PSYC 181 Drugs and Behavior EXAM 1 Review Sheet

Smoking

Smoking is number one preventable cause of death in the U.S. (mostly lung cancer).
About 430,000 people die from smoking-related illness in the U.S. each year (1/5 of all deaths).

Drug Abuse vs. Drug Addiction

Drug Abuse is the use of any drug in a manner that deviates from the approved medical or social patterns in a given culture. The medical definition takes into account the *pattern* of use:

1. Pattern of pathological use
2. Impairment in social or occupational functioning caused by the pattern of pathological use
3. Duration of at least one month

Note: A lot of drug use falls outside the realm of medical use, such as non-medical drug use, experimental drug use, recreational use, and circumstantial use.

HOWEVER, Drug Abuse is not the same as Drug Addiction!

Drug Addiction is a behavioral pattern of drug use, characterized by:

1. COMPULSIVE USE
2. COMPULSIVE DRUG-SEEKING
3. High tendency to RELAPSE after withdrawal.

Note: addiction does NOT necessarily imply dependence (ex. LSD).

Names of Drugs

Be able to distinguish between proprietary (trade, brand), nonproprietary (generic) and chemical names.

Classes of Psychoactive Drugs

- **Opiates (narcotics):** Similar to opium in composition or effect, has analgesic properties, causes sleepiness. Ex. morphine, heroin, codeine, hydrocodone (Vicodin), Dilaudid, Demerol
- **Depressants**: Depress the Central Nervous System (CNS)
  Barbiturates: Seconol, Nembutal
  Benzodiazepines: diazepam (Valium), Ativan, flunitrazepam (Rohypnol), GHB
- **Stimulants:** cocaine, amphetamine, methylphenidate (Ritalin), nicotine, caffeine
- **Hallucinogens:** LSD, psylocin, psylocibin
- **Dissociative Anesthetics:** PCP (phencyclidine), Ketamine
- **Cannabinoids:** tetrahydrocannibanol (THC – marijuana)
- **Designer Drugs:** MDMA (extasy)- has characteristics of both hallucinogens and stimulants

Sources of Psychoactive Agents

1. Naturally occurring – means originally extracted from plants, ex. opium
2. Semisynthetics – drug originally from a plant but has been modified, ex. heroin
3. Synthetics – never extracted from a plant, made in a lab, ex. Methadone

History of Drug Abuse

-Drug addiction emerged in the US with the use of morphine (opiate) in Civil War soldiers to treat pain (Soldier's disease).
-Morphine was marketed as a paregoric (alcohol/opium mixture), for teething aid for infants, etc.
-Heroin (diacetylmorphine) was introduced as a cure for morphine addiction.
-Cocaine was used for relieving toothaches, (local anesthetic effect) and was marketed as a panacea (a "cure-all"). Cocaine-fortified wines were popular prior to the temperance movement, which started in the south. Coca-cola replaced coca wines.
-Pre-1906 – all drugs were legal
-Pure Food and Drug Act (1906) – regulated food, drugs, and drug claims, created FDA
-Harrison Tax Act (1914) – opiates and cocaine outlawed due to trade war with China
-Boggs Amendment to the Harrison Act (1951) – criminalized illicit drug use
-Drug Abuse Control Act (1965) – tried to make drugs that were addictive illegal
-Controlled Substances Act (1970) – classified drugs into schedules
  Schedule I – no medical use (heroin, LSD, marijuana)
  Schedule II-V – various restrictions on medical use, varies by state
  Schedule VI – some states use this classification for inhalants (glues, paints) and Sudafed
  Unscheduled – aspirin, Tylenol
-Analogue Drug Act (1985) – passed power to make drugs illegal to the DEA
-Date Rape Prohibition Act (2000 – 2001) – outlawed GHB, Rohypnol

Drug Development Outline

Discover unmet medical need -> discover mechanism of action of disease -> identify target protein -> screen known compounds against target -> chemically develop promising leads -> find 1-2 potential drugs -> test for toxicity, pharmacology -> market evaluation-> clinical trials

Pharmacology: the branch of medicine that deals with the uses, effects and modes of actions of drugs.

Drug: Substance that is used primarily to bring about a change in some existing process or state, be it psychological, physiological or biochemical.

Pharmacokinetics: the ability of a drug to get to its target receptors

- **Route of administration:**
  Oral (via digestive system)
  Parenteral injection (through the skin)
    - Subcutaneous (sc) – under skin (relatively slow)
    - Intramuscular (im) – through muscle (slowest distribution)
    - Intravenous (iv) – through vein (fastest distribution)
    - Intraperitoneal (ip) – through the peritoneal cavity (relatively fast & easy)

  Pulmonary absorption – inhalation (quick route to brain)
  Topical application – applied externally on skin (really slow)
  Half-life *is the time for the plasma drug conc. to fall to half of its peak level, it varies as a function of route of administration – it is a measure of how long a drug lasts*
- **Absorption and Distribution**
  Drug transport across membranes is the most important factor in achieving active dose at the site of action.
  Mechanism of transport – Passive diffusion (down concentration gradient)
  Limits:
    - size and shape of drug molecule
    - lipid solubility of drug
    - degree drug is ionized (charged) – MAJOR FACTOR
      More ionized → less lipid soluble → less absorption → less effect

  Ion trapping – know the difference in absorption b/w acidic & basic drugs (aspirin example)
  Blood-Brain Barrier – limits the ability of drugs to reach the brain
- **Inactivation** – metabolism (biotransformation) to inactive forms (liver major site)
- **Elimination** – expulsion of metabolites or unchanged drug by kidneys, lungs, sweat, saliva, feces, or milk (kidney major site)

Pharmacodynamics: what the drug does when it reaches its receptors

Receptors: where drugs bind to produce a pharmacological effect

Dose-Effect Curve (related to **Law of Mass Action**: D + R = DR* > effect)

- The magnitude of drug effect should be proportional to the number of receptors occupied by the drug (log relationship – 10X as much drug to get 2X the effect)
- Drug receptor interactions involve weak non-covalent interactions that are reversible
- Potency decreases to the RIGHT (takes more drug to have same effect)
- Curve reaches a max and plateaus when all receptors are occupied
- Drugs w/ similar shaped curves & max response usu. use the same receptor system/mechanism of action

Potency: how strong a drug is, depends on receptor accessibility, affinity, efficacy

- ED_{50} (effective dose) – Dose that produces an effect in 50% of a population
- LD_{50} (lethal dose) – Dose that kills 50% (aka TD = toxic dose)
- TI (Therapeutic index) – (LD_{50}/ED_{50})
- Safety margin = $LD_{50} – ED_{50}$

Agonist: a drug that binds to receptor and has pharmacological effect

Antagonist: drug that binds to receptor and has no direct biological effect, blocks the action of an agonist or transmitter at that receptor

- **Competitive antagonist:** shifts dose-effect curve to RIGHT (need larger dose to produce same effect), effect can be overcome by sufficient dose
- **Noncompetitive antagonist:** shifts dose-effect curve to RIGHT, but cannot be overcome with dosage (decreases max. effect), can bind irreversibly or reversibly to prevent agonist from binding. Poisons are noncompetitive antagonists.

Tolerance and sensitization

Tolerance: decreased response with repeated administration, or a higher dose is required to produce the original effect (shift to RIGHT)

Cross tolerance: tolerance to one type of drug leads to tolerance to others (esp. in same class, but can occur across classes)

Sensitization: increased response with repeated administration, or a lower dose is required to produce the original effect (shift to LEFT)

Cross sensitization: sensitization to one type of drug leads to sensitization to others (ex. often seen in stimulants: sensitization to cocaine → sensitization to amphetamine)

Tolerance and sensitization may involve pharmacokinetic (dispositional) changes, pharmacodynamic changes (neuroadaptation), or behavioral factors (learning).

Behavioral Pharmacology: the study of the relationship between the physiological actions of drugs and their effects on behavior and psychological function.

-The behavioral effects of drugs are due to interactions amongst the pharmacological actions and drugs, the state of the organism ("set") and the surrounding environmental circumstances of drug administration ("setting")

-Evaluation of behavioral effects of drugs

1. Primary evaluation - unconditioned effects on behavior
   - motor activity
   - seizures
   - eating and drinking - big change here cannot facilitate consumer's satisfaction
2. Secondary evaluation - tests more specific functions; unconditioned or conditioned (learned)
   - analgesia
   - learning and memory: spatial radial maze task, Morris water maze test, augmented startle response, nonrecurring-items delayed nonmatching-to-sample test
   - anxiety: elevated plus maze
   - schedule controlled: used primarily to study addiction

-Schedules of reinforcement

Reinforcement increases the probability of a behavior. Punishment decreases the probability of a behavior.
"positive" = presentation of a stimulus, "negative"= removal of a stimulus
Operant procedures are used for two reasons:

- To question about the stimulus properties of drugs ("what it feels like")
- To question about the reinforcing/incentive properties of drugs ("will you work for it")

Ratio schedule: reinforcement is based in the # of responses made

1. fixed ratio schedule: reinforcement occurs after every 10 responses (FR10)
2. variable ratio schedule: reinforcement occurs after an average of 10 responses (VR10)

Interval schedule: reinforcement is based on amt of time spent since the last reinforcement (paycheck ex.)

1. fixed interval schedule: reinforcement occurs 3 minutes after a response (FI3)
2. variable ratio schedule: produces steadiest response

DRL schedules (Differential Reinforcement of Low rates)- deviant of fixed interval, reinforcement occurs after fixed amount of time, but if response takes place before time is up, clock resets.

-Drugs as discriminative stimuli (S_D)

S_D: stimulus that signals availability of reinforcement, related to interoceptive cues of drug

-Measurement of drug reward- to determine abuse potential of drugs and study mechanisms behind drug's rewarding effects and dependence

1. Effects on withdrawal
2. Self-administration paradigms: substitution procedures and choice procedures
   Notice mescaline and LSD do not maintain self-administration (not addictive)
   Progressive ratio schedules- progressive increase in response required
   "Breakpoint" - the highest ratio achieved in order to get drug; measures how hard the subject would work to get the drug.
3. Conditioned place preference: Pavlovian context conditioning; rewarding stimuli will elicit approach responses and maintenance of contact with the stimulus.

Synaptic transmission- synapse is the site of action for most psychoactive drugs.

Neurons receive action potential via dendrite (input) and axons (output) carry the AP to a target.

Types of cell to cell junctions include: tight junctions, gap junctions, and chemical synapses.

- **Steps in synaptic transmission**: synthesis-> transport -> storage-> release of NT -> inactivation

- Release in more detail – Excitation-secretion coupling (MEMORIZE, was a previous exam question)
Depolarization → open voltage-gated Ca^{++} channels → Ca^{++} influx → bind to Ca^{++}-calmodulin protein kinase → Phosphorylation of synapsin I → movement of vesicles to release site → Exocytosis → Diffusion
- **Inactivation**: reuptake of NTs by transporters followed by enzymatic degradation; NTs are recycled.

Neurotransmitters: classical vs. neuropeptides

1. "classical"- small water soluble molecules with amine, formed from dietary precursors
   includes phenylethylamines (DA, NE, E, tyramine, etc),
   indolamines (5-HT, tryptamine, melatonin, etc),
   cholinergics (acetylcholine, etc), and amino acids (glutamate, etc)
2. neuropeptides- via protein synthesis
   enkephalins, substance P, neurotensin

Receptors

•Classification by location

1. Postsynaptic
2. Autoreceptor: refers to transmitter receptors, on or near presynaptic terminals, which are sensitive to the transmitter(s) released by the terminal itself

•Classification by transduction mechanism

1. Ligand-gated channels:
   - either excitatory or inhibitory actions
   - rapid action & rapidly reversible
   - combine receptor & ion channel functions into a single mlc (binding site coupled to ion channel)
   - ionotropic receptors = receptors in which the ligand binding site is an integral part of the receptor molecule
   - ligand opens channel, ions travels down its concentration gradient
   - examples include:
     A) Nicotinic acetylcholine receptor (nAchR)
     -coupled to Na^+ channel, when drug binds, lets Na^+ in; primary actions observed in muscle contraction
     -drugs that bind nAchR include nicotine, curare, and acetylcholine
     -curare competitively blocks nAchR; depolarization cascade blocked ->muscle contraction occurs
     B) $GABA_A$ receptor
     - coupled to Cl^- channel, has an inhibitory effects
     - sedative-hypnotic drugs
2. G-protein-coupled receptors:
   - produces ambiguous/complicated effects
   - characterized by seven transmembrane domains; the binding of these receptors by agonists leads to the activation of intracellular G-proteins.
   - activated G-protein stimulates effector
   - slower in action than ion-coupled receptors, but usually bigger effect
   - two classes:
     A) Directly coupled to ion channel- effector is ion channel; works almost same as ligand - gates channel at a slower rate
     B) G-protein coupled to 2^{nd} messenger system
     - 2^{nd} messenger opens ion channels
     - types of 2^{nd} messenger include: Ca^{++}, cGMP, IP_3, DAG, cAMP
     - cAMP: activates protein kinase which phosphorylates protein, producing a biological response

•Protein phosphorylation alters the conformation of the protein and thus has an effect on protein function.

Ex) Gene regulatory proteins can activate transcription factors such as CREB, (cAMP response element binding protein) leading to enhancement or suppression of transcription. If transcription is enhanced, new gene products are made. Signaling pathways can alter gene transcription via same transcription factor. ("convergence on CREB" is an example)

Gene activation consists of two phases:
Initial phase – Induction of immediate-early genes, protein products initiate 2^{nd} phase of activation
Second phase – Induction of "late-onset genes", products alter cellular function (often permanent changes)

Psychomotor stimulants: cause increased alertness and motor activity, heightened arousal (ex. amphetamines and related compounds, cocaine) -β-phenylethylamine derivatives: all have similar structures/effects (ex. amphetamine, ephedrine, pseudoephedrine, phenylalanine) -Sympathomimetic amines: mimic the effects of the sympathetic nervous system -Naturally-occurring compounds:

1 Cathinone – active ingredient in Khat, chewed

2 Ephedrine – from Ma Huang (ephedra = plant extract), used for asthma (bronchiodilator), structurally similar to epinephrine (E), pseudoephedrine (Sudafed) is an isomer of ephedrine

Amphetamine

-Synthetic, structurally-related to catecholamines (DA, NE, E) -Widespread adoption since 1932 Benzedrine inhalers -Peak use in early 1970's, but new west coast popularity

Forms: -Racemic – mixture of d-and l-isomers (ex. Benzedrine, Adderall (for ADD), speed) -d-Amphetamine (dextroamphetamine) – stronger than racemic (ex. Dexedrine)

- o depletes DA, causes degeneration of DA terminals (primarily caudate) -l-Amphetamine (levoamphetamine) – less potent version, not really marketed for anything -Methamphetamine (dl-methylamphetamine) – strongest, most potent (ex. Methedrine, Desoxyn (for ADD), meth, crystal, crank, speed) -l-Methamphetamine – "desoxyephedrine", really weak, not even controlled, in Vick's inhalers -d-Methylamphetamine HCl – can be smoked (gets to brain faster = more addictive) or snorted b/c of purity (ex. ice, crank, crystal meth)
  - o synthesis from amalgam method → racemic methamphetamine
  - o synthesis form ephedrine (or Sudafed) → pure d-methylamphetamine HCl
  - o depletes DA and serotonin, causes degeneration of terminals (caudate DA, cortical and hippocampal 5-HT)

Amphetamine-related drugs: all bad for heart, raises blood pressure and heart rate, anorectic -Methylphenidate (Ritalin): treats ADD -Fenfluramine (Redux): anorectic (reduces appetite) -Phenmetrazine (Preludin): anorectic -Subitramine (Meridia): anorectic

Medical Uses: (1) Narcolepsy, (2) ADD, (3) no longer used for obesity

Major Effects: Autonomic effects (sympathomimetic effects) -increased blood pressure -increased body temperature -bronchodilation Effects on CNS -analeptic (awakening) -anorexia -psychomotor stimulant effects

- o decreased fatigue, increased alertness
- o arousal
- o elevated mood
- o euphoria

Effects of repeated administration: Tolerance -most autonomic effects -anorectic effects

Sensitization -psychomotor stimulant effects -rewarding effects (how reinforcing the drug becomes) -psychotomimetic effects (amphetamine psychosis), ability of drug to mimic schizophrenia Non-humans -Low doses: locomotor hyperactivity -Higher doses: stereotyped behavior (doing same thing over and over again) -Reinforcing effects: self-administration and conditioned place preference

Cocaine

-Naturally found in coca plant leaves -Local anaesthetic effects (unique to cocaine, does not occur with amphetamines) -History of use: been around forever, mostly in S. America, in U.S. mixed with wine, tobacco, Coca-

Cola was a response to the temperance movement in the south

Forms: -Raw leaves – chewed, low alkaloid content, not stable (degrades easily) -Coca paste – initial extraction around 80% cocaine, used for smoking -Cocaine HCl – crystalline form, purified and converted to HCl salt, snorted or IV use -Cocaine free base – extract with volatile solvents, smoked -Crack – free base made with baking soda & ammonia, crackles when heated, smoked

Major Effects: very similar to amphetamine but some major differences… -Duration of action – much shorter than amphetamine -Cardiovascular effects – danger of heart attack much higher than amphetamine -Convulsive properties – sensitize -Local anaesthetic effects – totally unique to cocaine (ex. lidocaine, novacaine, benzocaine)

Mechanisms of Action

Monoamine neurotransmission – compounds with one amine group, -NH_2) -Epinephrine (E), found mostly in periphery (outside brain) -Norepinephrine (NE), found in brain -Dopamine (DA), found in brain – mediates psychomotor stimulant & rewarding effects -Serotonin (5-HT), derived from tryprophan (tryptophan → 5-HTP → 5-HT)

Catecholamines (CA; catecholaminergic) – compounds with catechol nucleus and amine group -Epinephrine (adrenergic) -Norepinephrine (noradrenergic) -Dopamine (dopaminergic)

Indolealkylamines – compounds with indole and amine group -Serotonin (serotonergic) -Melatonin

Catecholamine Synthesis: TYROSINE –E1→ DOPA –E2→ DOPAMINE –E3→ NE –E4→ E

Enzymes that catalyze conversions:
E1 – tyrosine hydroxylase
E2 – amino acid decarboxylase
E3 – dopamine β-hydroxylase
E4 – phenylethanol amine N-methyl-transferase

MAO (monoamine oxidase) degrades monoamines

DA synapse (see diagram)
NE synapse (see diagram)
Distribution of NE: concentrated in LOCUS COERULEUS (where NE is made), diffuses everywhere
Distribution of DA: 2 pathways

1 **Nigrostriatial (dorsal striatum)** – involved in stereotyped behavior
SUBSTANTIA NIGRA → CAUDATE PUTAMEN (STRIATUM)

2 **Mesolimbic (ventral striatum)** – the pathway of addiction/reward and locomotor hyperactivity
VENTRAL TEGMENTAL AREA (VTA) → NUCLEUS ACCUMBENS

Primary Site of Action:

Cocaine: -blocks monoamine transporter -prevents reuptake -requires calcium

Amphetamine: -calcium independent -release of DA not blocked by reserpine (drug that dissolves MA vesicles) -release blocked by TH (tyrosine hydroxylase) inhibition -requires transporter (blocked by reuptake

blockers = cocaine)
Locus of Action: -Autonomic effects: sympathetic nervous system -Psychomotor and rewarding effects: brain monoamine systems, DA critical component
Dopamine Studies: -
Pharmacological -Lesion -
Neurochemical -Correlational
-Molecular Biological
DAT vs. VMAT: The DAT is highly regulated, the VMAT is not. Therefore, the VMAT and not the DAT provides a reliable indicator of DA terminal density.

Methylenedioxymethamphetamine (MDMA) – Extacy
-Illegal since 1985, 1st schedule I by DEA -Several analogues: DOM, DOB, MDA, MDMA, 2-CB -Synthesis: from Safrole (distilled from sassafras or nutmeg oil) -Typical use is in pill form -Different class of users than traditional drug users (clubbers, college students)
Behavioral and Affective Effects: -Low doses: relaxation, serenity, emotional closeness -Moderate doses: mild hallucinogenic effects, intensification of feelings, notorious memory impairment (unique to this class of drugs) -High doses: amphetamine-like effects, hyperthermia (heat stroke) *(biggest concern in terms of safety, most seen in ER),* "hangover"
Neurochemical effects:
Monoamine Neurotransmission:
-increase synaptic DA and 5-HT
-blocks 5-HT transporter
-enters neuron and causes calcium-independent release of 5-HT

Neurotoxic effects:
-potent neurotoxin (1-2 times street dose)
-depletes forebrain 5-HT (not DA)
-rapid degeneration of 5-HT terminals (MDMA & MDA)

PMA (paramethoxyamphetamine) is a substitute for MDMA because it is cheaper to make, however it has slower/longer effects and is more hallucinogenic, so the incidence of toxic side effects are much higher than MDMA (narrow safety margin). PMA is responsible for most ER visits instead for heat stokes

IMPORTANT DISTICTICTION: AMPHETAMINE NEUROTOXICITY
-d-Amphetamine: DA only
-Methamphetaime: DA and 5-HT
-MDMA (and MDA): 5-HT only