on one hand holding cardboard and the other with a marker
    - Try to touch the two, distance off is measured
    - Related to the stabiliometer
        - Device that quantifies body sway
- Behavioural ataxia measures
    - Tilting plane uses a flat surface that starts out horizontal and is raised slowly on an angle
        - Degree at which they slide down is measured
        - Mainly for animals
    - Rotarod task
        - Rod rotates and rats walk across
        - More drunk, more falls
    - Moving belt task
        - Animal version of walking the line
        - Animal must walk forward on a moving belt to avoid an electrified grid at the back

Effect on body temperature and vasodilation

- Alcohol lowers core temperature because alcohol increases peripheral vasodilation leading to heat loss
- Skin turns warm and red
    - Actually makes you colder
- Causes the jolly red nose and cheeks by breaking blood vessels in the nose and face
    - Associated with Silenus, the classical god of wine and merriment

Impairment specifically related to driving

- Approximately 50% of all fatal highway crashes involving two or more cars are alcohol related
- Approximately 65% of all fatal single car crashes are alcohol related
- 36% of all adult pedestrian accidents are alcohol related
- On average 4 people are killed in vehicle crashes in Canada each day

- Driving ability becomes increasingly impaired as BAC increases
    - Crashes are 4 times greater when the BAC is between .04 and .08, seven times greater when between 0.1 and 0.14, and 25 times greater over 0.15
    - Mainly due to slowed reaction times and reduced attention to stimuli in the peripheral visual field, and reduced judgement

Alcohol Impairments on cognitive tasks

- Alcohol interferes with inspection time, capacity to divide attention among demands, and capacity to sustain attention, capacity to ignore irrelevant stimuli and information processing
- The more complex, the lower alcohol required to interfere

Alcohol and cardioprotective effects

- The French Paradox
- Drinking 1 drink per day for women and 2 for men may lower the risk of cardiovascular disease
- Due to both an increase in high density lipoprotein, which eliminates cholesterol, and a decrease in low density lipoprotein

Alcohol and Sexual Behaviour

- Men
    - At BAC <0.025 sexual responsiveness may be increased but drops off after 0.05
    - 0.1 causes temporary impotency
- Women
    - Reduced by alcohol
    - Increases may occur in subjective arousal and pleasure
- Many men report being more sexual when drunk
    - Discrepancy may have to do with the role that expectancies play in drug effects
        - The effect the person expects
    - Balanced placebo design
        - 2*2 factorial in which one factor is what the participants are told about the substance (real or fake) and the other factor is the real nature of the substance (real or fake)
        - effect on sexual arousal & alcohol: men who thought they were drinking regardless of actuality, had greater penile responses, spent more time watching erotic pictures and reported greater subjective arousal than men who believed they had not consumed alcohol
            - less consistent in women

Alcohol, Violence, and Crime

- strong two way relationship
    - People who commit violent acts often are under the influence of alcohol and people who are victims of violence often have been using alcohol when they are victimized
- Roizen (1997) estimated 80% of homicides, 60% of sexual assaults, 60% of male domestic assaults, and 30% of female domestic assaults, and 15% of sexual abuse cases were committed by someone who is intoxicated
    - 30% of all homicides worldwide are alcohol misuse related
    - In the US and England 60% of males and 40% of females in prison were drinking at dangerous levels before arrest
- Dis-inhibitation Theory
    - Suggests that alcohol lowers inhibitions that normally keep aggressive behaviour in check

        - Based on the effect on serotonin
        - Low levels of serotonin lead to increases in impulses and violent acts
- Expectancies
    - People are more aggressive even if they think they have been drinking alcohol

Blackouts

- Period of amnesia without loss of consciousness
- High risk behaviour exhibited
- 2 categories
    - En Bloc blackouts
        - Inability to later recall any memories from the intoxicated period, even when prompted
    - Fragmentary blackouts
        - More common
        - Less entire
- Blackouts are likely at 0.25 BAC

Hangovers

- Acute withdrawal
- Does not require a history of drinking
- Effected by the level of congeners in the drink
    - Trace amounts of non-ethyl alcohols, oils, and other organic matter that are by-products of fermentation and distillation and that add flavor and color to beverages
    - Colored spirits have more than clear
- Also impacted by acetaldehyde or low blood sugar
- Only thing that will quickly neutralize a hangover is more alcohol

Acute and chronic effects on the liver, brain and other organs

- Consumption of any amount of alcohol will result in an acute fatty liver syndrome
    - Accumulation of triglycerides in the liver during the metabolism of alcohol
- Continued drinking can result in alcoholic hepatitis, accompanied by jaundice
    - Actual destruction of liver cells
    - Loss of appetite, nausea, fever, ascites (fluid accumulation in the abdominal cavity)
- Cirrhosis may be caused by extreme heavy, long term drinking
    - Degeneration of liver cells and thickening of surrounding tissue with a consequent decrease in hepatic blood flow
    - Liver is unable to metabolize toxins
    - Only 10% of alcoholics
    - 75% of all alcoholism related deaths
        - more in women than men
- Alcoholic Dementia
    - 75% of detoxified alcoholics show
- 2 cognitive-impairment syndromes
    - Wernicke’s encephalopathy

        - Confusion, loss of memory, inattentiveness, agitation, staggering gait, and a variety of ocular abnormalities
        - Due to a vitamin B1 deficiency by alcohols reduced absorption of thiamine
    - Korsakoff's psychosis
        - End stage of Wernicke's
        - Actual brain damage
        - Lack of insight, confusion, apathy, both anterograde and retrograde amnesia and confabulation
        - Imagining studies have provided evidence of brain atrophy in human alcoholics

Feminization in Chronic Alcoholics (Men)

- Reduction in testosterone and increase in estrogen
- Breast enlargement, testicular atrophy, loss of facial hair
- Alcohol is partially metabolized in the testes
    - Doing this a lot changes the organ's role away from testosterone production

Lethal Effect

- Death can be caused via respiratory depression
- The LD50 of alcohol in humans is estimated to be 0.45
- Unlikely to achieve this before passing out
- There is no antidote for alcohol poisoning like there is for heroin

## Neurochemical Actions of Alcohol

Alcohol seems to exert its sedative, muscle relaxant and behaviourally impairing effects primarily by action on two neurotransmitter systems: GABA and NMDA glutamate receptors

- GABA receptor unit involves a GABA receptor and several other sites where most sedative hypnotics may bind
    - When GABA occupies its receptor the ion channel opens to allow chloride ions into the neuron making it difficult to generate action potentials
    - When GABA occupies its receptor at the same time that alcohol is occupying the satellite receptors the ion channel remains open longer than usual allowing more chloride ions to enter
- Alcohol also dampens excitatory neurotransmission mediated by NMDA glutamate receptors by reducing the responsiveness of these receptors to glutamate
    - Chronic alcoholism may lead to regulation of NMDA receptors and when alcohol consumption is then terminated the up regulated glutamate receptors produce the signs of alcohol withdrawal
- Alcohol increases the release of endorphins which act to reduce the GABA transmission in the VTA
    - Normally dopamine is controlled here but alcohol causes in increased release
    - Leads to reinforcing effects
- Highlights:

    - Alcohol inhibits the release of acetylcholine in the CNS and since acetylcholine is importantly involved in learning and memory this may explain some cognitive effects
    - There is evidence that some alcohol effects may be mediated by cannabinoid receptors

## Tolerance to Alcohol

Several forms of tolerance:

Dispositional and metabolic tolerance

- Increased capacity of the liver to metabolize alcohol over repeated administrations
    - This reduces the amount that enters the blood stream
- Causes an increased metabolism of other drugs as well
- This however is not a major contributor to the overall level of tolerance

Acute or within session tolerance

- When administered, the BAC first peaks, and then falls making a bell shape
- Mellanby effect: demonstrated in dogs that there was less of an effect of a given blood level of alcohol on the falling or descending limb of the curve than on the rising or ascending limb
    - Aka. Acute of within session tolerance
    - Suggested to result from acutely recruited aaptive responses to alcohol perturbations and it is also suggested that it is these acute adaptations that eventually produce the more common type of tolerance called functional tolerance

Functional or chronic tolerance

- Reflects relatively long lasting adaptive changes in the CNS
- A shift to the right in the dose response curve
- Tolerance effects all symptoms of intoxication

## Classical Conditioning and Tolerance

- Mechanisms underlying the development of tolerance to a drug also underlie physical dependence to the drug
    - Withdrawal symptoms are most often directly opposite to the actual drug effects
        - Ex. A reduced temp during use means fever during withdrawal
- Psychic secretion – Pavlov's word for the dogs salivation upon trigger, the conditioned response
- Subclinical Withdrawal symptoms – withdrawal experienced long after detoxification, which comes on when the subject is exposed to the predrug cues they were used to when they were taking the drug
    - A craving is a the psychological or genitive correlate of the subclinical withdrawal syndrome

## Alcohol Use Disorder: Co-Morbidity and Physical Dependence

The co-occurrence of two or more disorders is termed comorbidity

- It is estimated that 40% of alcoholics have a comorbid disorder
- Most common is major depression, anxiety, antisocial personality disorder, and other drug dependence (40% of alcoholics)
- Comorbidity is a problem for treatment
    - Which first? No good answer
- Physical dependence is benchmarked by the occurrence of withdrawal symptoms consequent upon cessation of drug administration
- Delirium Tremens is used to describe alcohol withdrawal
    - 7-14 days
    - Severe tremors
    - Muscular weakness
    - Disorientation, confusion, hallucinations
    - Nausea, stomach cramping, anorexia
    - Convulsions in 10% of cases, usually 12 to48 hours after detoxification
    - Sometimes death
    - Severity dependent on duration and quantity of drinking
    - Managed by benzodiazepines or barbiturates

## Treatment of Alcoholism

8% of Americans aged 12 and over need treatment for alcohol related problems but only 15% of these people actually seek treatment

- Denial, not being ready, cost of treatment, belief that treatment is not effective, and stigma are holding people back
- Only 40% of people would suggest to a relative or friend to seek help even though they thought the person may have a drinking problem
- Women are less likely than men to seek help
- Two thirds of people were better or abstinent after treatment

Pharmacological Treatments

- Drugs are used as adjuncts to the psychological treatment of alcoholism
- For a long time the only alcoholism drug was Disulfiram (Antabuse)
    - The Disulfiram prevents the breakdown of acetaldehyde by blocking aldehyde dehydrogenase, thus leading to an accumulation of acetaldehyde
    - Upon consumption, the individual experiences a fairly unpleasant set of symptom

# Opiates

Narcotics – from the Greek word “Narke” meaning numbness, sleep, or stupor

- Naturally occurring opiates are alkaloids of the poppy plant Papaver Somniferum
    - The poppy that brings sleep
    - Large 4-5 inch flowers that are red, pink, white, or purple

- Poppy seeds come from this plant
- Of the 25 alkaloids in opium most important are
    - Morphine
    - Codeine
    - Thebaine
        - Not active alone but is the source of the opiate derivative oxycodone
- Poppy regions
    - Southeast Asia, Australia, Mexico, India, Iran, Afghanistan, China, Spain, Parts of the former Soviet Union, Turkey and SA
- Medical use of opium found in Sumerian and Assyrian/Babylonian cultures 4000 years ago (2000bc)
    - Spread to Europe through the Crusades of the 11$^{th}$ and 12$^{th}$ centuries
    - 1520, Paracelsus invents Laudanum (meaning something to be praised)
        - medical drink containing opium, wine, and spices
        - used until early 20$^{th}$ century
- Opium War of the 1840s
    - Britain was trading opium for tea with the East India Company in China
    - Chinese banned the use of opium for trade but Brits did not stop
    - Chinese destroyed shipments of opium
        - Brits declared war
- Opium is heated, not burnt to be smoked
    - Heated in the open and the smoke trailing off is inhaled with a straw
        - Chasing the dragon
- German Chemist Serturner isolated the principal active ingredient in opium in 1803 and named it Morphium after the Greek god of dreams, Morpheus
- Use was greatly improved with the invention of the hollow needle for injections in 1856
    - Used extensively in the American Civil War
        - Abuse became known as Soldiers' Disease
        - Much like the use in the Vietnam war by Americans
- Use was common in US and CAN in the 1800s mainly in the form of Laudanum
    - Common practice among women and children
        - Godfrey's Cordial, A Pennysworth of Peace, and Mrs. Winslow's Soothing Syrup
    - Most common user was middle to upper class, white, females, 30-50 YO
        - Outnumbered men 3:1

US Drug Control

- Began with the Harrison Narcotics Act of 1914
    - Did not outlaw opiate use
    - Required physicians prescribing opiates keep detailed records and pay a small fee

- With pressure from Harry Anslinger the courts ruled that opiate addition was not a medical condition and thus doctors could not prescribe opiates to addicts simply to ward off withdrawal
    - Beginning of criminalization

Canadian Drug Control

- Trace back to racial prejudice and economic problems
    - Chinese building the railroads were good workers but when the employment market came down they were blamed
    - Violence by anti-Chinese Americans
    - 1907 riot in Vancouver over Chinese workers
    - labor minister Mackenzie King dispatched to investigate
        - suggested bill to ban opium trade
            - violated Christian Ideals
            - Chinese were making too much profit
            - Use was increasing among white men and women
        - Failed to cite any health risks of smoking
- 1908 Opium Act made it illegal to import manufacture, or sell opium
    - Use and possession still legal
- 1911 Opium and Drug Act made possession a crime, expanded police powers and made cocaine illegal
- 1920s were harshly anti-drug
- Canadian Emily Murphy (Janey Canuck) wrote the first anti-drug book in Canada which was entitled the Black Candle
    - Called for stricter laws
- Minor changes made to the 1911 act in 1920
- Major changes in 1929
    - Physicians required to keep detailed records of distribution
    - Maintenance doses no longer considered acceptable
    - Cannabis included
    - Stiffer penalties
    - Writ of assistance – gave open search warrants to police
- More penalties were introduced through to the 1970s

Major Opiates, Prescription and Illegal

- Prescription opiates are the second most abused drug in the US, behind alcohol
    - Leading cause of accidental death in the US
- Naturally occurring opiates are Morphine and Codeine
    - Isolated from opium originally as liquid, later as tablets
    - Powder can be snorted or mixed with liquid
    - Abused when used in cough medicine
- Heroin is not naturally occurring
    - Synthesized by C.R. Alder Wright in 1874 by adding to acetyl groups to the morphine molecule
        - More lipid soluble
        - Less ionized

        - Accesses the CNS more readily
    - Introduced as Bayer Heroin in 1898 as a non-addictive analgesic good for coughs
- Fentanyl is a synthetic opioid up to 100 times stronger than morphine
    - Transdermal Patch, lollipops, lozenges, or injection
    - Associated with ODs
- Derivatives of Fentanyl
    - Sold by dealers
    - More potent than fentanyl
    - Added to other drugs sold on the street as a filler
    - Come from China
- Oxycodone
    - Combined with aspirin is called Percodan
    - Combined with Acetaminophen is called Percocet
    - Time release form called OxyContin
    - Synthesized from thebaine in opium
    - Crushing destroys the time release until recent efforts by companies
    - Very high abuse
- Hydrocodone
    - Combined with acetaminophen called Vicodin or Norco
        - Norco has less acetaminophen
    - High abuse levels
- Oxymorphone (Opana)
    - Available in extended release
    - High abuse potential
- Hydromorphone (Dilaudid) widely abused
- Opiate Antagonists used to prevent or reverse OD
    - Nalaxone (Narcan) or Naltrexone
    - Emergency situations

Current Use of Opiates

- Lifetime use in CAN aged 15+ at 0.4%
- Medical use of an opiate reported by 13%
- Abuse of a prescribed opiate at 2%
- Intravenous administration is least common
    - Other than for heroin
        - But may be snorted but not as effective
- Most can be smoked
- Oral administration is the most common method of use
    - Poppy tea is rare but recently noted
        - Really old method

Opiate Effects

- All produce the same effects
    - Tingling sensation and felling of warmth in the lower abdomen
    - Euphoria
    - Drowsiness known as nodding

    - Nausea especially in first timers
    - Depressed respiration
        - Can lead to death
    - Itching over the entire body
        - Red eyes
    - Pinpoint pupils in OD
    - Constipation
    - Cough suppression
    - Pain relief

Opiate receptors and the neurochemical actions of opiates

- Mu Receptors
    - Involved in almost all opiate effects including euphoria, analgesia, repertory depression, dependence
    - In the Ventral tegmental area opiates occupy Mu receptors inhibiting GABA transmission leading to disinhibition of Dopamine neurons in the nucleus accumbens
        - Leads to the rewarding feeling
- Sigma receptors
    - Mediate dysphoria and hallucinations
- Delta receptors
    - Main backup opiate receptor and seems to cooperate with Mu receptors in producing most opiate effects
- Existence of opiate receptors suggests there is an endogenous receptor ligand
    - Two labs in the 70s identified a peptide in brain extracts that mimicked opiates in its ability to bind to opiate receptors
        - Called endophines
            - Endo + orphine
        - Implicated in stress induced analgesia

Tolerance and Physical dependence

- Substantial tolerance occurs to most effects
    - Occurs more slowly and less fully to effects other than euphoria, analgesia, and respiratory depression
- Pavlovian conditioning plays a crucial role
    - Situational specificity of tolerance to the analgesic effects of morphine
    - Loss of tolerance to morphine is largely dependent on the use of extinction trials
    - Lethal effects were seen without predrug cues while those with the cues were largely okay and tolerant
- Users able to control their use are known as chippers
    - Most do not have this control
- Dependence depends on many factors
    - Type, dose, regularity, method
- Withdrawal is typically not life threatening and mainly resemble flu symptoms
    - First is craving, 4-6 hours after use
    - Others peak 24-72 hours after use

        - Dilated pupils
        - Lacrimation (tearing)
        - Intestinal spasms, Diarrhea
        - Rhinorreha (dripping nose)
        - Chills and standing hairs
        - Pain in muscles bones and joints
        - Twitching of extremities
        - The skin takes on a gooseflesh appearance
        - The symptoms will disappear within 7 to 10 days
    - Only administration of an opiate will avoid symptoms
        - Negative reinforcement (to avoid unpleasantness)

Treatment

- Revolving door scenario is common
    - Relapse is the most predictable outcome among treated opiate addicts
    - 80% of treated and released patients relapse within 6 months, most within a week
- Methadone Maintenance
    - Addict is given methadone in place of their typically used opiate
        - Petroleum based synthetic analgesic developed in WW2 as a sub for diminishing supplies of morphine
        - Weaker euphorient but equal analgesic
    - Harm reduction philosophy
    - 20% of heroin
    - widely used in the US since inception in 1958 by Dole and Nyswander
    - Methadone first used in Canada in the early 1960s
    - Taken orally, long duration (10-24 hours)
    - Typically for long time users 2+ years of use
        - Must be drug free before starting
    - Dose must be large enough to hold back withdrawal but not so large as to produce euphoria
    - Some are given 'carrying privileges'
    - Only 20% are able to totally stop opiate use
- Buprenorphine (Subutex or Suboxone)
    - Suboxone (mixed with naloxone) is common
    - Taken sublingually (under the tongue)
        - No antagonistic effect unless crushed and injected
    - Less opiate effect than methadone
    - For less dependent users
    - Longer half life than methadone
- Some countries have used heroin as a maintenance drug

# Cannabis

- Marijuana is the typical street name for the leaves of the Cannabis plant
- Contains several hundred chemical agents of which 60-80 are called Cannabinoids
- Grown in hot dry climates, resin thrives and fibres fall
    - In cool humid climates, resin production falls, and fibres thrive
- Early use traces back 10000 years for use of the fibre and not as a psychoactive substance
    - Oldest cultivated plant not used for food
- Used for psychoactive properties in China around 2800 BC
    - Discovery of effects attributed to Shen Nung
- Introduced to Canada in 1606 by the British and into America by Royal order in 1611
    - Use was entirely as a source of hemp
- In the mid 1800s cannabis, eaten as hashish, was a rage in Europe
    - Hashicins used hashish in the form of a 'sweetmeat' called dawamesc made from the flower tops, boiled in butter, strained and seasoned with vanilla, cinnamon and pistachio
- Ingredient in several patent medicines in the heyday of the trade in the late 1800s
    - Tilden's Extract of Cannabis Indica
- During alcohol prohibition in the 1920s use increased with use common in 'tea rooms'
    - Harry Anslinger waged a campaign against all drug use and got the attention of lawmakers
    - Justified that it was being used by minorities
- In Canada it was classified as a narcotic and was the subject of legislation in 1929

Use

- 45% if Canadians 15+ have used cannabis in their lifetime
    - higher in males than females
        - 52-37%
    - 12% in the past year
        - 15-10%
    - 72% in the past month
        - 33% as daily users
- median age for beginning use is 17

Consumption

- Main ingredient is delta-9-tetrahydrocannabinol (THC)
    - Isolated and synthesized in 1964
- An average 1.5g joint in 1970 would contain 30mg of THC
    - Today the same would contain 60mg
- Hashish is made from the trichromes of the flower bud and leaves
    - Cannabinoid-rich glandular hairs which are separated from the plant material
    - Kief is the product that is then pressed to make hashish
    - Generally 10% THC
- Hash oil is prepared by boiling cannabis material in a solvent which extracts the cannabinols
    - THC content varies but averages 40%
- Most common consumption method is by Joints

    - 50% is typically available for absorption although much less than 100% actually is
    - generally 10mg is absorbed
- First time users feel little effect
    - Inefficient in smoking technique and absorption
    - Less so if they smoke cigarettes
- No evidence that sensitization occurs with repeated use
    - One explanation of this idea is that people get better at smoking properly
- Onset of effects is within seconds
    - Peak blood content is in about 10 minutes
    - Peak effects occur 30-60 minutes, lasting 2-4 hours
- Elimination half-life is approx. 5 days
- Can be taken orally mixed with brownies or cookies
    - Slowly and poorly absorbed through the digestive tract
    - Equivalent effects are produced by an oral dose that is 3x greater THC content than an inhaled dose
    - Peak effects orally come 1-3 hours after ingestion lasting up to 5 hours
- Cannabinoids are lipid soluble easily crossing the blood brain and placental barriers and are deposited in organs and fatty tissue
- Long half life leads to positive tests days after use

Effects

- Low doses produce mild euphoria and peacefulness
- Moderate doses produce perceptual and time distortions, and drowsiness
- High doses (about 2 joints) produce hallucinations, delusions, and distortions of body image although rare and not the usual sought after effects
- Suggested to be an aphrodisiac
    - Low use causes a slight rise in testosterone
    - Continued use can cause impotence and reduced libido
- Come common physiological effects include
    - Bloodshot eyes
    - No effect on pupil diameter slight droop in eyelids
    - dry mouth and thirst
    - hunger and overeating indicating that endogenous cannabinoid system is involved in the control of eating
- some effects may reflect placebos based on peoples expectations
    - Metrik et al. used 2x2 factorial method to test
    - Found large effects of expectancy on ratings of potency, strength, taste, smell, and satisfaction
- THC has been suggested to be potentially useful in a variety of medical conditions
    - Dronabinol (Marinol) is sesame oil THC
        - Or synthetically as nabilone (Cesamet)
        - Sativex is an oral spray of THC
            - Prescribed for MS
    - Marinol and Cesamet are better anti-nauseas than smoking
    - Clear evidence it is effective as a pain reliever

        - Decreased pain sensitivity, increased pain tolerance, decreased subjective ratings of intensity
- Substantial debilitating effect on cognitive and motor performance and hence has a strong potential to impair driving ability
    - THC caused a dose dependant reduction in performance on tasks measuring memory, divided and sustained attention, reaction time, tracking, and motor function
- Short term and working memory is particularly impaired
    - Fewer effects on long term or reference memory

8-Arm Radial Maze Task

- 4 of 8 arms on a maze have food
- rats are trained where to go
- rewards are not replenished and the rats only go down each one once when sober
    - if it did, it's a working memory error
    - visiting a non baited arm is a reference memory error
- THC has an effect on learning when rats were trying to learn the task
- Once learned, THC administration caused more working memory errors, but not reference memory
    - Shows that THC reduces cholinergic neurotransmission in the hippocampus, area with many cannabinoid receptors
        - Involved in learning and working memory

More testing results

- Clear evidence of acute and chronic cognitive, learning, and memory impairments in human users of Cannabis
    - Heavy users made more errors in tests on sustained and shifting attention, and in registering, organizing and using information
- Bolla et al.
    - Concluded that heavy use of marijuana is associated with persistent decrement in neurocognitive performance even after 28 days of abstinence but they did caution it was unclear if these decrements would resolve with continued abstinence
- Comparing with pre-use IQ tests from youth
    - Heavy users showed significant deficiencies in verbal and math abilities and impaired memory
- Lane et al.
    - Examined effect on working mem. In humans using a delayed matching to sample task (DMTS)
    - Significant impairment was seen with both doses given to testers

Tolerance and dependence

- Tolerance has been noted to virtually all the effects of THC in humans including self reported intoxication
- Takes sustained use for extended periods

    - Typical use patterns cause little tolerance therefore many recreational users do not develop tolerance
- Physical dependence was unclear
    - Now there is agreement that with the appropriate dosing regimen and/or by the use of a THC antagonist, a clear withdrawal syndrome occurs following chronic THC ingestion
    - Rimonabant
    - In rats
        - Wet dog shakes, facial rubbing, head shakes, retropulsion, drooping eyelids, chewing, licking, and arching the back
    - In monkeys (without antagonists)
        - Tremors, twitching, aggression, anorexia, and hyperirritability
    - In humans in controlled administration
        - Hot flashes, sweating, runny nose, stomach pains, loose stools, hiccups, loss of appetite, disturbed sleep, aggression, inner unrest, craving
        - Starts hours after cessation, lasts 7-10 days

Cannabinoid Antagonists

- Most common is Rimonabant
    - Advertised as Acomplia in Europe as an anti-obesity medication
    - Suggests that the endogenous cannabinoid system is involved in eating
        - Quite effective in controlling hunger
- LeFoll and Goldberg concluded that antagonists block the subjective effects of THC and prevent relapse to smoking in marijuana users
    - Cannabinoid antagonists seem to block the reinforcing effects of opiates, cocaine, and nicotine
        - Suggests cannabinoid receptors participate in the reinforcing effects of drugs other than THC

Neurochemical Actions of THC

- Endogenous cannabinoid system is involved in many functions such as appetite, pain, mood, and memory
    - Activated by naturally occurring cannabinoid ligand which has been named anandamide
- 2 Cannabinoid receptors have been identified
    - CB1
        - Only this one is found in the CNS and thus being the most important
    - CB2
- Both are thought to be presynaptic and primarily involved in modulating or controlling the release of other neurotransmitters
    - Reducing the acetylcholine release in the hippocampus (learning and mem.)
    - Increasing dopamine release in the VTA primarily by reducing GABA (Rewarding)
    - Reducing glutamate (interfering with long term potentiation involving learning)
- Recent research has provided evidence that subjective reactions to marijuana may be under genetic control
    - Identical twins show high congruence than paternal

Harmful effects of smoking

- THC is acutely nonfatal in Humans
- Although potentially harmful effects derive from the manner of consumption (smoking)
    - General agreement that marijuana has more and higher concentrations of harmful constituents than tobacco smoke
    - Smoking one joint is equivalent to 5 cigarettes of carbon monoxide, 4 cigarettes of tar, and 10 cigarettes of microscopic damage to cells lining the airways

Treatment

- National Institute of Drug Abuse in the US reports that 16% of the approximately 290000 admissions for drug treatment in the US had Marijuana and the primary drug of abuse
    - Typically, white, male, and young
- 13% of approx. 48000 drug treatment admissions in Ontario in 2000 had marijuana as the primary drug of abuse
    - male, single, less than 20, in high school
- 9% of recreational marijuana users will become dependent
- No specific forms of treatment,
    - Most involve the same types of psychotherapeutic interventions used with other drugs
    - Mainly cognitive/behavioral restructuring, relapse prevention, situational self-efficacy, handling high-risk situations, quit contracts, etc.
    - Treatment success is similar to that for other drugs
        - Fairly high rate of success very soon after treatment, but substantial loss of those gains the longer the post treatment period
- Conclusion:
    - Suggests that many patients do not show a positive treatment response, indicating that marijuana dependence is not easily treated

Synthetic Cannabinoids

- Class of drug that has recently become available and is being increasingly used by young adolescents
- Some use for legitimate purposes
    - HIV/AIDS, MS, Chemo
- John W Huffman synthesized one of the first synthetic cannabinoids
    - Street chemists have been modifying this to produce other synthetics
- Produce severe sometimes fatal effects in users
    - Was estimated that there were about 30000 emergency room visits in 2011
- Sold as a liquid that can be sprayed on herbs for smoking or using in e-cigs
    - Sold as K2, spice, black mamba, and kush
- Work on the same receptors as THC but are more potent agonists
- Most are ID-ed by number-letter names
    - HU-210 most common
        - 800 times more potent than natural THC and has an extended duration of action

# Stimulants

A long history:

Ma Huang and Ephedrine

- Naturally occurring psychostimulant Ma Huang
- Chinese herb that comes from a leafless desert shrub known as the horsetail plant
- Documented as far back as 3000BC
- Main active ingredient is ephedrine
    - A bronchodilator
        - Occurs in many over the counter medications for asthma and nasal congestion
    - Today, is intended for legitimate medical purposes
        - But is often diverted into the illegal production of methamphetamine

Khat and Cathinone

- From the Catha edulis plant in Africa since at least the 1300s
- Early use was in the form of Abyssinian tea
    - Today, chewing leaves, at afternoon and evening social parties
- Extensive in Africa
- Characterized by mild mental stimulation, feelings of contentment, mild psychomotor excitation, suppression of fatigue and anorexia
- Active ingredient is Cathinone
- For a long time not illegal in CAN and US but became so under the Controlled Drugs and Substances Act 1997 in CAN
- Methcathinone
    - Modified version of the active ingredient synthesized in the Soviet Union in the 1930s
    - History of abuse in Russia
    - Limited use in NA
    - Effects similar to Meth
- Other synthetic Cathinones
    - Bath Salts (zoom, cloud nine, vanilla sky)
    - Mephedrone and methylenedioxypyrovalerone (MDPV)
        - Gained attention in Europe and UK in 2010
        - Excited delirium

Coca and Cocaine

- Of all CNS stimulants, Coca leaves are most important
- Indigenous to South America and southern central America
- Evidence of use as far back as 1000BC
    - Clear evidence in the $6^{th}$ century
    - Present in the Inca Empire
- Spanish originally tried to suppress use to dissolve bonds between natives, but allowed it once they noticed the natives would work longer and eat less

    - Chewing leaves was most common adding crushed shells (alkaline) to aid absoption
        - Only mild mental and physical sensation
- The leaves brought back to Europe caused little interest
- Changed dramatically with the isolation of cocaine
    - Active alkaloid in the coca leaf isolated by Albert Niemann in 1859
    - Could now be used in tonics and elixirs
        - Method preferred over chewing
- Many favorable papers came out about the drug
    - Sigmund Freud praised it and pushed it on all those he knew
        - Eventually turned against once he realized the addictive and destructive potential
- Cocaine containing potions were popular in the late 1800s in Europe and NA
    - Vin Mariani was a French wine with cocaine
        - Endorsed by 6 presidents of France, President of Argentina, 3 popes, 2 US presidents, etc.
- In the US, John Pemberton produced an imitation drink called French Wine Cola
    - Later following with another drink called Coca-Cola
        - 'the intellectual beverage and temperance drink'
        - remedy for headaches
        - cocaine was removed from the leaves used after 1906
- Cocaine was not included in the first drug legislation in 1908 but it was included in the next, passed in 1911
    - Very successful
    - Aided by public shift to use amphetamines
- Resurgence in the 1950s peaking as the drug of choice in the 70s and 80s
    - Due to cocaine producers getting better organized and mobile
    - Heaviest use from 1975 to 1980
    - Cadillac of drugs
- 400 pounds of coca leaves make 1 pound of cocaine
    - injected or snorted
    - burning it destroys most of the drug (does not volatize at low temps)
- mid 1980s saw the rise of crack
    - treated cocaine hydrochloride with an alkaline solution like water or baking soda
        - frees the base from the salt
    - freebase alkaloid cocaine volatizes at low temps and thus can be smoked
    - produces a more rapid effect without having to inject
    - and could be marketed in very affordable quantities
    - sold as rocks for $3-$20
    - euphoria is only about 10-20 minutes
        - requires continuous use

Modifying Ephedrine: The Amphetamines

- first synthesized in 1887 in a search for a substitute for the naturally occurring stimulant ephedrine
    - marketed as Benzedrine, Dexedrine, Adderall
- methamphetamine (marketed as Methedrine, Desoxyn) synthesized in 1919
- Not popular in the midst of patent medicines and powders
- Neither got any attention until the 30s
    - No real recorded reason
- Amphetamine was sold as Benzedrine in 1932 as a nasal inhaler for asthma
    - Also as Dexedrine starting in 1937
        - Recommended for narcolepsy, weight reduction, and ADD
- Didn't take long to notice euphoric psycho-stimulating effect
    - People broke open inhalers and brewed the soaked cloth inside
    - Available without prescription
    - Coincided with drug laws and prohibition
- After prominent use in WW2 amphetamine psychosis became apparent
    - The US in 1965, required prescriptions
    - Listed as a controlled substance in 1971
- Mostly had been oral and inhalation until now with little injection use
    - Meth was used for heroin addiction in the 60s
    - Already common among heroin users (speedballing)
    - Increasing association with injection use painted a negative picture
- Fell out of fashion as psychosis became more common
    - 'speed freaks'
    - aggression and psychotic behaviour
    - associated with criminal behaviour and gangs
- Phenmetrazine (anti-obesity drug Preludin, street name bam)
    - Synthesized in the wake of legal amphetamines
    - Early 70s
- Cocaine came back in the 80s
- Meth grew back in the 90s and is still a problem today
    - Biggest problem is the ease of supply
    - While cocaine must be smuggled, meth can be made anywhere
    - Ephedrine and Pseudoephedrine are available in decongestants OTC
        - Large purchases are suspicious as they can be used to make meth
    - Used as tablets, injection powder, and smoking crystals

Effects of Stimulants

- All produce essentially the same effects
    - Cocaine however has a local anesthetic effect and vasoconstriction
        - Still considered a medical drug useful for surgeries
- Some are more intense than others, and timed differently
    - Meths are most potent
    - Also, affected by method
- All activate the sympathetic nervous system producing physiological symptoms associated with the fight or flight reaction
    - Increased heart rate
    - Increased body temp
    - Increased blood pressure
    - Increased respiratory rate
    - Sweating
    - Vasoconstriction
    - Bronchodilation
    - Pupil dilation
- Combining Alcohol and Cocaine
    - Produces a metabolite called coca-ethylene
    - Increases the half life of cocaine thus prolonging the same actions
    - 25 fold increase in the risk of immediate death
    - more pleasurable than either alone
- most sought after effects are euphoria and initial feeling of well-being
    - primarily due to the drugs ability to block the reuptake of dopamine
- Cocaine, amphetamine, and methamphetamine are called psychomotor stimulants
    - Increase motor behavior
- Technology aids the research of effects on a quantitative level but loses the qualitative description of motor effects of stimulants
- Rating scale from Robbins et al.
    - Hyperactive – the first drug effect will be a noticeable increase in motor behaviour characterized by running and rapid, jerky changes in position
    - Slow-patterned – the actual pace of movement will have slowed but there is now a discernable pattern such as moving around the perimeter of the box
    - Fast-patterned – the pace of movements increases, there is a pattern to movements, but there are sudden stops and starts
    - In-place, restricted – One of the more interesting effects and very relevant to stimulant psychosis in humans: patterned behaviour is broken up by prolonged periods of remaining in one place and making repetitive movements with the head, legs, or entire body
        - There repetitive, ritualistic and non-functional behaviours are called stereotypes
    - Dys-kinetic, convulsive – retro-pulsion, jumping in place, convulsions, and possibly death
- Due to release and blocking reuptake of dopamine

Stimulants in Treating ADD

- 5% of children under 7 have ADD
    - half continue into adulthood
- 2 clusters of symptoms
    - inattentiveness
    - hyperactivity/impulsiveness
    - separately or together
- 1902 description by Sir George Frederick shows first recognition of what is now ADD
- The realization of stimulant aid was an accident
    - Many ADD children were given spinal taps causing headaches
        - Stimulants prescribed for headaches
    - Found to help the original behavioural symptoms
- A variety of stimulants are used
    - Methylphenidate (Ritalin, Concerta, Daytrana)
    - Amphetamine (Adderall, Dexedrine)
    - Methamphetamine (Desoxyn)
- Improvements noted in 80% of cases
    - Produce a focusing of attention
- Cases of abuse are rare among those prescribed but can be diverted to recreational use
    - University, college, and high school students use diverted ADD stimulants in order to work or study longer
    - Estimate prevalence at 10% of students
    - Risk factors include being white, in a frat or sorority, having lower GPA, showing higher rates of substance use, and attending a more competitive university

Paradigms to Study Drug Reinforcement

- Operant Self Administration Paradigm
    - Animals are prepped with small intravenous tubes that are externalized and allow researchers to unobtrusively inject drugs
    - A lever in a Skinner box administers the drug
        - Control are given saline
    - In order for a drug to be considered as having positively reinforcing properties, it must maintain responding at levels higher than that of saline
    - Animals self-administer many of the drugs that humans do the same
    - For mice, oral doses and nose pressing mechanisms are implemented to make this easier
    - One interesting aspect is the ability to gauge the relative reinforcing properties of different drugs or even drugs in relation to other reinforcements like food, water, or sex
- Progressive ratio procedure
    - A self-administration paradigm that provides information on the relative reinforcing properties of drugs
    - The ‘price’ of the drug is increased once the subject has received some amount already

        - This is done until the animal is no longer willing to meet the response requirement
        - The largest number of responses the animal is willing to make is called the break point
        - Break points of different drugs can be compared to determine their relative reinforcing value

Findings on reinforcing effects of different drugs in the self-administration procedure

- Alcohol
    - IV difficult – oral Good
    - It is difficult to get SA with IV
        - Oral admin is good if sweetened
- Opiates
    - Rock solid
    - All opiates will be SA
        - The pattern is a slow steady increase in dose over weeks to a stable maintenance dose
- Cannabis
    - Good recent evidence
    - SA of THC in naïve monkey
    - Stopped when swapped to saline
    - Started when swapped back
- Stimulants
    - Rock solid
    - All produce SA
        - Show highest breaking points with cocaine among the highest of all drugs
        - Rapid increase in dose to point of convulsions, then sleep, then more
        - Like binging in humans
        - Stopped by blocking dopamine receptors
- Caffeine
    - No
    - No SA
- Sedative-Hypnotics Barbiturates
    - Rock Solid
    - Intermediate or short acting at best
    - High break points
    - Slow steady increase to stable maintenance dose
        - Like opiates
    - Methaqualone particularly noteworthy
- Sedative Hypnotics Non-Barbs
    - Rock solid
- BZs
    - Weak at best

- Inhalants
    - Nitrous
        - Inconsistent
        - Not a lot of research
    - Toluene
        - Rock solid
        - Same DA reward system as stimulants
    - Nitrites
        - ?
- Nicotine
    - Rock solid
    - Easy to get SA across wide range of doses
    - High break points
- Hallucinogens
    - Cholinergic
        - No
        - No evidence of reinforcement
    - Serotonergic
        - No
        - No
    - Noradrenergic
        - No/Yes
        - Mescaline like ones produce no evidence
        - Amphetamine like once good evidence (MDMA)
    - Misc
        - Yes
        - PCP/Ketamine are good in SA
- Steroids
    - NO
    - Not surprising

Neurochemical effects of Stimulants

- Increases dopaminergic activation in the VTA-NAcc neural pathway
- A number of different dopamine receptors have been IDed
    - D1 through D5
- The D1 receptor is thought to be the most important one involved in the rewarding effects of stimulants
- 2 mechanisms by which they cause or prolong a period of dopaminergic activity
    - some primarily cause the release of more dopamine per action potential or actually cause the leakage of dopamine in the absence of action potentials
        - Amphetamine & methamphetamine
    - Other stimulants primarily block the reuptake of released dopamine
    - One of these will predominate for each type of stimulant
- Both cause further dopaminergic activity

- Stimulant Blues
    - If one goes on a stimulant binge using a stimulant at short intervals the rewarding effects will diminish, almost to absence
    - Often leads to depression and an inability to feel pleasure
        - Called anhedonia
        - Caused by the blocking of reuptake, thus not having dopamine for reuse
    - After long enough the newly synthesized dopamine will be available for release and the blues go away

Chronic Administration of Stimulants

- Tolerance
    - Tolerance to anorectic effects is common
    - Has an applicability to tolerance in general
        - Development of tolerance requires the contingent presentation of both the stimulant and the availability of food to food deprived animals
        - If food is not available the tolerance will not develop
        - Without experiencing anorexia for real, the subject will not develop tolerance
- Sensitization
    - Behavioural activating effects of stimulants
    - A small dose starts to act like a bigger dose with regards to behaviour
        - Left shift in dose response curve
    - Dangerous as more severe effects may be seen with repeated users
    - However, those adhering to ADD prescription regimens will likely not have this if they do it properly
    - Behavioural elements may be sensitized by reacting to the predrug cues in addition to the drug itself
- Stimulant Psychosis
    - Can cause psychotic, schizophrenic-like episodes
    - Characterized by unpredictable swings between intense emotion and blunted affect, hallucinatory phenomena, and paranoid ideation in a setting of clear consciousness
    - Can cause formication syndrome
        - Feeling bugs under the skin and picking at them
        - Speed bugs or crank bugs
    - Causes OCD in humans
- Physical dependence
    - Stimulants are capable of producing compulsive drug seeking and drug taking
        - There is clearly a mental or medical condition
    - But there is disagreement on whether there are physically dependent behaviours and withdrawal

# Hallucinogens and Designer Drugs

- Word hallucinogen comes from the Latin term alucinere meaning to wander in mind, talk idly, or prate
- Many drugs here do not cause outright hallucinations
- As defined by DSM V: "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ"
    - Many in reality involve distortions of sensory information and some of the drugs primarily cause mental confusion or delirium
    - Also known as psychedelics, illusinogens, and deliriants
    - 6000 different plants that contain substances capable of producing hallucinogenic or deliriant effects
- hallucinogens comprise a very chemically heterogeneous class of drugs
    - most are sub-categorized in three categories based on neurotransmitter characterizations and the fourth is a miscellaneous group
        - Cholinergic Hallucinogens (atropine, scopolamine, ibotenic acid)
        - Serotonergic or 5-HT like hallucinogens (LSD, psilocybin mushrooms, DMT, lysergic acide amide, bufotenine)
        - Methylated amphetamines/noradrenergic hallucinogens (mascaline from the peyote cactus, MDMA, or ecstasy)
        - Other Hallucinogens (the dissociative anaesthetics PCP and ketamine, salvinorin)

## Cholinergic Hallucinogens

- Large numbers of plants contain cholinergic-affecting chemicals to serve a protective function
    - Humans quickly learned that they could be used to activate delirium or as poison
- Drugs acting as both agonists and antagonists in the cholinergic nervous system produce psychoactive effects

*Cholinergic Agonist Hallucinogens* – Stimulate primarily muscarinic cholinergic receptors producing greater than normal neural activity in the cholinergic system

- CNS is involved in many life sustaining physiological functions and is also critically involved in learning and memory

Amanita Muscaria – the fly agaric mushroom is found widely distributed in temperate zones of the northern hemisphere

- Called the fly mushroom as it was used to kill flies when put in milk
- Vikings consumed amanita when they were preparing to raid a village
- Produces a state of agitated raving, and invincibility which lead to the attacking Vikings being called 'berserkers'
    - Not typical today
- Contains ibotenic acid (metabolite muscazone) and muscimole
    - Excreted in urine largely unchanged and an active dose may be had by ingesting the urine of someone who has previously ingested mushrooms
    - Symptoms include initial feeling of good humor and light euphoria, giving way to feelings of detachment and unreality, increased power, agitated raving,

twitching and trembling, visions of the supernatural and illusions of grandeur, along with unpleasant physiological consequences such as lacrimation, salivation and sweating, pinpoint pupils, severe abdominal pains and diarrhea coma, convulsions, and potentially death

Ibogaine – plant found in central Africa used by native hunters who chew the root of the plant for low doses that act mainly as a stimulant allowing them to endure long treks and search for food

- The main compound is ibotenic acid
- Sold in France in the 60s as an over the counter medication for fatigue
    - Some took a lot so they could experience a type of mystical or meditative effect during which what they identified as repressed childhood memories were unlocked
    - Heroin addicts found it useful for quitting with a healing experience
        - Called a 'street cure'
        - A true study did not find enough of a positive result to accept ibogaine
        - Now is schedule 1

*Cholinergic Antagonist Hallucinogens* – Some substances block muscarinic cholinergic receptors and in doing so produce a set of effects that justify their classification as deliriants or hallucinogens

Atropa Belladonna – An alkaloid of this is Atropine known as deadly nightshade

- Found in Europe, North Africa and Asia
- Member of the tomato/potato family
- Isolated from the plant in 1831
- Name was given to represent Atropos, the eldest of the three fates in Greek mythology, who had the duty to cut the thread of life at the time appointed for a persons death
    - And belladonna comes from an ancient use in which women would instill the juice of nightshade berries in their eyes to cause pupil dilation as it was style at the time
- Blocks cholinergic receptors causing rapid heartrate, dilated pupils, loss of balance and staggering, blurred vision, feeling like one is suffocating, extremely dry throat, husky voice, flushing, paleness followed by rash, urinary retention, constipation, pain, convulsions, and uncontrollable movements
- Low doses cause an initial increase in arousal
- Slightly higher doses begin to show sedative effects, semi-awake dream like state in which the user may experience pleasing hallucinations, vivid erotic dreams and a sense of weightlessness reported as a sense of flying
    - Upon awakening the user may have a difficult time realizing that the hallucinations and dreams were not real and may exhibit amnesia
- Higher still doses are more powerful and frightening
    - Line between pleasant and potentially lethal is fine

Datura Stramonium – Atropine, scopolamine and hyoscyamine (all cholinergic antagonists) are found here known as jimsonweed, Jamestown weed, or thorn apple

- Long history of use
- Feelings of flying and weightlessness

    - Colonial American women would rub it on sticks and straddle them to absorb the drug through the vaginal membrane
    - Used to fortify marijuana and opium from Asia
- Used to be sold in cigarettes to help asthma
    - Bronchodilation
- Low doses produce drowsiness and a dream like state with euphoria and amnesia
- Higher doses are capable of producing more unpleasant hallucinations, delirium and mental confusion
- Jimsonweed aka Devil's Trumpet for the flowers' shape
    - Now used for decoration but any part of the plant contains the drug, especially seeds

Henbane – Scopolamine and hyoscyamine are found here, commonly used in sexual orgies in the middle ages and native to the northern hemisphere

- Effects are similar to other cholinergic antagonists

Mandragora Officinarum – the Mandrake (Potent Man) plant, containing atopine scopolamine and hyoscyamine is another potato/tomato relative found in southern Europe, north Africa and Western Asia

- Medieval lore says the plant grew wherever a hanged man's semen fell to the ground
    - Lol wtf
    - Hanged men would be erect and ejaculate when their necks snapped
- Mandrake has been used in potions and as an aphrodisiac
- Low doses are depressant and sedative, high doses are hallucinogenic and produce the same symptoms as above

## Hallucinogens of the Serotonergic Type

- A number of drugs resemble the neurotransmitter serotonin producing effects of hallucinations
- Most commonly identified is Lysergic acid diethylamide (LSD, trade name Delysid) first synthesized in 1938 by the Swiss chemist Albert Hoffman who was studying derivatives of the ergot fungus for their vasoconstrictive action and ability to give muscle tone to the uterus
    - Comes from a parasitic fungus ergot found in grains
        - First used to aid childbirth in 1582 by contracting the uterus
    - Hoffman accidentally found that the 25$^{th}$ derivative was hallucinogenic
        - On April 16$^{th}$, 1943 Hoffman accidentally dosed himself with LSD on his hands
        - He retested it on purpose with what he thought was a small dose (250microg) but was really five times larger than the minimal psychoactive dose
        - Established that the minimum psychoactive dose is the size and weight of a grain of salt
    - Lead to more researchers

        - Dr. Humphrey Osmond coined the term psychedelic so commonly associated with these drugs
        - In the early 60s Timothy Leary and Richard Alpert freely distributed the drug to youth to 'turn on acid'
        - Used in the 50s and 60s in psychotherapy as people would more openly communicate about feelings and be more open to suggestions
    - LSD remained legal in the US until 1966, when it was schedule 1-ed
        - Use peaked in the late 60s, early 70s
        - From 67 to 71 college self-reports of use rose from 1% to 18%
    - LSD is odorless, tasteless, colorless, readily absorbed from the gastrointestinal tract, and fairly easily crosses the blood-brain barrier and the placental barrier
        - Taken orally or on an absorbent paper decorated with figures
    - Street doses are generally 50 micrograms
        - One quarter of the typical dose in the period of peak use (200mcg)
    - Effects in 60 minutes, peak in 90 min, lasting 5-12 hours
        - First effects are activation of the sympathetic nervous system: tachycardia, increased temp, increased blood pressure, dilated pupils, sweating, chills, tremors, increased salivation and analgesia
        - Stronger analgesic than opiates but few desire a second dose
        - Hallucinations after 1-2 hours, primarily visual and are often experienced with eyes closed
    - Symptoms:
        - Wave like rhythmic movement in objects
        - Object trails
        - Form constants – kaleidoscope-like visions & patterns
        - Synaesthesia – perception of one sense in another sense modality
            - Seeing sounds
            - Seeing or hearing tastes
        - Distortions in time perception often reported as small periods of time seeming to be very long
        - Ego disintegration – difficulty distinguishing himself from surroundings
            - Feeling like part of the couch
            - Due to the analgesic effects – like novocaine
        - Bad trips or panic attacks
            - Common in novices
            - Fear that the effect is permanent
            - Only about 5% get bad trips
        - Flashbacks – unexpected psychedelic experiences long after the most recent use of LSD
            - Short, self-terminating and not particularly distressing
            - 1 in 3

        - Hallucinogen persisting perception disorder (HPPD) – a more long lasting distressing, recurrent, and only slowly, if at all, reversible psychedelic experience occurring well after the last drug use
            - Prevalence est at 4%
            - May result from a neuroplastic change in the brain
        - Can be fatal but the LD50 is estimated to be 14000 micrograms, 300 times the minimum psychoactive dose (50)
        - Tolerance occurs to most of the hallucinogenic effect of LSD in as little as 3 to 4 days of once daily exposure
            - Also occurs rapidly to other serotonergic and noradrenergic hallucinogens
            - There is cross tolerance
            - Evidence of Pavlovian conditioning contributing to the development of tolerance
        - No evidence of physical dependence/withdrawal

Neurochemical Actions of LSD and Other 5-HT Hallucinogens

- Much evidence that serotonergic hallucinogens produce hallucinogenic effects by acting on serotonergic neurons
- Early research suggested that LSD suppressed firing of serotonin neurons in the raphe nuclei by acting as an agonist at presynaptic 5-$HT_1$ receptors which serve a negative feedback regulatory function on serotonergic activity
    - Part of what is called the ascending reticular activating system (ARAS) which is involved in the filtering of sensory information and thus the hypothesis was that LSD interfered with this filtering leading to sensory distortions
- Subsequent research showed that LSD produced its effects mainly via an agonistic action at postsynaptic 5-$HT_2$ receptors
    - New evidence that the original mechanism is also relevant (5-$HT_1$ action suppressing Ralphe activity)
- Lysergic acid amide is a less potent but naturally occurring form of hallucinogen related to LSD
    - Also found in ergot (aka cockspur) as well as other seeds and plants like morning glory seeds
    - Historical evidence of use refers to Holy Fire or St. Anthony's Fire
        - May have come from strong vasoconstrictive actions of lysergic acid amide found in bread made from infected grains
        - Leads to a sensation of warmth from vasoconstriction which if prolonged can lead to limb death and detachment
        - People were sent to St. Anthony's shrine in France to be cured, and it would work because they were no longer in the locality with the infected grains
    - Ergotism outbreaks would occur causing afflicted behaviour by ingestion of ergot; still rarely occurs
    - One tenth the potency of LSD though

- Psilocybin is a naturally occurring substance in a variety of mushrooms native to Mexico and Central America
    - Isolated in 1958 by Hoffman
    - Used by Aztecs and Mayans – called Teonanactl meaning flesh of the gods
        - Found identifiers in ruins as far back as 1000BC
    - Consumed by eating or drinking a brew
    - 4-8mg for psychoactive effects, more than 15mg for hallucinogenic effects
        - could be 2-40 mushrooms depending on strain
        - onset in 30 minutes, duration of 2-6 hours
    - Psilocybin is converted into psilocin in the body which is more lipid soluble and is thought to be the actual active ingredient
    - Tolerance occurs to the effects and cross tolerance is present to other hallucinogens
    - Psilocybin is stronger than LSD visually, less emotionally intense, more euphoric, and less likely to produce a panic reaction
    - Aka Shrooms
- Dimethyltryptamine (DMT) is found in several species of the plant genus Virola or Poptadenia peregrine native to the jungles of South and Central America where it is used by indigenous as an entheogen
    - Naturally occurring plant substances used to produce mystical or religious experiences are called entheogens
    - Reddish bark is used as snuff
    - Effects are rapid and short lived, onset occurs with inhaled doses in as little as 10 sec, peaking in 10-15 minutes, and lasting about 60 minutes
    - May be taken as a drink although quite ineffective due to being rapidly metabolized by monoamine oxidase
        - Harmaline alkaloids from other plants may be mixed/drank at the same time blocking the action of monoamine oxidase, allowing DMT to be more effective ingested
        - One common one is ayahuasca
            - Increasingly used to treat PTSD recreationally
    - Effects include excitability and other worldly experiences, numbness of the limbs, twitching of the facial muscles, nausea, and hallucinations
- Bufotenine (5-Hydroxy-DMT) is found in a variety of plants, fish, and toads
    - Used by indigenous peoples in the form of snuff or licking toads or drying and smoking the secretions
    - One side effect unique to bufotenine is cyanosis, in which the skin turns purplish blue

## Phenethylamine Type Hallucinogens

Hallucinogens of the Norepinephrine Type and Methylated Amphetamines

- A number of naturally occurring plant substances which resemble the neurotransmitter norepinephrine (noradrenaline) have hallucinogenic properties

Mescaline – Prototypical naturally occurring norepinephrine type hallucinogen

- The active alkaloid in the peyote cactus found in Mexico, southwestern US and South America
- Pincushion-like plant with a carrot shaped root
    - 'Button' is sliced and dried to form hard brownish discs which remain potent indefinitely
- isolated by Arthur Heffter in 1896 and synthesized by Ernst Spath in 1918
- absorbed readily through the GI tract but does not cross the blood-brain barrier very well
    - may be smoked but unusually
- Peak effects in about 60 minutes, last 4-16 hours, with 10 hours as an average
- Peyote intoxication is characterized by brilliantly colored visions in kaleidoscopic movement often accompanied by auditory, taste, olfactory and tactile hallucinations
    - User senses weightlessness, depersonalization and alterations in time
    - Nausea, vomiting, headaches, hangover
    - Indistinguishable effects compared to psilocybin, or LSD
- Tolerance occurs to the psychedelic effect over the course of only a few days of once daily exposure
- Resembles norepinephrine but produces hallucinations in the same manner as serotonergic hallucinogens having an agonist action at 5-$HT_2$ receptors

Amphetamine modifications have brought about drugs with stimulant and hallucinogenic characteristics

DOM or STP – (Serenity, tranquility, and peace, or Super Terrific Psychedelic

- DOM was synthesized by Dow Chemical in 1964 as an appetite suppressant
    - But produced euphoria and stimulant effects along with psychedelic feelings
- 3-5mg produces euphoria and stimulant effects, 10mg or more for hallucinations
    - lasts 16-25 hours
    - bad trips common

MDA – First synthesized in 1910 as an appetite suppressant, antidepressant and Parkinson's Treatment

- Metabolite of MDMA and is responsible for many of MDMA's effects
- Usual dose is between 80-160 mg and effects last 8-12 hours
- Enhances emotions and empathy and thus tends to promote a strong emotional link with other people who are present
- Roots of the Sassafras tree, used for rootbeer (now banned) contain safrole or shikimo that can be converted to MDA
    - Happens a little in the body anyways

MDMA – 3,4-Methylenedioxymethamphetamine, ecstasy, XTC, or Molly

- First synthesized in Germany by Merck in 1914 as an appetite suppressant
- Used in tablet or capsule form at a dose of between 50-200mg
    - Well absorbed from the GI tract with onset in 1 hour, and duration of 4-6 hours
- Effects include a variety of positive mood changes, increased energy, and at higher doses, hallucinogenic effects
    - Suggested for use as a psychotherapeutic adjunct, but not approved

- Undesirable effects include sweating, blurring vision, tension in jaw, teeth grinding (users often carry pacifiers) dry mouth and thirst
    - High body temps, dehydration can cause death
- Causes the release of serotonin and dopamine and is particularly effective for the former
    - Blocks the reuptake of serotonin thereby causing a prolonged and intense period of serotonergic action
    - Evidence that drugs that cause a concomitant excess activation of serotonin and dopamine can cause permanent damage to these neurotransmitter systems
    - Can cause changes in serotonergic functioning at doses only slightly higher than the typical recreational dose
- Major serotonin metabolite was lower in persons who had used MDMA between 80 – 100 times compared to non users
    - Reduced serotonin binding and transporter densities in people who had 50 or more lifetime uses and these effects were more pronounced in women
    - Brain areas involving sleep and appetites there is excess regeneration resulting in excess serotonin release
- More or less persistant problems include memory impairment, decision making deficits, loss of impulse control, panic attacks, recurrent paranoia, and depression

Myristicin and Elemicin – found in the fruit tree myristica fragrans where nutmeg and mace are derived

- Fairly weak hallucinogens even at high doses but because of availability are abused by youth
- Taken in the form of a tea made from one to wo teaspoons of the spice
- Initial effects include nausea and vomiting for 2 hours followed by a weak hallucinogenic effect
- Commonly reported that one use dissuades from further

## Miscellaneous Hallucinogens

Phencyclidine and Ketamine – called dissociative anesthetics

- Produce total anesthesia but at lower doses, a feeling of detachment (dissociation) from the environment and self, ‘out of body experience’
- Analgesia and amnesia common
- Phencyclidine was developed in 1926 but not marketed until the 1950s under the trade name Sernyl
    - Made a good anesthetic but produced undesired hallucinations and seizures and was removed from human use, later animal use
    - PCP, Angel dust, horse tanks
    - Oral as liquid or powder
    - Can be added marijuana and smoked
    - Doses of 1-10mg produce euphoria, numbness, loss of motor coordination, catatonia, initial nystagmus but eventually a fixed stare, distortion of body image with the perception that parts are particularly large or small, paranoia, auditory

hallucinations, extreme mood changes going from almost no emotion to outbursts, aggressive hostility, and stereotypies
    - Generally lasts 4-6 hours but can persist for days
    - Larger doses cause convulsions and psychosis
    - Bad trips are frequent (80%)
    - Tolerance and physical dependence are reported in animals
        - Rare in humans due to infrequency of use
    - Withdrawal in animals involves tremors, oculomotor hyperactivity, bruxism, fearfulness, vocalizations, diarrhea, emesis, and convulsions
    -
- Ketamine (Ketalar) was developed in the early 60s as a drug with potentially fewer of the unwanted side effects
    - Special K, or CAT
    - Powder or liquid that is snorted smoked taken orally or injected
    - Same effects as PCP but with a 2 hour duration at most
    - 'entered the k-hole'
- PCP and Ketamine bind to sigma opiate receptors to produce hallucinogenic effects
    - Reduce neuronal activity produced by glutamate
    - This antagonism of glutamate is thought also to produce an increase in dopaminergic activity in brain reward canters producing the drugs rewarding effects

Dextromethorphan – DM, a common cough suppressant which stimulates sigma opiate receptors and blocks glutamate receptors, the same as PCP and Ketamine

- DM is less potent for these actions than PCP/Ketamine but is able to produce hallucinations at sufficiently high doses
- Abuse of DM containing medications enjoys some popularity among youth
- Called robo-copping, roboing, robo-tripping, or chug-a-tussin primarily because Robitussin is one of the main sources of abuse
- Indicated medical dose is 15-30mg
    - 200mg produces a euphoric effect
    - 400mg produces more intense euphoria and closed-eyes hallucinations
    - 600mg produces strong alterations in consciousness, out of body experiences, and psychotic like reactions

Salvia Divinorum – Diviner's Sage is a member of the mint family

- history of use with Mazatec tribes in Mexico
- Recently added to Schedule IV of the controlled substances act
    - But personal possession is not prohibited
- Commonly used by chewing, smoking, or making tea
- Active ingredient is salvinorin A
    - Shown to have an agonistic effect at kappa opioid receptors
    - Produces hallucinations for a few minutes when smokes or a few hours if taken orally
    - Pure Salvinorin A is said to produce a strong effect

Thujone – Found in plants including sage but most notable in wormwood

- Wormwood was used in the production of the alcoholic drink absinthe that became popular in mid 1800s France
- Has a methanol odor like absinthe
- Reports of acting strangely and hearing voices and seeing things, sometimes convulsions
- Acts as a $GABA_a$ antagonist, increasing neural activity which may produce convulsions
    - Also interacts with 5-$HT_3$ receptors
- Absinthe with wormwood was banned in 1910 but is now available with controlled levels of thujone
    - Sometimes called the Green Fairy
    - Green in color and has a high alcohol content (50-75%)
- Taken by lighting an absinthe soaked sugar cube on fire in a special slotted spoon, allowing it to burn, dropping it into a shot of absinthe, letting it ignite, putting it out with water
    - Turns from green to opaque greenish white, and is taken as a shot

# Steroids

- One third of all college and professional athletes use steroids
    - 6% of male and 2% of female high school students use steroids
- 50% of respondents answered yes to the following:
    - If there was a drug that allowed you to win all your competitions for the next number of years but after that you would die, would you take it?
- Development of synthetic steroids occurred in the 1930s but attempts to enhance performance have a long history
- Used to build muscle mass or to speed recovery from training and injury
    - In males the desire to attain a muscled physique has been identified as the drive for muscularity and is related to a condition known as muscle dysmorphia
    - Women two, but on a smaller scale
- Cholesterol is the main building block of steroids
    - Some are naturally occurring in the body but those that are abused are called anabolic-androgenic steroids (AAS)
    - Developed to treat hypogonadism
    - Early results showed muscle gain and fast recovery in animals
- Steroid use in sport was kicked off by Soviet weightlifters in the 1954 Olympics
- Anabolic refers to the capacity of the steroids to promote muscle growth
    - Particularly effective in women
    - Greater gains in upper body
- Androgenic refers to the masculinizing effects of these drugs
    - Steroids are made up of male hormone testosterone and a number of synthetically produced structural derivatives
- Steroids differ from each other mainly in terms of their resistance to metabolic breakdown in the liver
    - Orally, steroids are subject to first pass metabolism destroying a large portion in the liver

    - Injection bypasses this issue
- Medically used, (like when testosterone is low) a dose is small, at about 100mg per week
    - Abuse is different involving 'stacking' or 'pyramiding'
        - Takes for several weeks regularly increasing dose and then slowly reducing as a competition approaches to reduce detection
        - Abusers take much larger doses, in excess of 1000mg/week
- Controlled in Canada and the US
    - Athletes may get it from an authorized doctor or coach
    - Others obtain them from sellers of illegally diverted medical steroids or smuggled ones from other countries
- Ideally, steroids would have strong anabolic effects and weak androgenic effects
    - Promote muscle growth and minimize masculinization
    - Not the case in reality
- Adolescent use is associated with stunted statue if use occurs before growth is complete
    - Premature closing over of the ends of bones
- Lowers the levels of beneficial lipid carrying proteins in blood, while raising the level of harmful cholesterol resulting in an increased risk of heart disease
    - For men, Testicular atrophy, impaired sperm production, reduced libido, protracted and painful erections, acceleration of male pattern baldness, severe acne
    - For women, deepening of the voice, increased body hair, male pattern baldness, menstrual cessation or irregularity, an enlarged clitoris
- Psychiatric consequences occur too
    - Roid Rage – increased aggression and violence – uncontrollable outbursts of aggression that are uncharacteristic
    - Increase in manic episodes characterized by an extremely elevated positive mood, rapid speech, racing thoughts that intrude on the persons ability to function normally, decreased sleep, impulsiveness, and grandiosity
- No SA with infra-humans and thus would not appear to be reinforcing in the same way as opiates, stimulants, or sedatives
    - Unlikely because effects are delayed days or weeks
    - However, used compulsively and used despite knowledge of adverse effects justifying a diagnosis of steroid use disorder according to DSM V

# Sedative-Hypnotics

2-4% of the general population has at some time had a disorder classifiable as an anxiety disorder

- Substances that blunt or alleviate the feelings of anxiety are termed anxiolytics
- Ideally it would do so without side effects
- Most depress the CNS, induce sleep, and dull awareness

The above is closely related to Sedative-Hypnotics

- A drug that depresses the activity of the CNS and typically has medical uses of relieving anxiety and inducing sleep
    - Earliest was ethanol
    - Alcohol was used for this purpose but has extensive side effects
- Recreational use and abuse are common and receive more attention than typical medical use
    - Relates to the desre of people to have some easy means of ameliorating the effects of stress and escaping from feelings of discomfort, tension, anxiety, and dysphoria

## Early Sedative Hypnotics

Potassium Bromide

- Discovered to have a calming and soothing effect in the mid 1800s and had a high popularity up to the early 1900s as a sedative
- Used recently in medications but weened out due to toxicity
- Bromoseltzer was used as a hangover remedy
- Toxicity occurs because it is slowly excreted by the kidneys
    - Half life of 12 days
    - Intoxication symptoms include memory and thought impairment, delirium, hallucinations, mania, and coma

Chloral Hydrate (Noctec, Somnos, Felsules)

- Synthesized in 1832
- Widely abused in the mid to late 1800s, continues today
    - Marylin Monroe, Anna Nicole Smyth
- Combined with alcohol to create “knock out drops” or “Mickey Finn”
    - Mickey Finn is an early date rape drug

Paraldehyde

- Sedative used for over 100 years
- Used in hangover control
- Tastes bad and is expired through the lungs creating a terrible breath
- Many who are addicted were initially exposed by use as a alcoholism treatment

## Barbiturates

- Initiated the modern age of the pharmacological management of anxiety
- Parent compound synthesized by Adolph von Baeyer in 1864 from malonic acid and urea
    - Formed malonylurea but came to be known as barbituric acid
    - Not effective as a sedative hypnotic itself but substitutions in the number 5 position on the molecule gave compounds hypnotic potency
- First modification was accomplished in 1903 by Fischer and von Mering
    - Called diethylbarbituric acid

    - Ethyl groups C2,H5 replaced the hydrogens in position 5
    - Generic name Barbital and trade name Veronal
    - Popular for facilitating sleep and daytime anxiolytic properties
    - Long onset and long duration
- One goal of research was to shorten duration as users would wake up drowsy
    - Thus barbiturates are classified by speed of onset and duration of action
        - Influenced by lipid solubility
        - High solubility readily get into and out of the brain
            - Good for sleep induction and mgmt. of seizures
        - Lower solubility do not as readily enter and exit the brain
            - Good for mgmt. of chronic anxiety or epilepsy
    - Long acting barbiturates
        - Onset in one hour and duration of at least six hours
        - Prototypical compound in this class is Phenobarbital (Luminal)
            - Synthesized in 1912
            - Tablets, capsules and liquid
    - Intermediate acting barbiturates
        - Onset in about 30 min and duration of 4 hours
        - Prototypical compound is Amobarbital (Amytal)
            - Synthesized in 1923
            - 'truth serum'
            - Although people become talkative, does not induce truth telling
    - Short acting barbiturates
        - Onset in 15 minutes, duration of 1-4 hours
        - Pentobarbital (Nembutal) and Secobarbital (Seconal)
            - Both synthesized in 1930
    - Ultra-short acting barbiturates
        - Introduced as intravenous anesthetics in the 1930s
        - Hexobarbital and Thiopental
- Although not a Barbiturate, Propofol (Diprivan) has largely replaced the barbiturate iv anesthetics and is probably now the most commonly used iv anesthetic
    - Sometimes used recreationally
    - 'milk of amnesia'
    - medical professionals are the most common abusers due to access
    - Death of Michael Jackson
    - Small therapeutic index meaning a high risk for accidental death
    - Does not generate a high but rather blocks out the world
        - Used for PTSD and sexual trauma victims
- Barbiturates were abused from inception
    - Todays health in 1942 called an article on barbiturates '1250000000 Doses a Year
    - Intended on making the public aware of the dangers

    - Soon made illegal without prescription resulting in the development of an illegal market for the drugs, and by the 50s barbiturates had become one of the most widely abused drugs
    - Doctors were still commonly prescribing the drugs
    - Peaked in the late 50s early 60s
    - Decline was caused by the introduction of benzodiazepines
    - Typical abusers were Caucasian females aged 30-50, middle or upper class
        - Same as patent medical abusers of the late 1800s
- Barbiturates are commonly referred to as 'downers'
    - Specific street names are typically referring to the colour of the tablet or capsule
        - Amobarbital – blue angels, blue dolls, blue birds, blue bullets, blue devils, heavens, blues
        - Pentobarbital – Nebbies, nembies, or nemmies (for Nembutal), yellow dolls, jackets, bullets, abbotts, yellows
        - Secobarbital – seccies, or seggies (for Seconal), red devils, red dolls, M&Ms, Mexican reds, redbirds, red bullets, reds
        - Tuinal – A combination of secobarbital and amobarbital that is available as red or blue capsules – called Christmas trees or rainbows
- All barbiturates exert similar effects, with the main difference being onset and duration
    - Relaxation
    - Reduction of anxiety
    - Euphoria with low doses
    - Sedation, drowsiness, dizziness, lightheadedness, lethargy
    - Reduced time to onset of sleep and increased total sleep time but with reduced REM sleep
        - REM rebound upon discontinuation
    - Anesthesia
    - Coma at high doses
    - Death induced by respiratory depression at high doses
        - Low therapeutic index leading to accidental deaths
        - No fast acting antidote
            - Very hard to save someone overdosing
        - Common when combined with alcohol
            - Act synergistically – not additive but multiplicative
- Main effect on the CNS is to depress neuronal activity
    - Enhance the inhibitory actions of GABA
    - When GABA binds with the GABA receptor complex it induces a conformational change that opens ion channels allowing negatively charged chloride ions to pass into the neuron
        - Hyperpolarizing the nerve membrane making the neuron less excitable
        - Barbiturates bind to specific sites on the GABA receptor and increase the affinity of GABA for its receptor
        - Prolongs the time that the ion channel remains open fourfold or fivefold

        - Sedative Hypnotic and Anesthetic effects of barbiturates is due to this action in the GABAergic system
        - Evidence that barbiturates attenuate glutamate transmission
            - Importantly involved in memory forming and the attenuation of glutamate transmission may underlie the potent amnestic properties
        - Neurochemical basis for the rewarding effects are unclear
            - Enhancing GABA would be expected to reduce dopamine release
            - Clear that the ARE reinforcing but HOW is not specified
- Loss of effectiveness is a clear signifier of strong tolerance development
    - Occurs to virtually all induced effects including the behaviourally impairing, sleep inducing, reinforcing, and lethal effects
    - Occurs more rapidly to the reinforcing effects than to the lethal effects thereby increasing the chance of OD
    - Abusers use more and more to receive the reinforcing effects but move ever closer to a lethal dose
    - Tolerance involves Pavlovian conditioning as demonstrated by tests of situational specificity, placebo CR testing, and loss by extinction
    - Drug experienced rats receiving a normally lethal dose of bentobarbital in the presence of their usual predrug cues survived the lethal dose but similarly rats without the PD cues died from the lethal dose
- Clear evidence of physical dependence, and withdrawal symptoms from chronic use
    - Similar to those seen with alcohol and are actually diminished with the administration of either drug
    - Isbell and associates 1950 studied withdrawal following a 140 day increasing dose regimen
        - Symptoms begin 24-36 hours after termination
            - Hypotension and fainting, tremulousness, and muscular fasciculation, anorexia and vomiting, weight loss, confusion, delusions, auditory and visual hallucinations, and convulsions
            - 5% death rate without medical supervision
    - Reinforcing effects related to the speed of onset with the intermediate and particularly the short acting drugs being the most reinforcing
        - Amobarbital, secobarbital, pentobarbital
        - Strong self-administration results – rock solid reinforcement
        - High break points, slow steady increase in dose over weeks to stable maintenance dose – like opiates

## Other Anxiolytics: Neither Barbiturates nor Benzos

- A number of drugs were developed to produce the same effects as barbiturates and BZs without the undesirable side effects
- Each enjoyed a period of popularity

    - Glutethimide (Doriden), Methyprylon (Noludar), ethchlorvynol (Placidyl) and Methaqualone (Quaalude)
- Methaqualone deserves the most attention
    - Initially synthesized in India as an antimalarial drug
    - Noted to have calming effects and introduced as an anxiolytic in 1965
        - Now recognized to have no medical value and high abuse potential
    - Heroin-like high – called 'ludes' and 'disco biscuits'
    - While available it was commonly used with alcohol, called 'luding out'
    - No longer available or legally manufactured but is still scarcely available in illegal manufacturing
    - Produces physical dependence and withdrawal
        - Celebrity deaths are many
- Propanediols
    - Researchers trying to modify a disinfectant to produce a compound that would kill bacteria resistant to penicillin produced the compound Mephenesin Carbamate
    - Did not have the sought after antibacterial effect it produced muscle relaxation and a sleep like condition from which animals could be easily aroused
    - Lead to further research on anxiolytic effects
        - Used extensively in the 40s to allay anxiety but duration was short causing frequent administration and high dosages
    - Later modifications lead to the development of meprobamate (Miltown, Equanil) in 1955
        - Coined tranquillizer
        - Differed from barbiturates in that it induced a tranquil state without suppression of general CNS excitation
        - Appeared to be an ideal anxiolytic and it was widely used in the late 50s and throughout the 60s
        - Further research demonstrated it was subject to abuse and produced physical dependence with severe withdrawal
        - However the lethal dose was large compared to the therapeutic dose

## Benzodiazepines

- Leo H Sternbach synthesized several compounds as potential anxiolytics while a postdoctoral researcher in Cracow Poland in the 1930s
- When initial testing produced no promising effects the remaining compounds were shelved

- In 1957 a clean up of Sternbach's lab previously untested compounds were tested and one gave some interesting results in terms of the ability to calm or soothe animals
    - RO-5-0690
- First marketed benzodiazepine called chlordiazepoxide, Librium
- Closely followed by Diazepam (the second) and Valium

How is a drug identified as being potentially useful in treatment of psychological conditions?

- Screening tests have been developed to ID drugs that may have a desirable effects
    - Different tests for different conditions
- Preclinical screening tests involve the use of animals before the start of human clinical trials
- Tests are established by recording the outcome of known drugs and seeing the effect in the potential test
    - If all drugs currently used produce a similar outcome in a particular test then that test is considered a useful screening test
- 2 common tests for anxiolytics that are strong in psychopharmacology
    - The Elevated Plus Maze
        - Apparatus in the form of a + that is on legs in an illuminated room
        - Two arms are walled and two are not
        - Most un-drugged rats spend more time in the walled arms, avoiding the un-walled arms
            - Natural tendency to avoid open spaces
        - Drugs which have anxiolytic potential alter rats preference for the arms leading to a substantial increase in time spent in open arms
    - The Geller-Seifter Procedure
        - Multiple schedule of reinforcement
            - Specifies what an animal must do in order to receive the reinforcer
        - Test takes place in a Skinner Box (box with 2 levers)
        - Typical schedule is a VI 2 minute / FR1 with shock
            - VI 2 minute: dictates that on average a reinforcer becomes available every 2 minutes and if the animal presses the lever after the interval it will get a reinforcer
                - Produces a stable moderate level of lever pressing
            - FR1 with shock dictates that *every* bar press will result in food but also a shock
        - The two are never in effect at the same time and a light signifies which is in effect
        - Un-drugged animals quickly learn to press for the VI 2 schedule and not to for the FR1 schedule although reinforcement is greater
        - Anxiolytics produce a specific result here called release from punishment
            - When an animal is given a drug that is anxiolytic it will now lever press even when the FR schedule is in effect
            - This could be due to some sort of analgesia – less pain – but it is not produced by analgesics like opiates
            - No other class of drug produces this result

Benzodiazepine Classes – Based on duration of action

- Long acting – Metabolized into long lasting active metabolites
    - Primary metabolite of diazepam is nordiazepam which has a half life of 60 hours

    - Most common of this type are Valium, chlordiazepoxide (Librium), flurazepam (Dalmane), and chlorazepate (Tranxene)
- Intermediate acting
    - Lorazepam (Ativan), clonazepam (Klonopin), and flunitrazepam (Rohypnol)
    - Rohypnol (roofies) is used as a date rape drug smuggled from Mexico
- Short acting
    - Midazolam (Versed), Oxazepam (Serax), alprazolam (Xanax), and triazolam (Halicon)
    - Used as sleep inducing agents
    - Halicon was introduced in 1983 and soon became the most widely prescribed sleeping pill in the world
        - Soon reports of aggressive dys-control appeared called 'rage reaction'
        - Temporary ban until makers reduced the dosage
- Abuse potential was quickly recognized especially for the middle aged female demographic mentioned above
    - As heard in Rolling Stones' "Mothers Little Helper"
    - There is heightened use of BZs by opiates and alcohol addicts
        - Both for withdrawal reduction and boosting
    - BZs are called minor tranquillizers to distinguish them from antipsychotics which are called major tranquillizers
        - The latter produces a much more profound tranquillizing effect
- BZs produce much of the same effects including reduced anxiety, sedation, muscle relaxation, anticonvulsant action, and sleep induction
    - Decrease latency to fall asleep, decrease waking during the night, increase total sleep time, and reduce REM sleep
        - Tolerance develops to all effects
        - Withdrawal includes REM rebound, bizarre dreams, and restlessness
    - Interfere with learning and memory suppressing long term potentiation, a brain process involved in the storage of new information
    - Produce anterograde amnesia, ie, memory failure from administration to near zero blood content
    - Reduce neuronal excitability making them useful in the mgmt. of alcohol withdrawal and epilepsy

Brain Processes

- Exert effects by interacting with the receptors for GABA
    - Although do not directly act on GABA receptors
    - Exert effects only in the presence of endogenous GABA
- Increase or enhance the affinity of GABA for its receptors
    - Specific BZ receptors that exist as satellite receptors on the GABA receptor itself

    - When BZ occupies the satellite receptor the GABA receptor switches to a high affinity binding state and GABA activity is enhanced
- Flumazenil (Anexate, Romazicon) is a BZ antagonist
    - It binds to the BZ receptor on the GABA receptor complex but does not exert any action
    - It is primarily used as an iv injection in the mgmt. of BZ OD and other cases where the effects need to be terminated

Tolerance and dependence

- Develops fairly rapidly to the muscle relaxing, sedating, sleep inducing, and anticonvulsant effects
- Less certainty about the development of tolerant to the anxiolytic effects
    - Much slower and less complete than other effects
- Dependence is shown in humans and animals
- Withdrawal symptoms include tremor, hot foot walking, and rigidity when induced by Flumazenil in animals
    - in humans as well normally
- Uncertainty about how long it takes for dependence to develop
    - Regime of less than 4 weeks is unlikely to produce dependence
    - Shorter acting drugs most likely to produce dependence and stronger withdrawal, more prone to abuse
- Withdrawal from BZ in humans sees increased neuronal excitation ranging from tremors to seizures, agitation and potential aggressive outbursts, insomnia, the return of anxiety at a more intense level, memory impairment, numbness and tingling in feet and hands, diarrhea, and upset stomach, muscle cramps, and headache

## Other S-H Not Otherwise Covered

Gamma hydroxybutyrate or gamma hydroxybutyric acid (GHB, Xyrem)

- Produces effects similar to barbiturates and BZs
    - Relaxation, euphoria, drowsiness, loss of consciousness, and amnesia
    - Called liquid ecstasy, Easy Lay, and natures Quaalude, used as date rape
    - Odorless, colourless liquid with slightly salty taste
- Can be synthesized by a combination of degreasing solvent, floor strippers, and drain cleaner
- Has an anxiolytic effect like BZs as evidenced by an increase in the time spent on the open arms in the elevated plus maze test
- Antagonized by flumazenil suggesting similar mechanical action to BZs
- Evidence of tolerance and physical dependence with withdrawal
- Activates the central dopamine reward system

# Inhalants

Unlike most drug classes this is grouped primarily because of the method of administration

- Those that are burned are not included
- Inhalants include:

    - Anaesthetic Gases – With some medical uses
    - Solvents – Without any medical use
    - Nitrites
- Solvents are popular among young drug users particularly in impoverished areas

## Anaesthetic Gases

Ether and Chloroform

- Raymundus Lullius, Spanish chemist, distilled alcohol and sulphuric acid together to produce what he called sweet vitriol in 1275
    - Introduced into medicine under the name Anodyne by Friedrich Hoffman in the late 1600s
    - In 1730 German chemist Frobineus gave it the name ether which comes from the Greek word meaning Heavenly
    - Recreational use dates from the 1700s in the from of ether frolics
    - Could be inhaled or drank although it is difficult to swallow because it burns the mouth and causes vomiting
    - Easier to drink mixed with alcohol
        - Popular 'medicine' called Hoffman drops, 3 parts alcohol, 1 part ether
    - Historically used to replace alcohol when supply was short
    - During a high alcohol tax era in mid 1800s England, ether was sold by the spoonful for a penny to get drunk
    - Rare today
- Chloroform was synthesized in 1831 by Samuel Guthrie in America
    - Like, but more potent than, ether
    - Can be used to get drunk-like effects

Nitrous Oxide – Laughing Gas

- Discovered in 1776 by Sir Joseph Priestly
- Many early chemists used it at parties for friends
- Produces euphoria for several minutes followed by a sense of well being that may last for hours
- Analgesia, giddiness, dreaminess, ringing in the ears, sometimes loss of consciousness, and a sense of flying
- Users can inhale it from spray food cans
    - Whipped cream canister refills of nitrous are used recreationally called whippets
- Used often in the late 60s through the 70s but declined in the 80s and now is rare
    - Growing now among young adults as an after dinner or clubbing drug
    - 'hippie crack'
- Limited danger other than hypoxia (lack of oxygen)
    - Although there is evidence of permanent peripheral nerve damage following extended exposure
    - Dependence in rats and mice
    - Handling induced convulsions occur shortly after cessation of chronic exposure but can be avoided by administration of nitrous or alcohol
- It is thought that all anaesthetic gases increase the GABA mediated inhibition

    - Enhance the effects of glycine, another inhibitory neurotransmitter, and reduce the effectiveness of the NMDA receptor for the excitatory neurotransmitter glutamate

## Solvents

- Household products contain psychoactive substances that are subject to abuse
    - Hobby glue (Toluene, methyl benzene, trichloroethylene)
    - Paint thinners
    - Lighter fluid (butane)
    - White out
    - Felt markers
    - Gasoline
    - Etc
- Toluene is the highest in abuse potential
- Administration involves soaking a cloth and then inhaling it through the mouth (**huffing**) or spraying it into a plastic bag and then inhaling with the bag over the nose and mouth (**bagging**)
- Psychoactive ingredients in solvents are highly lipid soluble
    - Most soluble is toluene and it has received the most research as such
- Toluene and other solvents have euphoric, hallucinogenic, and rewarding effects
    - Toluene activates the mesolimbic dopaminergic reward system
    - Produces a conditioned place preference and supports a nose poking self-administration response in mice
- Onset is very rapid and duration is about one hour
    - Summary of effects would be a quick drunkenness
        - Euphoria
        - Weightlessness
        - Ringing in the ears
        - Hallucinations
        - Double vision
        - Drunkenness
        - Vomiting
        - Weakness
        - Confusion
        - Seizures and possibly death
    - Death often results from disorientation
- Tolerance and physical withdrawal are readily produced in experimental studies involving animals
- Chronic use is associated with weight loss, weakness, disorientation, inattentiveness, lack of coordination, personality changes, fatigue, depression, headaches, insomnia, and loss of initiative
    - Worse than cocaine abusers
- MRI scans indicated more significant brain abnormalities and degeneration in solvent users than cocaine

- Evidence of organ damage and permanent nerve damage

## Nitrites

- Include Amyl, butyl, and isobutyl nitrite
    - Chemicals that are yellow volatile and flammable liquids that have a fruity odor
- First synthesized and used medically in 1867
- Related to nitroglycerin
- Amyl nitrite used medically for angina pain and as an antidote for cyanide poisoning
- Abused nitrites are called poppers because in medical form they come in glass ampules that make a popping sound when broken to gain access
- Butyl and isobutyl are not used medically but can be mail ordered or bought in some sex shops
    - Names of these commercial products are associated with sex and homosexual male sex
    - Aroma of Man, Climax, Cum, Heart On, Jac Aroma, Locker Room, Thrust, and Toilet Water
- Nitrites are vasodilators and have been used in treatment of angina pain and congestive heart failure
    - Relax smooth muscles that control the diameter of blood vessels, the iris of the eye and the anal sphincter
    - Effects include euphoria, increase in libido, dilation of genital blood vessels with penile engorgement, anal sphincter dilation, delayed ejaculation, headache, flushing, dizziness, physical sense of warmth, giddiness, and postural hypotension
- Effects are rapid, vasodilation occurs within 30 seconds, and short lived, only about 5 minutes
- Initial effects may be followed by nausea or vomiting
- Tolerance does develop as well as withdrawal
- Intended for inhalation only
    - Oral ingestion can result in serious problems as a result of reduced oxygen carrying capacity of the blood

# Tobacco

## History

- First users of tobacco were probably the Mayans in Central America as far back as 300 AD
- Explorers saw natives rolling leaves lighting them and putting them in their noses, so they conveyed tobacco back to Europe in the mid 1500s where its modern popularity began to grow
    - Suggested to have life restoring powers being blown into the rectum of dying people

- Consumed primarily by pipe in the 1600s
    - Common in all segments of society with men and women
- In the 1700s the most popular form of tobacco use was as snuff
    - Finely ground tobacco and pinches taken from highly ornate snuff boxes were snorted into the nasal passages
    - Books were written on snuffing techniques
- In the 1800s chewing of tobacco rose in popularity
    - As loose leaf tobacco or ground and mixed with molasses and pressed into chewable cubes
- Rolled tobacco in the form of cigars became popular in North America in the early to mid 1800s
    - Cigarettes in the 1850s
    - Grew very popular when the cigarette machine was invented in 1881 by James Bonsack
    - Modern machines make 20000 a minute
- Although it was readily accepted or ignored it always had a group of opposing people
    - Bans and protests had periods of popularity
    - King James I of England published A COUNTERBLASTE TO TOBACCO refuting medical claims
    - In 1624 Pope Urban issued a worldwide ban among Catholics
    - In 1633 Sultan Murad of the Ottoman Empire prohibited smoking and roamed the streets to enforce it himself – offenders beheaded
    - Czar Micheal of Russia did the same in 1634
    - All eventually failed and Tobacco joined coffee wine and opium as one of the four cushions on the sofa of pleasure
- An anti-tobacco movement flourished in Canada and America during the time of prohibition and drug bans
    - The anti cigarette league was formed in the US in 1899 headed by Lucy Gaston
    - Gaston called cigarettes ‘coffin nails’
    - Canadian Parliament debated bans for 15 years beginning in the 1900s
        - Some legislation was passed to ban sale to minors but that was it
- With the beginning of WW1, protests diminished and sending cigarettes to soldiers was common
- Per capita consumption:
    - 1900: 54
    - 1910: 151
    - 1920: 665
    - 1930: 1485
    - 1940: 1976
    - 1950: 3522
    - **1964: 4300 peak**
        - **40% if US adults were smokers**
        - **70% of Canadians in 1950**
- Consumption has declined ever since the US surgeon general’s report in 1964

- 1970: 4000
- 1980: 3851
- 1990: 2827
- 2000: 2092
- 2005: 1716
- **Current: 1028 in the US, 809 in Canada**
  - **About 18% of Canadian adults smoke now**
  - **22% males, 16% females**

## Costs of Use

- Primarily in the form of health consequences
  - Costs Canadians more in health care, lost productivity, and premature death than alcohol or illegal drugs
    - $17 billion
  - estimated that a person loses 14 minutes of their life for every cigarette they smoke
    - Smokers die as much as 12 years earlier than non smokers
  - Damage is also done to those who inhale the smoke exhaled by smokers (Mainstream smoke) or the smoke emanating from lit tobacco (sidestream smoke)
    - Side-stream is worse as it is unfiltered and burning less fully
  - Living or working where smoking is permitted increases the nonsmokers' risk of developing heart disease or cancer by up to 30%
    - Babies exposed to second hand smoke are at increased risk of death from SIDS
- What identifies smokers from nonsmokers?
  - There is evidence for genetic influence
  - Certain demographic factors such as adolescent age, low socioeconomic status, less education, high levels of coffee and/or alcohol consumption, are more common in smokers than nonsmokers
  - Females more than males see smoking as a means of weight control
    - 39% of women in one study reported this as the primary reason for smoking
  - Smokers tend to exhibit low conscientiousness, low agreeableness, high extroversion, increased neuroticism, more anxiety, less self control, and less morningness-more eveningness
  - Relationship between adverse childhood experiences and smoking leading to the suggestion that smoking may be used as a form of pharmacological relief from unpleasant experiences
  - Social influences such as peers or parents dispose toward smoking
  - Higher instance of mental illness
  - Smoking occurs in 23% of individuals with no history of a mental disorder but 41% of those with a current mental disorder
    - The most frequent disorder comorbid with smoking is depression

        - And alcoholism
        - There is evidence that nicotine may have anti-depressant effects
            - Transdermal nicotine patches showed substantial improvement in depressed nonsmokers

## Nicotine: The Active Ingredient

- Primary psychoactive ingredient in tobacco
    - First purified in 1828 by two French chemists, Posselt and Reimann who named it after the French ambassador to Portugal, Jean Nicot
- Oily, either colourless or brownish substance with an unpleasant smell
- Most efficient consumption is by inhalation, where absorption is rapid and 90% complete
    - Reaches the brain in 7 seconds
- Also readily absorbed by the skin
- The main metabolite of nicotine is cotinine
    - Presence of cotinine in urine is used as a marker for tobacco use or second hand smoke
- As much as 30-40% of inhaled nicotine is excreted unchanged and the amount of nicotine excreted is dependent on urine pH
    - Since its basic, alkalinizing the urine leads to greater renal reabsorption
    - A diet high in alkaline foods could help reduce smoking by keeping nicotine in the blood longer
- Smokers smoked at a higher rate when nicotine excretion was increased by acidification of urine (by ingestion of vitamin C and ascorbic acid)
    - Stress results in acidification of urine leading to more smoking

## Brain Stuff

- Nicotine activates nicotinic cholinergic receptors
    - One important location of such receptors is on the dopaminergic neurons in the mesocorticolimbic dopamine system
- Activation of nicotinic receptors located on dopamine neurons in this system leads to stimulation of dopamine release thus nicotine is rewarding because it increases dopamine levels
- Nicotine also interferes with the modulatory action of GABA towards dopamine
    - Usually GABA acts to inhibit the release of dopamine if there is over activity in dopamine neurons such as would be caused by nicotine itself

    - Nicotine prevents this negative feedback action of GABA thus leading to even more dopaminergic activation

## Back to Nicotine

- A typical cigarette contains 0.5-2.0 mg of nicotine only 20% of which is inhaled and reaches the bloodstream
- The amount of nicotine, tar, carbon monoxide and other constituents inhaled from cigarette smoke is very dependent on smoking topography
    - Refers to characteristics of how the cigarette is smoked with some of the most important characteristics in term of delivery of constituents being depth and volume of inhalation, how long the smoke is held and whether the holes in the filter are covered or uncovered
- Machines used to measure the constituents of cigarettes and standardize the measures printed on packages
    - No longer acceptable as the reality of constituent content is vastly different than the machine
    - Further explains why light or mild branding of cigarettes is no longer allowed – Misleading
    - Light cigarettes have ventilation holes that allow air to enter the smokers mouth diluting the smoke but if they are plugged the effect does not occur and the cigarette is much stronger
- Nicotine affects the vomit center of the brain, increases heart rate and blood pressure, and constricts blood vessels leaving smokers with cold clammy hands and feet
    - Male smokers are likely to experience impotence over the course of long term smoking
    - Nicotine is toxic, the lethal dose being about 60mg in an adult
        - A typical cigar contains about two lethal doses of nicotine but not all is inhaled
- There are over 4000 compounds released during the smoking of a cigarette
    - Tar and carbon are two particularly pernicious compounds
        - Tar is any of the substances in tobacco smoke other than nicotine and carbon monoxide
        - Can be seen in filter
- Marijuana is worse in terms of tar and carbon though
- Carbon monoxide preferentially binds to hemoglobin forming carboxyhemoglobin which reduces the oxygen carrying capacity of blood
    - The smoking of one cigar reduces the oxygen carrying capacity of blood an amount equal to the loss of 250cc of blood
    - Smokers have 10 times as much carboxyhemoglobin
- Cholinergic nervous system is involved in learning and memory
    - Nicotine acts in this system so it is likely to have an effect here
    - Nicotine is capable of improving information processing and memory
    - Enhances performance in tasks requiring concentration over long periods of time

    - Seems to reduce interference from irrelevant stimuli and increase attention related to relevant stimuli
        - Stroop task: shown color names printed in colors not corresponding to the name – name the colour of the text
        - Challenging since the semantic content preferentially gains attention
        - Nicotine reduces the interference from the irrelevant semantic content and naming the colors is faster under nicotine compared to no nicotine
    - Nicotine may help to alleviate some of the cognitive deficits seen in Alzheimer's and even in the non-demented elderly
        - Cholinergic hypo-functioning is common in Alzheimer's patients which nicotine helps alleviate
- One cognitive process thought to be involved in SUD is biased attention to drug related stimuli
    - This process is studied in a modified Stroop task
        - Ex. For depression: Ps are shown words associated with negative moods (target words) and words not associated with negative moods (neutral words) and asked to name the color of the print
            - Depressed people are slower to name target words than non-depressed people (called Stroop interference
        - Used to determine whether people with a disorder have an attentional bias toward stimuli related to that disorder
        - People with SUD readily show Stroop interference with related stimuli

Self-Administration and Conditioned Place Preference

- Nicotine is a reliable reinforcer in the SA procedure
- Several drugs have been shown to block the acquisition and/or expression of nicotine self-administration
    - Mexamylamine (blocks nicotine receptors)
    - Rimonabant (blocks cannabinoid receptors)
    - Naloxone (blocks opiate receptors)
- These indicate that the reinforcing effects of nicotine involve a complex interaction of several neurotransmitter systems affecting the dopamine reward system

Tolerance and Physical dependence

- Tolerance develops to most of the physiological effects of nicotine but there is less evidence to psychoactive effects
- There is little evidence of tolerance to performance, locomotor, reinforcing, or dopamine releasing effects
- Evidence of physiological tolerance is consistent with the occurrence of a number of physiological withdrawal symptoms
    - Noted symptoms include teeth chattering, abdominal writhing, gasps and chews, ptosis, wet dog shakes, and tremors in animals

- In humans recognized symptoms include an increase in negative affect, decrease in arousal, sleep disturbances, restlessness, attentional deficits, tension, irritability, headaches, increased appetite with consequent weight gain, and cravings for cigarettes
- 10-30 days duration for most symptoms but cravings continue for years

Treatment of Tobacco Addiction

- The typical scenario is numerous cycles of quitting and relapsing
  - The relapse rate for returning to smoking after quitting is quite high
    - Some estimate no lower than 80%
  - Being older, male, and married, smoking fewer cigarettes , having a lower addiction level, having smoked for fewer years, having more previous quit attempts and having higher self efficacy, increase the likelihood of staying abstinent
  - Women find it harder to quit than men
    - Suggests that women may smoke less for nicotine than men
    - Women tend to smoke fewer cigarettes per day
    - Less dependent on nicotine
    - Nicotine replacement is more effective in reducing withdrawal symptoms and leading to continued abstinence in men than women
    - More influenced by the sensory effects of smoking, conditioned cues for smoking or social pleasures involved in smoking rituals
- Pharmacotherapies for smoking cessation
  - Nicotine replacement therapy – delivered by some means other than smoking such as transdermal patch, gum, nasal spray, or oral inhaler
    - Smokers attempting to quit are likely to relapse because of withdrawal symptoms which can be alleviated by maintaining some level of nicotine in the blood
    - There is evidence that the reinforcing effects of smoking are not solely due to the delivery of nicotine
    - Success rates are still low for several reasons
      - Primarily that self reported craving levels are nearly unaffected by nicotine replacement although withdrawal symptoms are
      - Also doesn't give the nicotine hit that users are used to
  - Sustained release bupropion (Zyban, Wellbutrin) – a nicotine receptor antagonist blocking dopamine reuptake
    - Originally an antidepressant
    - Twice as successful as placebo
    - Seems to be somewhat more helpful than nicotine replacement
    - Combining both is better than either alone
  - Varenicline (Champix/Chantix) – Partial receptor agonist at nicotinic receptors
    - Attaches to nicotinic receptors but does not produce the same level of agonism (activation) as nicotine
    - Blocks nicotine from the receptors leading to an actual reduced level of nicotine stimulation and thus reduced dopamine release

        - Effective in reducing both withdrawal symptoms and craving and has been shown to be more effective than either nicotine replacement or bupropion
        - May produce psychiatric side effects

New Trends in Nicotine Use

- Increasingly socially unacceptable leading to more novel methods
    - Vaping – inhaling vapors produced by some electronic device that heats and atomizes an e-liquid that may contain nicotine
        - Can just be propylene glycol and vegetable glycerin with flavouring though
        - Called e-cigarette
        - Goes back to the 1960s
        - Can backfire by attracting young people, getting them addicted, and possibly switching to cigarettes
        - 1 in 4 Canadians 15-19 have tried an e-cig
    - Heat-not-burn cigarettes
        - Heat actual tobacco to a point just below combustion to vaporize the nicotine but avoid burning
        - Introduced in the 90s
            - Not very successful
- Concerns that both these methods may re-normalize smoking