

### The Psychopharmacology of Mental Illness and Substance Misuse

**Regulation of Brain Activity :** All behaviors, effects of all therapeutic and abusable drugs are the result of changes in chemicals called "neurotransmitters", their quantity, and their activity in the central nervous system (CNS)

1. Neurotransmitters: characteristics
  - a. Chemicals produced by the body,
  - b. Act on areas of nerve cells that "receive" these chemicals. (Latter = "receptors")
  - c. Change in the level or availability of a neurotransmitter changes the level of CNS activity
  - d. Amount of neurotransmitter available in nervous system is regulated by chemicals called "enzymes" These chemicals can work with other substances in the brain to break down the neurotransmitters for removal from the body or increase the amount of a neurotransmitter that's available to act in the nervous system as is the case in all of the body, what you take in, i.e. - food, drink and drugs, will have some effect on the amount and type of neurotransmitters available.
2. Neurotransmitter Effects:
  - a. can increase or decrease activity in the CNS depending upon where they are in the brain
  - b. Action of a neurotransmitter can be different in different locations
3. Examples: of neurotransmitters: Dopamine (DA), Norepinephrine (NE), Epinephrine (Epi), Serotonin (5HT), GABA, glutamate (New ones being discovered annually)
4. Catecholamines neurotransmitters: a family of related neurotransmitters
  - a. Examples: DA, NE, Epi, 5-HT
  - b. Tyrosine → DOPA → Dopamine (DA) → Norepinephrine → Epinephrine  
With the help of enzymes, each is made from the other, so anything that affects one can have some effect on the others.
  - c. Phenylalanine is a chemical available in foods. It is made into tyrosine in the body by a particular enzyme not enough enzyme results in excessive amount of phenylalanine intellectual deficits  
(phenylketonuria) See warnings on diet pop bottles about this condition
  - d. Dopamine (DA)
    - 1.) Neurotransmitter implicated in pleasurable activities including sexual activity.
    - 2.) all substances of abuse affect the amount of DA available in the "pleasure center" of the brain located in the part of the brain called the thalamus
    - 3.) Excessive amounts can result in psychosis. (Too much of a good thing?)
    - 4.) Cocaine can induce paranoia and psychotic behavior because it increases the amount of DA acting in the nervous system
    - 5.) All antipsychotic drugs effect the DA system to decrease the amount of this neurotransmitter acting on brain cells
  - e. Epinephrine and Norepinephrine (NE and epi)
    - 1.) Broken down by the enzyme MonoAmine Oxidase (MAO), so decrease monoamine oxidase increase NE and Epi
    - 2.) Epi and NE = activating neurotransmitters, i.e., they increase CNS activity. This action can result in a decrease in depression and an increase in ability to enjoy activities
    - 3.) Early antidepressants worked here:
      - a.) MAO inhibitors = group of antidepressants that keep MAO from breaking down EPI and NE (i.e. they inhibit its action)

- b.) Still used occasionally
- c.) Examples:
- d.) Not as widely used because can get too much EPI and NE accidentally by taking in some food and medications. This has resulted in severely increased blood pressure, seizures, and death. Opiates in general, such as morphine, demerol, codeine, heroin can all cause such an increase in NE and Epi that they have resulted in deaths
- e.) Quite safe in reliable patient with good information about potential interactions
- f. Serotonin (chemical name is 5- hydroxytryptamine, or 5-HT for short)
  - 1.) Made from tryptophan (sources:                   ), so dietary tryptophan has significant influence on CNS serotonin
  - 2.) Levels are regulated by "reuptake" I.e. - being pulled back into the cell and destroyed
  - 3.) SSRIs = antidepressants Selective Serotonin Reuptake Inhibitors (prozac, paxil, zoloft)
  - 4.) Serotonin (5HT): can increase or decrease DA depending upon part of brain affected
- 5. GABA:
  - a. Usually an "inhibitory" neurotransmitter: i.e. -- increase in GABA would cause a decrease in brain activity
  - b. Decrease GABA causes stimulation:
  - c. Anti anxiety agents (benzodiazepines, barbiturates) and alcohol may stimulate GABA, inducing relaxation ( Increase GABA activation → decrease CNS activity → sedation/ relaxation)
- 6. Glutamate:
  - a. Primary receptor is "N-methyl-D-aspartate" (NMDA)
  - b. This receptor is extremely important for learning, memory, and pain perception
  - b. Anything working here will cause significant cognitive changes (see PCP)

### Psychiatric practice

Diagnoses made using the nationally accepted rating system: DSMIV: Diagnostic and Statistical Manual of the Social Sciences – Fourth revision

1. "Multi-axial:" Uses five "axes" to describe psychiatric and medical conditions, current level of functioning and stressors acting upon the individual
2. Means of quantifying conditions so that the relative severity can be easily described in a fashion that is transportable to anyone working with patients
3. Forces the attention to be focused to direct and help prioritize treatment
4. The axes:
  - a. Axis I:
    - 1.) usually the target of treatment
    - 2.) Major psychiatric conditions: e.g. schizophrenia, post traumatic stress disorder, major depression, bipolar disorder, schizoaffective disorder, alcohol and other drug dependence
  - b. Axis II:
    - 1.) Developmental disorders such as mental retardation
    - 2.) "Personality disorders" e.g. narcissistic, borderline, antisocial, histrionic personality disorder: "pattern of maladaptive coping mechanisms with typically life long duration
  - c. Axis III:
    - 1.) medical conditions

- 2.) May or may not have significant influence on psychiatric condition
- 3.) Examples: diabetes, hypertension (high blood pressure), cancer, hyperthyroid (raised thyroid), hypothyroid (low thyroid).
- d. Axis IV: stresses in individual's life e.g. incarceration, homelessness, unemployment, loss of a spouse
- e. Axis V: Current level of functioning – i.e. how the person is doing at this time.
5. Problems in dealing with psychiatric disorders
  - a. For many years viewed as character flaws, not legitimate medical/ chemical conditions
    - 1.) Common to “blame the victim:”
      - a.) Individuals with major depression told to “get over it”
      - b.) Parents of individuals with schizophrenia told the condition was due to being brought up by a controlling mother and a distant, aloof father
    - 2.) Individuals reluctant to admit they were unable to overcome the condition on their own, thus, not seeking/ receiving help and continuing at a marginal level
  - b. Historically:
    - 1.) Medieval times:
      - a.) some early “witches” likely schizophrenic
      - b.) exorcism used in attempt to drive out demons from individuals who hallucinated/ spoke to spirits
    - 2.) “Bedlam”: Bethlehem hospital in London: sold tickets to public to watch the behaviors of patients in locked areas
    - 3.) Public feared the severely psychiatrically ill because of concerns over violence and because individuals looked different
      - a.) studies in 50's and 60's showed very small percentage of all violent acts are committed by psychiatrically ill individuals
      - b.) Recent data show increasing incidence of violent acts committed by the mentally ill: trend appears to exactly parallel the trend toward deinstitutionalization. Thus, individuals who at one time would never have left hospitals are being placed in nursing homes unable to care for them, or back on the street.
  - c. Both medical and psychiatric treatments have changed the complexion of hospital psychiatry
    - 1.) 19<sup>th</sup> century: large numbers of individuals with hypothyroidism, hyperthyroidism, tertiary (neurosyphilis) lived and died in “insane asylums”
    - 2.) Penicillin almost eradicated neurosyphilis and need for hospitalization, until increase following onset of AIDs epidemic
    - 3.) Treatment of thyroid disease resulted in near eradication of hospitalization for these conditions
    - 4.) Now hospitalization common only for true psychiatric conditions
      - a.) Much data that majority of psychiatric conditions = chemical in origin
      - b.) Changes in brain chemistry result in changes in psychiatric functioning
6. Common Axis I disorders
  - a. Post traumatic stress disorder (PTSD)
    - 1.) Response to overwhelming trauma outside the realm of normal human experience
    - 2.) Onset: within one year of traumatic event
    - 3.) Examples: Physical abuse, sexual assault, war; could add World Trade Center
    - 4.) Characteristics: Anxiety, depression, “flashbacks” to traumatic event, reliving experience
    - 5.) Associated conditions: suicide, alcohol and other drug abuse

- 6.) Poses significant problem in treatment of alcohol and other drug use disorders: individual may experience increase in PTSD symptoms as gain sobriety, acts as relapse trigger
  - 7.) Females > males; appears due to increased incidence of sexual abuse among females
- b. Major depression
- 1.) Onset females: at puberty. Females > males until menopause, then females = males as a result of increasing incidence in men over the age of fifty
  - 2.) Characteristics: easy/ frequent tearfulness; fatigue, irritability out of proportion to events, lack of interest/ ability to enjoy anything, sleep disturbance, appetite disturbance
  - 3.) Associated conditions: suicide, alcohol and other drug abuse
  - 4.) Causes: not a personality flaw, appears to be chemical
    - a.) Can occur naturally or as a result of substance use (especially alcohol, cocaine)
    - b.) Hereditary predisposition: runs in families
    - c.) Not necessary to have a precipitating event, though there may be one
    - d.) Appears unable to make sufficient NE, epi or 5HT to permit normal functioning
  - 5.) Treated with either abstinence (if caused by substances) or with antidepressants
    - a.) Most antidepressants function to increase epi, NE, or serotonin either by supplying it externally, or by encouraging the body to make more of its own
    - b.) Examples: prozac, paxil, zoloft, norpramin, tofranil, amitriptyline
- c. Anxiety disorders:
- 1.) Examples: agoraphobia, social phobia, obsessive compulsive disorder, panic disorder
  - 2.) Various medications and psychotherapeutic approaches have been employed
  - 3.) Agoraphobia: fear of leaving one's home.
    - a.) Can be very debilitating
    - b.) Individuals become housebound, unable to seek help
    - c.) Panic occurs if forced to leave own comfort zone
    - d.) Difficult to treat, since individuals can't come to treatment
    - e.) Medications and psychotherapy helpful
  - 4.) Social phobia: fear of meeting new people, being in crowds, speaking in public
    - a.) generally not as debilitating, though in some careers can be quite limiting
    - b.) medications and psychotherapy help
  - 5.) obsessive compulsive disorder: (OCD)
    - a.) obsessions: thoughts that come into one's conscious awareness repeatedly and often distressingly
      - (1.) Common ones: belief in contamination, believing that one is "secretly" homosexual, belief that one has committed an unpardonable act
      - (2.) Individual may have some degree of awareness of the irrationality of the belief, but this seldom gives relief
    - b.) compulsions: acts one is "compelled" to perform because not doing so causes a great deal of anxiety and distress
      - (1.) May be in response to the obsession: e.g. — one repeatedly washes one's hands throughout the day in order to relieve the "contamination," one refuses to even look at individuals of the same sex for fear of acting in a way that might be interpreted as "homosexual"
      - (2.) Again, may or not be aware of the irrationality of the act
    - c.) Treatable with medication and very focused psychotherapy. Tends to relapse
    - d.) Onset in twenties is common
  - 6.) Panic disorder: can be quite debilitating

- a.) characterized by "panic attacks": these may occur with or without a "trigger" event"
  - (1.) very frightening to individual
  - (2.) sometimes interpreted as having a heart attack: frequently diagnosed in the emergency room
- b.) symptoms of panic attacks: heart racing, "palpitations," shortness of breath, feelings of impending doom, feeling like one is "going crazy," feeling that one is going to die, feeling that the "walls are closing in"
- c.) Often goes hand in hand with agoraphobia: if one stays in own comfort zone, maybe won't have panic attacks
- d.) Again, medication and psychotherapy very helpful.
- e.) Problem: withdrawal from substances can resemble panic attacks. Most popular meds to treat them are benzodiazepines (e.g. valium, xanax, librium) all of which are addictive, and withdrawal from them can induce panic attacks (more on this later)
- d. "Thought disorders:" conditions characterized by bizarre or idiosyncratic thinking, inability to "think straight," disconnected or disjoint thinking
  - 1) Examples: schizophrenia, schizoaffective disorders
  - 2) Symptoms: hallucinations (especially auditory, though may be visual); delusions (false beliefs – common ones include thinking one is God or that one has special powers such as ESP), paranoia, loosening of association, flight of ideas. Individual may be incomprehensible
  - 3) Symptoms can occur naturally or may be response to alcohol/ other drug use
    - a.) Paranoia: alcohol, cocaine, amphetamine
    - b.) Hallucinations: alcohol withdrawal, LSD, PCP, mushrooms, +/- marijuana
    - c.) Delusions: alcohol, cocaine
  - 4) Schizophrenia
    - a.) 1% of population
    - b.) Strongly hereditary
    - c.) Onset: late teens, male; early twenties, female
    - d.) Prognosis improving with new meds
    - e.) Increase risk of 1) alcohol and other drug use; 2) suicide); 3) homelessness, 4) poverty
    - f.) Likely requiring life long medication with antipsychotics. No evidence that psychotherapy will adequately treat the condition
      - 1.) Antipsychotics in general decrease DA in various parts of brain
      - 2.) e.g. – haldol, clozaril, risperdal, zyprexa, geodon
- e. Bipolar disorder ("manic depression")
  - 1) Characterized by episodes of extreme highs and severe downs: a "high" (mania) doesn't necessarily follow a "low" (depression). May have several episodes of one or the other in a row.
  - 2) Condition can have catastrophic effect on individual and/or family members
  - 3) Individual may or may not be "psychotic"
  - 4) During highs:
    - a.) individual may engage in very risky behaviors: e.g. – promiscuity, wild spending, increased drinking/ drugging.
    - b.) May be in danger of harming self due to belief in self as having special powers or capabilities
    - c.) Has increased energy and decreased or absent need for sleep
  - 5) During lows, may be extremely depressed, has increased risk of suicide

- 6) Must be treated with medication – often lifelong. No evidence that psychotherapy will adequately treat the condition
    - a.) May require an antidepressant or antipsychotic, depending upon the phase of the illness
    - b.) Responds to “mood stabilizers,” meds that keep the highs from being too high, the lows from being too low
      - (1.) Examples: depakote, lithium, tegretol
      - (2.) Meds have side effects that individuals often find difficult to accept (see below)
      - (3.) Problem: individuals may perceive manic episodes as “fun” and dislike meds. In addition, meds themselves may causing cognitive “dulling”
  - 7) Associated with increased risk of alcohol and other drug use, especially cocaine, which may mimic the “high” of mania.
  - f. Post partum depression
    - 1.) Increased risk in women with h/o major depression and bipolar illness
    - 2.) Onset within four weeks of delivery
    - 3.) Characteristics
      - a.) All typical characteristics of depression
      - b.) With or without psychotic features
      - c.) One episode associated with 50% risk of episodes with subsequent pregnancies
      - d.) May have delusional thoughts re: infant; terror at being alone with
    - 4.) Dangers
      - a.) Especially increased risk to infant if mother delusional
      - b.) Physical harm/ death of infant
6. Common Axis II disorders
- a. Narcissistic personality disorder
    - 1.) Characteristics pervasive need for attention, exploits others for own needs, inflated sense of self importance, grandiose, easily angered when admiration he feels he is due is not given, believes he is superior to others
      - a.) This is the person who insists that only the boss take care of him
      - b.) Tends to devalue others
      - c.) Self esteem very fragile
      - d.) Strong sense of entitlement, angered to a rage if doesn't receive what they feel they are due
      - e.) Insensitive to others
    - 2.) Individuals with traits of this may be quite successful. As with other personality disorders, full blown narcissists fail to achieve what is predicted
    - 3.) Much higher incidence in males than females
  - b. Antisocial personality disorder
    - 1.) Pervasive disregard for, and violation of, others' rights
    - 2.) Characteristics
      - a.) Has onset in childhood or adolescence
      - b.) Also called psychopath, sociopath
      - c.) May be repeated law breakers
      - d.) Often deceitful, manipulative liars
    - 3.) Common in prison populations
    - 4.) High association with substance abuse
    - 5.) 3% of male population; 1% of female population
    - 6.) May improve after forty (behaviors not as pronounced)
  - c. Dependent personality disorder

- 1.) Excessive need to be taken care of leading to submissiveness, clinginess, fear of separation
- 2.) Characteristics
  - a.) Great difficulty making even simple decisions
  - b.) Let others make all their decisions for them
  - c.) Can't express disagreement out of fear of separation
  - d.) Have trouble initiating projects due to fear of disapproval
  - e.) May take on particularly difficult or onerous tasks in order to avoid receiving disapproval
- 3.) May have a higher incidence in females than males, data equivocal
- d. Borderline personality disorder
  - 1.) Pervasive difficulty with relationships, with modulating affect, and with self image
  - 2.) Characteristics
    - a.) Excessive response to minor events
    - b.) "Splitting," i.e. turning individuals on each other
    - c.) Over idealizing of individuals with rage response when perceived needs not met by the individual
    - d.) Often self mutilate: act often provides temporary relief of anger/ depression/ rage
  - 3.) Increased suicide risk, especially in the younger ones
  - 4.) Diagnosed primarily in females
  - 5.) May improve after middle age

### Psychopharmacology

1. Problem: oldest of "psychoactive pharmaceuticals" is only fifty years old.
  - a. Long term data lacking regarding effects of these powerful agents on the brain
  - b. How medications are used has changed
    - 1.) fifteen years ago: six months of antidepressants and then off
    - 2.) Studies over last ten years show high rate of relapse with this approach
  - c. Drugs themselves may be changing the profile/ course of the illnesses they treat
    - 1.) Bipolar disorder: increase in "rapid cycling" type
    - 2.) Schizophrenia: increasingly more difficult to treat with each episode of psychosis
2. Antidepressants
  - a. In general, increase levels of NE, epi, serotonin
  - b. Tricyclic antidepressants
    - 1.) Earliest of antidepressants: around since the 1950's
    - 2.) Examples: imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), nortriptyline (Pamelor)
    - 3.) Less often used now for depression; may be used to treat anxiety, help with pain management
    - 4.) Benefits
      - a.) Long history so more known about outcome
      - b.) Generic = cheap
      - c.) Effective up to 75% of the time
      - d.) Non addictive
      - e.) Appear safe in pregnancy
    - 5.) Drawbacks:
      - a.) Lethal in overdose and in combination with alcohol
      - b.) May be quite sedating
      - c.) Cardiac effects can be dangerous
      - d.) Side effects: dry mouth, constipation, blurred vision, impotence/ erectile dysfunction, delayed orgasm

- e.) May take several weeks to show effects
- c. MAO inhibitors
  - 1.) Known since
  - 2.) Examples: parnate, nardil
  - 3.) Benefits
    - a.) More effective in refractory depression
    - b.) Generic = cheap
    - c.) Non addictive
    - d.) Helpful with anxiety
  - 4.) Drawbacks
    - a.) Dietary restrictions substantial: red wine, powerful cheeses
    - b.) Medication restrictions: combination may be lethal (Libby Zion)
    - c.) Interactions with alcohol/ other drugs of abuse dangerous
    - d.) Lethal in overdose
    - e.) May take several weeks to work
- d. Selective serotonin reuptake inhibitors (SSRIs)
  - 1.) First one, prozac, marketed in mid'80's
  - 2.) Examples: prozac (fluoxetine), zoloft (sertraline), paxil (paroxetine), cylexa (
  - 3.) Benefits
    - a.) Effective up to 75% of the time
    - b.) Some improvement may be seen within a couple of weeks
    - c.) Appear safe in pregnancy
    - d.) Non addictive
    - e.) No lethal overdoses have been reported
    - f.) Little problem with concomitant alcohol/ other drugs
  - 4.) Drawbacks
    - a.) Only prozac is generic, i.e. quite expensive
    - b.) Common complaint of "numbing" effect
    - c.) Sexual unresponsiveness/ anorgasmia very common
    - d.) Only paxil seems to really help with anxiety, but paxil may be quite sedating
- 3. Antipsychotics
  - a. Traditional:
    - 1.) thiorazine (chlorpromazine), prolixin (fluphenazine), navane (thiothixene), haldol (haloperidol), mellaril (thioridazine)
    - 2.) In use since the 1950's, so much known about longer term consequences of use
    - 3.) Reduced need for long term hospitalization
    - 4.) Benefits
      - a.) Generic = cheap
      - b.) Non addictive
      - c.) Effective up to 65% of the time
      - d.) Two of this group available in "depot" form, i.e., they can be given intramuscularly for slow release: very helpful in individuals prone to stopping meds and becoming violent
    - 5.) Drawbacks:
      - a.) Side effects very uncomfortable, may be disfiguring, may be permanent
        - (1.) "Akathisia," a need to be in constant motion, can't relax, feels "jittery inside." Treatable with medication.
        - (2.) "Dystonia," severe contraction of muscles, usually of face/neck. Person may be pulled sideways, drools because muscles of mouth are pulled back, may find it difficult to breathe. Treatable with medication
        - (3.) "Tardive dyskinesia," disfiguring movements of mouth, tongue. Permanent.

- b.) Can be very sedating
- c.) Patients find that they are not able to think as well
  - (1.) studies support this belief on the patients' part
  - (2.) Very high incidence of cigarette smoking among individuals with schizophrenia and those on antipsychotics. Nicotine decreases effectiveness of traditional antipsychotics, but also improves individual's ability to think.
- b.) Non traditional
  - 1. Examples: clozaril (clozapine), risperdal (risperidone), zyprexa (olanzapine), seroquel (), geodon (ziprasidone)
  - 2. First and best = clozaril
    - a.) Effective for nearly half of refractory cases
    - b.) Interesting side effect: decreases appetite for nicotine and alcohol
    - c.) Problem: weekly blood tests required or drug not dispensed; thus in patients prone to dropping out of treatment or coming late/ days late, will be off the meds
  - 3.) Others:
    - a.) Side effects
      - (1.) much less uncomfortable.
      - (2.) zyprexa is associated with appearance of diabetes in individuals of even normal weight
      - (3.) Weight gain a big problem with clozaril and zyprexa; less with others
    - b.) Individuals find improved ability to think
    - c.) Safer with combo of alcohol and other drugs
    - d.) None quite as effective as clozaril, but no blood test required
    - e.) No "depot" forms available
- 4. "Mood stabilizers"
  - a. Purpose: as noted above, to "smooth out" the highs and the lows
  - b. Examples: depakote (valproic acid), tegretol (carbamazepine), lithium (lithium)
  - c. Depakote
    - 1.) Original purpose: as a seizure medication
    - 2.) Tends to work more quickly than others to smooth out mood swings
    - 3.) Best agent for treatment of rapid cycling bipolar disorder (which is more common in women)
    - 4.) Problems:
      - a.) Side effects: hair loss, weight gain, can cause trouble with the liver and pancreas
      - b.) Must monitor blood levels about twice a year
      - c.) Can cause profound sedation or death in overdosage; comas have occurred
  - d. Lithium:
    - 1.) First mood stabilizer discovered - accidentally observed in lab rats to decrease aggressive behavior
    - 2.) Works well in about 75% of population
    - 3.) Problems:
      - a.) Side effects: weight gain, sedation, acne
      - b.) Must monitor blood levels
      - c.) Causes thyroid problems in a substantial number of people
      - d.) Fatal in overdose due to kidney failure
  - e. Tegretol
    - 1.) Also originally used as a seizure medication
    - 2.) Not as predictably useful as lithium and depakote
    - 3.) Problems:

- a.) Monitoring of blood levels necessary
- b.) Side effects can include severe anemia that has resulted in death
- c.) Fatal in overdose

#### 5. Anti-anxiety agents

- a. Earliest: barbiturates
  - 1.) Examples: phenobarbital, butalbital, nembutal
  - 2.) Significant problems
    - a.) Therapeutic dose and lethal dose rather close
    - b.) High mortality in overdose
    - c.) Fatal in combination with other sedatives e.g. alcohol
    - d.) Addictive
- b. More recent: benzodiazepines
  - 1.) Examples: xanax, valium, librium, ativan, klonopin
  - 2.) Benefits:
    - a.) tend to work quickly and well to relieve anxiety
    - b.) Safe when used by selves (hard to overdose just on a benzo)
  - 3.) Problems
    - a.) Can be lethal in combination with other sedatives
    - b.) Addictive
    - c.) Individuals with h/o addictive disorders have high likelihood of abusing these agents if given access to them

#### Substance Use and Abuse

1. What makes a substance desirable?
  - a. Drugs abused by humans increase DA in "limbic areas" of brain, especially Nucl Acum
  - b. Limbic = most primitive part of brain necessary for the most basic needs for survival i.e. seeking of food, shelter, water, mating
  - c. Animals that work primarily on a very instinctual level e.g. snakes have almost no brain beyond this very primitive, basic level brain
  - d. Animal studies: lesions in some areas of brain but not others result in decreased drug seeking behavior
  - d. Except for marijuana, animals will use and abuse most of the substances abused by man.
2. Determinants of abuse potential
  - a. How quickly something works and how quickly something wears off:
    - 1.) The speed of onset of action is determined by how easily the substance gets to the target organ. In the case of many medications and all drugs of abuse, the target organ is the brain
    - 2.) Nerve/ brain tissue is largely composed of fats, or "lipids." Substances that are "lipophilic" i.e. "lipid loving" get into the lipids easily, and will thus be able to act in the brain more quickly
    - 3.) How quickly something works is also partly determined by how one uses it – i.e., by mouth, snorting, intravenous injection (IV), smoking.
      - a.) Oral: slowest: has to be absorbed through lining of mouth, esophagus, stomach, intestines before acting. This doesn't mean not effective, just slower. Example: smoking marijuana results in more rapid onset of action and higher dose of THC than baking it in brownies. The latter will work, just doesn't result as quickly or as strongly
      - b.) Snorting: faster than above, but slower than smoking. Has to be absorbed through lining of nose before making its way to brain

c.) Smoking: extremely rapid: smoke goes into lungs which have a huge area for absorption, absorbed very quickly, since lining of lungs is made specifically for rapidly taking in gases (usually oxygen), quickly and in a huge dose goes to brain almost instantly

d.) IV: quite rapid: inject → immediately into bloodstream → absorption quickly throughout body and in large amounts → quickly to brain, almost instantly

Example: if one has a headache and takes an aspirin for it, the headache will gradually, over time, decrease in severity. Thus, one notices the effect only gradually and not dramatically. If one has an anxiety attack and takes a drug that stops the attack within minutes one realizes that the drug must have made the discomfort go away. If the drug wears off fairly quickly and the attack resumes, one will want to take the drug immediately

b. Desirability of result

- 1.) If one takes in a substance and feels the onset of a pleasurable sensation, one is more likely to be willing to take that substance again
- 2.) If the result of taking in a substance results in the quick onset of a negative sensation, one will not wish to use it again. For example, ipecac is a drug used to induce vomiting. It is a medication that families are advised to keep handy in the case of accidental poisoning from taking in any of a large variety of household poisons. It is taken in and results in almost instantaneous vomiting. Obviously it is not a drug that many people will crave

c. Where the substance works in the brain and on what brain chemical (see below)

3. Substances of abuse

a. Alcohol

- 1.) A "dirty" drug: multi-site effects, but very important effect at increasing GABA activity
- 2.) Alcohol usually increases GABA (i.e. – sedates the brain), thus is a sedative or downer
- 3.) Initial response to alcohol is one of increased energy because it lowers the individual's inhibitions. This is why people talk more, dance more, etc early in an episode of alcohol use
- 4.) With time, progressive sedation occurs. Can result in death because "sedates" or reduces the individual's breathing
- 5.) Decrease in alcohol results in a decrease in GABA, which results in sudden increase in brain activity. This increase is reason alcohol withdrawal results in shakiness, increased heart rate, flushing, and possible seizures

b. Cocaine (and other stimulants such as methamphetamine)

- 1.) Other examples: ritalin, CAT, benzedrine
- 2.) Stimulants "stimulate" or increase activity in the nervous system
- 3.) Blocks breakdown of catecholamines both in the central nervous system (CNS) and in the peripheral nervous system (PNS)
- 4.) Increase NE, Epi, and DA
  - a.) Positive: increase activity/ energy, euphoria
  - b.) Negative: psychosis due to too much DA and stroke because increase NE and epi → increase heart rate and blood pressure

c. Cannabis (marijuana, hashish, etc)

- 1.) Active ingredient: tetrahydrocannabinol (THC)
- 2.) Very "dirty" drug – i.e. – multiple effects because THC actually includes a large number of other substances than the most common one (Delta 9, THC)

- 3.) Interacts with special receptors in brain that also bind opiates results in analgesia, vomiting
- 4.) Listed as a hallucinogen, but primary effect is of euphoria and an altered time sense, usually without hallucinations

d. Opiates

- 1.) Examples: heroin, morphine, oxycontin, methadone
- 2.) Opiate receptors in CNS: pre-eminent is Mu
- 3.) Potent DA effect, resulting in euphoria, pain relief
- 4.) Other receptor stimulation results in the sedation of opiate use

e. PCP

- 1.) Appears to work on glutamate
- 2.) Action to increase glutamate results in usefulness of PCP for pain relief (original purpose)
- 3.) Action also accounts for why those who have abused PCP appear to have problems learning/ retaining new information

f. Inhalants

- 1.) Examples
  - a.) Solvents: paint thinners, dry cleaning fluids, gasoline, glue
  - b.) Gases: butane, propane, whipping cream aerosols, fabric protectors
  - c.) Nitrites: amyl nitrite, butyl nitrite
- 2.) Effect
  - a.) Minutes to hours
  - b.) initial slight stimulation followed by loss of control
  - c.) May lose consciousness
- 3.) Problems
  - a.) hearing loss
  - b.) peripheral nerve damage
  - c.) brain damage (especially toluene as found in paint spray, glue)
  - d.) damage to blood producing cells (especially with gasoline)
  - e.) liver and kidney damage

i. "Club drugs"

- 1.) Meaning: drugs used in raves and "trance" events
- 2.) Examples: GHB, "Ecstasy," ketamine
  - a.) MDMA (ecstasy)
    - (1.) similar to stimulants and to hallucinogens
    - (2.) usually taken as a pill, though sometimes inject or snort
    - (3.) appears to cause long term damage to various areas of brain
  - b.) GHB (gamma hydroxybutyrate)
    - (1.) Causes euphoria
    - (2.) Has been used in body building
    - (3.) Addiction similar to alcohol
    - (4.) Withdrawal similar to alcohol including seizures
    - (5.) Possible to overdose
  - c.) Ketamine (Special K, Vitamin K)
    - (1.) can cause hallucinations
    - (2.) can cause high blood pressure, shut down of respiration

4. Commonly abused prescription drugs

a. Narcotic analgesics:

- 1.) Examples: demerol, vicodin, oxycontin, tylenol #3 and #4, talwin, dilaudid, percocet, lortabs
- 2.) Onset often quite innocent

- 3.) Cause tolerance
- 4.) Withdrawal the same regardless of agent, except in terms of timing of onset and length of syndrome
- b. Benzodiazepines
  - 1.) Examples: ativan, valium, librium, xanax
  - 2.) Sedating, relieve anxiety
  - 3.) Cause tolerance/ habit forming
  - 4.) Withdrawal may be severe including seizures and coma if untreated
- c. Weight loss drugs:
  - 1.) Examples: Adapex, Ionamin, Desoxyn
  - 2.) Action: all = stimulants, cause elevation of mood, initial appetite suppression.
  - 3.) Problems: withdrawal may result in life threatening depression, appetite effect is transient
- d. Breathing medications
  - 1.) Examples: ventolin, primatene
  - 2.) Action: stimulant
  - 3.) Problems: as with all stimulants: hypertension, seizure, etc.

#### Detoxification

1. Alcohol
  - a. Withdrawal:
    - 1.) Symptoms: increased heart rate and blood pressure, slight increase in body temperature, tremors, shakes, +/- seizures
    - 2.) "DTs" very significant condition
      - a.) 10 - 15% mortality
      - b.) Not all withdrawal from alcohol is "DTs"
  - b. In mild cases can be done as out patient
  - c. In patient or outpatient, withdrawal usually done now with benzodiazepines
    - 1.) Onset of symptoms: 24 - 72 hours after decrease in blood alcohol level
    - 2.) Complete resolution in 5 - 7 days
    - 3.) Peak around 72 - 96 hours
    - 4.) Example scheme for withdrawal
2. Cocaine
  - a. Withdrawal:
    - 1.) Not physiologically significant
    - 2.) May be associated with life threatening depression
      - a.) if latter occurs, hospitalization necessary
      - b.) Usually resolves without treatment in about 3 days
  - b. Many treatment providers give nothing
  - c. Something for agitation, disturbed sleep may be helpful (examples)
3. Opiates
  - a. Withdrawal
    - 1.) Not life threatening in an otherwise healthy individual, but very uncomfortable
    - 2.) Onset: depends upon "half life" of specific drug. For heroin, within about 6 - 8 hours
    - 3.) Symptoms: nausea, vomiting, diarrhea, runny nose, runny eyes, gooseflesh, muscle spasms, bone aching
  - b. Can usually be accomplished out patient
  - c. Some withdrawal schemes
4. Marijuana
  - a. Not physiologically significant

- b. May be quite lengthy abstinence syndrome
- c. Symptoms: irritability, sleep disturbance, attention problems
- d. No medications really indicated, though may help with something for sleep
- 5. Benzodiazepines
  - a. Withdrawal
    - 1.) symptoms: very similar to that of alcohol, but add "derealization," tunnel vision. Also can be fatal if seizures occur
    - 2.) Onset and length of time depend upon "half life" of agent.
      - a.) Short acting drug such as Xanax, start within four hours after last dose; over in about a week
      - b.) Long acting such as klonopin, onset 2 – 3 days, lasting a couple of weeks
  - b. Detoxification schemes
    - 1.) In patient can be accomplished with almost any drug in 5 – 7 days, but the individual will not be highly functional
    - 2.) Out patient will take quite a while, but individual can keep functioning
    - 3.) Detox with same drug as using. For example, individual on xanax.
      - a.) Give one week of usual dose
      - b.) Every seven days, decrease total dose by 25%, in divided doses
    - 4.) Detox by changing to long acting drug
      - a.) Use conversion table; change patient over to equivalent dose of klonopin
      - b.) Give klonopin in two doses per day
      - c.) Decrease total daily dose by 25% per week
      - d.) Patients often less comfortable and compliant with this approach

Treatment of substance misuse: A brief introduction to methadone maintenance

#### 1. History

- a. Invented by Nazis as long acting pain killer
- b. Dole and Nyswander: opiate addict different, "self-medicating"
  - 1.) Believed if replaced whatever was missing, individual would do better/ stop using
  - 2.) Original purpose never to completely stop opiate, since believed it was replacing something necessary

#### 2. Purpose of treatment

- a. Complete abstinence vs. adequate functioning
- b. Prognosis of opiate addiction
- c. Goals of methadone maintenance
  - 1.) Improved health
  - 2.) Decreased criminal activity
  - 3.) Improved ability to work, support family

#### 3. Success of methadone

- a. Single most successful approach to opiate dependence
- b. Longer on methadone is associated with decreased incidence of HIV, Hep B and C
- c. John Ball, M.D., Head, Division of Addictions, Mt. Sinai Hospital, New York City: "judging the success rate of methadone maintenance by the number of people who relapse when they stop it makes no more sense than judging the effectiveness of birth control pills by the number of women who become pregnant when they stop it."

#### 4. How long?

### Substances of abuse and psychiatric conditions:

#### 1. Schizophrenia

- a. Alcohol: general depression of cognition this just like rest of population problem: already have problems with thought, alcohol worsens this
  - b. Cocaine:
    - 1.) transient improvement of negative symptoms/ improved cognition/
    - 2.) worsening of positive symptoms
    - 3.) stimulants in general do this. Nicotine also briefly improves ability to think/ perform on specific tasks. Response is only transient, however.
    - 4.) Worsening of positive symptoms means increases paranoia, delusions, hallucinations
  - c. Marijuana: variable according to dose
    - 1.) Low dose: no real data to say a small amount of THC worsens the condition. Problem: what's a "low dose" and how does one keep the "dose" of THC low?
    - 2.) High dose: worsens ability to think, may result in increased hallucinations
  - d. Opiates: ?Not a lot of data regarding opiate use among individuals with schizophrenia
2. Major depression:
- a. Alcohol: transient improvement in symptoms
  - b. Cocaine: increased risk of self injurious behavior
  - c. Opiates: transient improvement in symptoms
  - d. Marijuana: variable/ dose dependent
3. Post Traumatic Stress Disorder (PTSD)
- a. Alcohol: transient improvement in symptoms likely due to sedative effect  
alcohol interferes with sleep patterns, worsens depressive symptoms over time, thus worsening symptoms of PTSD
  - b. Cocaine: increased risk of self injurious behavior
  - c. Opiates: transient improvement in symptoms
  - d. Marijuana: variable/ dose dependent
4. Substance Use and Bipolar Disorder
- a. Alcohol: worsening of cognition, lessened effect of medication
  - b. Cocaine: transient mood improvement, worsening of aggression
  - c. Opiates: ?
  - d. Marijuana: low dose (?); high dose worsen paranoia

#### Alcohol effects on medications:

1. Antidepressants:(e.g. tricyclics, SSRIs)
  - a. Increase sedative action of tricyclics (interaction can be fatal)
  - b. SSRIs: little risk - reduces efficacy
  - c. Anti-anxiety agents (e.g. buspar, benzodiazepines such as valium, librium,serax, xanax)
    - 1.) Benzos: Combination can be fatal
    - 2.) Withdrawal from alcohol can mimic panic reaction
    - 3.) Buspar: interaction - negligible effect
2. Mood stabilizers (e.g.lithium, depakote, tegretol)
  - a. Lithium: danger with dehydration
  - b. Depakote: liver toxicity issues
  - c. Tegretol: bone marrow suppression
3. Anti-psychotics (e.g. haldol, prolixin, clozaril, risperdal, zyprexa)
  - a. Clozaril: Bone marrow/ blood issues
    - 1.) Sedative effect
    - 2.) May have beneficial effect on craving
  - b. Haldol/prolixin/risperdal/ zyprexa:
    - 1.) Little danger of interaction effect
    - 2.) Reduce blood level due to competition for metabolism

**Cocaine effects on medications:**

1. Antidepressants:
  - a. TCA's: increase risk of cardiac dysrhythmias
  - b. SSRIs: minimal risk
2. Anti-anxiety agents:
  - a. Post cocaine tension/ anxiety unchanged
  - b. Typical agents less helpful
3. Mood stabilizers:
  - a. Ineffective in countering "high" induced by cocaine
4. Anti-psychotics:
  - a. More antipsychotic necessary due to competition and worsening of psychosis