Examples

- Studies show that at least 70% of patients with a mental illness also have a substance abuse disorder. aka:
  - Co-occurring
  - Co-morbid
  - Concurrent
  - Coexisting

Term “dual diagnosis” is a misnomer
Examples

**Schizophrenia**
- 47% of patients with schizophrenia have an alcohol or drug disorder
- CNS depressants such as alcohol & benzodiazepines have a sedating effect and decrease the intensity and volume of auditory hallucinations
- Psychostimulants such as cocaine and methamphetamine increase hallucinations and increase the likelihood of violent behavior & suicide

**Bipolar Disorders**
- Bipolar: 61% of patients with BPAD have an alcohol or drug disorder
- Alcohol, amphetamines and cocaine are most widely used, depending upon the current mood.
  - In a manic episode, cocaine or amphetamines can be deadly
  - When depressed, alcohol will increase the depression and increase suicidality
Examples

- **Depressive Disorders:**
  - In 30-60% of patients with depressive symptoms, alcohol is the cause
  - 76% of patients in detox exhibit moderate to severe depression
  - By 28 days of abstinence, the % has dropped to 8%

Examples

- **NEJM Journal Watch:**
  - 10 yr study of 500 heavy alcohol drinkers identified as heavy drinking at least 16 days per month
  - 74% men, mean age 37.6
  - Mental health questionnaires done every 2 years
  - **Conclusion:** alcohol consumption is strongly influenced by mental illness

  • NEJM Journal Watch March 19, 2015
Accurate Assessment is Key

- Substance use **causes** psychiatric symptoms and **mimic** psychiatric disorders
  - Stimulants cause signs and symptoms similar to mania, panic, delirium and delusional disorders
  - Hallucinogens cause symptoms similar to psychotic disorders such as Schizophrenia

Accurate Assessment

- Substance abuse can **induce** the development, **trigger** the re-emergence, or **exacerbate** the severity of psychiatric disorders:
  - Alcohol has been associated with first breaks of Schizophrenia
  - Stimulants have been associated with the precipitation of a Bipolar disorder
Accurate Assessment

- Substance abuse can **mask** psychiatric symptoms and disorders:
  - Patients **self-medicate** distressing psychiatric symptoms or to relieve uncomfortable side effects of medications
    - Alcohol and drugs counteract negative symptoms of Schizophrenia such as apathy & social withdrawal
    - Stimulants may counteract sexual side effects of psychotropics

Pharmacotherapy

- Starts in the brain
Key Concepts

- Dependence
- Addiction
- Rebound
- Relapse

Dependence

- Physiological state of *neuroadaptation* produced by repeated administration of a drug

- Necessitates continued administration and increasing doses to prevent withdrawal known as *tolerance*
Addiction

- A *behavioral* pattern of drug abuse characterized by:
  - Overwhelming compulsive use
  - Alteration in brain functioning
  - Activation of the Pleasure pathway

*Addiction is about avoiding relentless and unremitting despair*

Rebound & Relapse

- **Rebound**
  - Occurs after discontinuation of a drug
  - Similar to original symptom drug is used to treat, but more frequent and severe than the original

- **Relapse**
  - Reoccurrence of disease symptoms upon discontinuation of an effective medical treatment
  - Can be in relapse without using
The Chemical Brain

1899 –a Spanish neuroscientist drew this remarkable diagram of a pigeon brain:
The Chemical Brain

- For decades the concept of the brain and central nervous system was of electrical communication, resembling a telephone system with trillions of miles of intricately crisscrossing wires
  - This implied that the brain was “hard wired” from birth and stayed that way forever
  - The 1990’s were called the Decade of the Brain, and research found how incorrect this concept really was

The Chemical Brain

- Communication between the brain and central nervous system is fluid, malleable and ever changing.
- Each “wire”, is called a neuron, and consists of a cell body, an axon resembling a tail, and dendrites, which look like the branches of a tree.
- The space between these branches is called the synaptic gap, or cleft
- Receptors: the sites of drug action
For a chemical to work in the body, something must “receive” it.

Called receptors, they are the binding sites, or ports, for all chemicals.

Formerly thought of as a “lock to a key”.
Receptors

- A typical neuron has millions of receptors on its surface
- They function as scanners
- Waiting for the right chemical to swim by and bind with it
- Receptors are in constant, rhythmic motion as they respond to chemical cues
Receptors

- Binding occurs in one of three ways:
  - Full agonists – occupy the receptor and activate the receptor 100%
  - Partial agonists – occupy the receptor, but activate only to a set point (40–60%) or ceiling
  - Antagonists – occupy the receptor and blocks both full & partial agonists but do not activate

- Key concept: Once created, receptors are never reabsorbed, but remain dormant when not in use – they light up like a Christmas tree with one beer, one pill, one cigarette
Chemical Brain

- **Neurotransmitters** are the “ferry boats” that cross the synaptic gap
  - They are chemical messengers which either excite or inhibit the receiving cell

Neurotransmitters

- **Neurotransmitters** help determine if the cell will send a message down its axons to the cells with which it communicates.
Neurotransmitters

- Initially thought to be several dozen
- Now thought to be several hundreds to several thousands

Neurotransmitters

- Classic neurotransmitters include:
  - Serotonin
  - Norepinephrine
  - Dopamine
  - GABA (gamma-aminobutyric acid)
  - Glutamic acid
  - Acetylcholine
Neurotransmitters

- Serotonin (5-HT)
  - The feel good neurotransmitter. It helps control the regulation of mood, appetite, sleep, temperature, sexual arousal and the sensation of pain.
Neurotransmitters

- Norepinephrine (NE)
  - Primarily involved in control of alertness including the ‘fight or flight’ response and wakefulness.
  - Also called noradrenalin
Neurotransmitters

- **Dopamine (DA)**
  - This transmitter is involved in movement, attention, learning and pleasure
  - It is the primary chemical in the “Pleasure Pathway”.

Dopamine “Pleasure” Pathway

- High levels of dopamine in the brain produces:
  - agitation and irritability
  - aggressiveness, paranoia
  - hallucinations and bizarre thoughts & behavior similar to schizophrenia
  - activates a feedback loop, which **desensitizes pleasure** and the cravings start anew
  - Dopaminergic functioning can now be seen on PET scan (single-photon emission computed tomography)
Monoamine Hypothesis (The Big Bang Theory)

- Formulated in the 1960's
- Postulates that symptoms of depression were caused by the underactivity of the amines: serotonin, norepinephrine and dopamine
- Symptoms were relieved in only one third of the patients treated, leading to the development of the glutamate theory

Glutamatergic System

GABA
Glutamate
Acetylcholine
Neurotransmitters

- **GABA**
  - Involved in regulation of anxiety, sleep, seizure activity and muscle relaxation.
  - are the primary binding sites for Benzodiazepines, Barbiturates and Alcohol.
  - Major **Inhibitory** chemical

![GABA Receptor Complex]

**Glutamic acid** (**NMDA**)  
- Plays essential role in memory & learning.
- Has opposing effects from GABA
- Major **excitatory** chemical
Neurotransmitters

- Acetylcholine (ACh)
  - Both inhibitory and excitatory effects on smooth muscles
    - Decreased heart rate
    - Relaxes eye muscles
    - Slows GI tract
    - Neurotransmitter associated with Alzheimer's and myasthenia gravis

- Endocannabinoids
  - CB receptors
    - Involved in anxiety, memory, appetite, sensory, motor behavior
  - Deficiency linked with:
    - Andedonia
    - Impaired cognition
    - Inability to process emotions
Neurotransmitters

- **Orexin**
  - Plays a key role in wakefulness
  - Antagonists effective in treating insomnia

Peptides

- **Oxytocin (OT)**
  - Responsible for the attachment between mother (or primary caregiver) and infant
    - Mother’s OT regulates infant for several months
    - Impaired caregiving negatively influences OT with life-long consequences such as **anxiety** and **depression**
    - May play role in disorders linked with poor social interaction such as **autism** and **schizophrenia**
Opioid Peptides

- Primary peptides:
  - Beta Endorphins: the body’s naturally occurring opiates
  - Dynorphin
  - Met-enkephalin
  - Leu-enkephalin
  - Kyotophin

Pathophysiology

- **Alcohol**
  - Opens the floodgates and initially releases Serotonin, Endorphins and Dopamine, then
  - Glutamate (excites, causing euphoria) then
  - GABA (inhibits, causes sedation)
Benzodiazepines

- Benzodiazepines
  - Receptor binding site located on the same protein molecule as GABA
  - Thought to be how GABA modulates anxiety, and prevents seizures

Benzodiazepine abuse

- No class of anti-anxiety (anxiolytic) medication has demonstrated the:
  - potent broad spectrum activity
  - rapid onset of action
  - abuse potential of benzodiazepines.
Psychostimulants

- Cocaine prevents dopamine reuptake extending the firing of the postsynaptic neurons
- Experienced as increased energy, mental alertness and sexual arousal

Psychostimulants

- Methylenedioxymethamphetamine (MDMA, Ecstasy, Molly)

MDMA releases all stored Serotonin at once:
- flooding the synapse
- overwhelming the receptors
- disabling the body’s ability to control temperature
- can result in death
Psychostimulants

- Methamphetamine (MA) has a similar effect as cocaine, plus
  - rapid heart rate, elevated blood pressure and body temperature, dilated pupils and irreversible damage to blood vessels in the brain (stroke)
  - Psychosis is a common long term complication.
Psychostimulants

- **Tetrahydrocannabinol (THC, Cannabis, Marijuana)**
  - Binds to specialized cannabinoid receptors that control memory, concentration time, depth perception and coordination of movement

Hallucinogens

- **Lysergic acid**
- **PCP**
- **Ketamine**
- **Anabolic Steroids**
Hallucinogens

- **Lysergic acid (LSD)**
  
  Binds to *serotonin* receptors causing rapid mood swings, delusions and visual hallucinations.

Hallucinogens

- **PCP (Angel Dust)**
  
  - Interferes with functioning of *glutamate* and causes release of *dopamine*.
  
  - Mimics schizophrenia with delusions and mental turmoil.
Hallucinogens

- **Ketamine** (Special K)
  - interferes with functioning of **Glutamate** and causes release of **Dopamine**
  - used as a general anesthetic in humans and animals.
  - creates a dream like state, hallucinations, delirium and potentially fatal respiratory depression

Hallucinogens

- Researchers at the National Institute of Mental Health are studying the effects of **Ketamine**:
  - To determine if blocking the **Glutamate** neurotransmitter, which accounts for approximately 60% of the brain's neuron's, will provide a "jump start" in the treatment of depression.
  - 71% of patients responded to IV Ketamine within 24 hours, comparable to response rates of up to 8 weeks with conventional antidepressants.
  - *Current Psychiatry, 2007*
Hallucinogens

Recent Ketamine studies indicate:
- Psychotropic side effects are of major concern
  - Hallucinations
  - Paranoia
  - Dissociation
  - Abuse potential


Hallucinogens

- **GHB** (Gamma-hydroxybutyrate)
  - Acts as an inhibiting neurotransmitter similar to GABA
  - GHB intoxication resembles alcohol or a sedative-hypnotic intoxication, such as a benzodiazepine
  - Known as the date rape drug
Anabolic Steroids

- Synthetic variations of the male sex hormone testosterone
- Known as Gear, Juice, Roids and Stackers
- Clinically used to treat delayed puberty and illnesses that cause muscle loss. Ex: cancer, AIDS
- Illicit use to increase strength in sports and body building

- Applied as cream, gel or patch in various ways:
- Cycling – stopping and restarting
- Stacking – combining two or more types
- Pyramiding – slowly increasing dose, reaching a peak, then tapering off

Anabolic Steroids

- Short-Term Effects
  - Paranoid (unreasonable) jealousy
  - Extreme irritability
  - Delusions – false beliefs or ideas
  - Impaired judgment
  - Extreme mood swings called “roid rage” that may lead to violence
Anabolic steroids

■ Long-Term Effects
  – Kidney impairment or failure
  – Liver damage
  – Enlarged heart, high blood pressure
  – Shrunken testicles
  – Baldness
  – Breast development
  – Increased risk of prostate cancer

Psychotropics

■ Classification of Drugs
“It’s better to be lucky than smart.”

Stephen M. Stahl, MD, PhD

Antidepressants

- First antidepressant was discovered serendipitously during the treatment of tuberculosis in the 1950’s
  - Iproniazid, a non-selective, irreversible monoamine-oxidase inhibitor was noted to make some patients “inappropriately” happy (possibly manic).
  - withdrawn in 1961 related to the high incidence of hepatitis
  - less hepatotoxic MAOI’s were developed as the first class of antidepressants
Antidepressants

Monoamine Oxidase Inhibitors (MAOI’s)
- Parnate (tranylcypromine)
- Nardil (phenelzine)
- EMSAM (selegiline)
  - Transdermal patch

- Side effects:
  - drug interactions
  - weight gain
  - hypertensive crisis

Antidepressants

Tricyclic Antidepressants (TCA’s): increase serotonin, norepinephrine and dopamine, thought to be a safer class of medications than MAOI’s

- Imipramine (tofranil)
- Amitryptyline (elavil)
- Desipramine (norpramin)
- Nortriptyline (pamelor)
- Clomipramine (anafranil)
- Doxepin (sinequan)
Side effects

- Symptoms include:
  - Dry mouth
  - Constipation
  - Sedation
  - Sexual dysfunction
  - Hypotension
  - Weight gain
  - Cardiac arrhythmias
    - Can be fatal in OD

Serotonin Reuptake Inhibitors
SSRI’s

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Paxil (paroxetine)
- Luvox (fluvoxamine)
- Celexa (citalopram)
- Lexapro (escitalopram)
- Viibryd (vilazodone)
Viibryd

- In addition to blocking **serotonin** reuptake:
  - Has a moderate effect on **dopamine** and **norepinephrine** reuptake blocking
  - Increased benefit for those with both depression and anxiety, DSM-5 refers to as “**anxious distress**.”

Side effects

- Sexual dysfunction
- Gastrointestinal upset
- Sleep problems
- Emotional numbing
- Discontinuation syndrome
- Serotonin Syndrome
  - “**SHIVERS**”
Serotonin Syndrome – “Shivers”

- Shivering
- Hyper reflexes & sudden jerking of muscles
- Increased temperature
- Vital sign instability – elevated heart rate and respirations, labile BP
- Encephalopathy - agitation, confusion, delirium
- Restlessness and in coordination
- Sweating – an autonomic response to excessive serotonin stimulation

Serotonin and Norepinephrine Reuptake Inhibitors -NSRI’s

- Effexor (venlafaxine)
- Pristique (desvenlafaxine)
- Cymbalta (duloxetine)
- Fetzima (levomilnacipran)
Fetzima

- Reuptake of **Norepinephrine** is more potent than of serotonin
- Increased benefit on pain
- Increased benefit on cognitive functioning:
  - Concentration
  - Motivation
  - Social functioning

Side effects

- Sexual dysfunction
- Gastrointestinal upset
- Sleep problems
- Headaches
- High blood pressure
- Rare liver failure
Atypical Antidepressants

- Desyrel (trazodone)
- Wellbutrin (bupropion)
- Serzone (nefazodone)
- Remeron (mirtazapine)
- Trintellix (vortioxetine) – formerly called Brintellix

Side effects

- Trazodone: sedation, dry mouth, priapism
- Wellbutrin: agitation, insomnia, seizures, abuse potential, weight loss
- Serzone: GI upset, liver failure
- Remeron: sedation, weight gain
- Trintellix: GI upset
Trintellix

- Serotonin stimulator rather than a reuptake inhibitor
- Increased benefit for depressed patients with cognitive deficits:
  - Slowed thoughts processes
  - Memory impairment
  - Especially the elderly

Key Points

- Antidepressants are effective specifically for unipolar depression
- Antidepressants may trigger a manic episode in bipolar depression
Mood Stabilizers

FDA approved:
- Lithium
- Depakote (valproate)
- Tegretol (carbamazepine)
- Lamictal (lamotrigine)

Non FDA approved:
- Trileptal (oxcarbazepine)
- Topamax (topiramate)
- Neurontin (gabapentin)
- Lyrica (pregabalin)

Side effects

- Lithium (LiCO3): weight gain, sedation, tremor, polydipsia, polyuria, hypothyroidism, renal insufficiency, cardiac block, seizure
  - mechanism of action unknown – alters neuronal transport of sodium

  - recent study of 6,671 patients showed patients taking Lithium have lower rates of self-harm and unintentional injury compared to patients taking other mood stabilizers
  - *JAMA Psychiatry online, May 11, 2006*
Side Effects

- **Tegretol**: GI upset, ataxia, decreased white blood cells, Stevens-Johnson rash (potentially fatal)
  - mechanism of action: unknown
- **Depakote**: GI upset, weight gain, hair loss, sedation, liver abnormalities, acute pancreatitis, decreased platelets necessary for blood clotting
  - mechanism of action unknown: thought to increase GABA and inhibit Glutamate
- **Lamictal**: headache, tremor, dizziness, serious skin rash, Stevens-Johnson syndrome
  - mechanism of action: inhibits sodium channels and decreases presynaptic glutamate

Side effects

- **Trileptal**: sedation, hyponatremia
  - Mechanism of action: alters sodium channels
- **Topamax**: weight loss, cognitive impairment, kidney stones
  - Mechanism of action: augments GABA, antagonizes glutamate receptors
Side Effects

- **Neurontin**: sedation, ataxia, dizziness, urinary incontinence during sleep
  - Abuse potential ("jonnies")
  - Suicidal behavior
  - Mechanism of action: modulates excitatory neurotransmitter release

Novel Anticonvulsants

- **Felbatol** (carbamate):
  - aplastic anemia risk
- **Gabitril** (tiagabine):
  - not effective anticonvulsant or mood stabilizer
  - potential benefit on anxiety
  - mechanism of action: inhibits GABA reuptake
- **Keppra** (levetiracetam):
  - well-tolerated.
  - potential as a mood stabilizer
  - mechanism of action: unknown
**Novel Anticonvulsants**

- **Lyrica** (pregabalin): now approved for Fibromyalgia, most common widespread pain condition in US.
  - life-threatening swelling of face, mouth and neck (angioedema)
  - potential for abuse
  - mechanism of action: reduces neurotransmitter release

- **Zonegran** (zonisamide):
  - renal stones
  - weight loss
  - mechanism of action: stabilizes neuronal membranes, blocks sodium and calcium channels

**Anticonvulsants – common SE’s as a class**

- Sedation
- Headache
- Blurred vision
- Anorexia or
- Weight gain
- Nausea

- Rash (SJS)

- Blood dyscrasias
  - Aplastic anemia (body stops making blood cells)
  - Decreased white blood cells
  - Elevated serum creatinine and blood urea nitrogen
Key Points

- **Lithium** is the only psychotropic
  - proven to prevent suicide and prolong life
  - the only mood stabilizer not an anticonvulsant

- **Neurontin** appears to have benefit as an anti-anxiety drug
  - not effective in the treatment of acute mania
  - suicides have been reported
  - abuse potential and deaths reported when used with other drugs

Neuroleptics – Antipsychotics Traditional

- Classified as to strength of blockade at the dopamine receptors
  - Thorazine (low)
  - Mellaril (low)
  - Trilafon (mid)
  - Stellazine (mid)
  - Haldol (high)
  - Prolixin (high)

- Formulations:
  - by mouth
  - immediate release injection
  - decanoate (long acting) injection
Side Effects as a class

- **Parkinsonian extrapyramidal symptoms** (EPS): rigidity, tremor, involuntary muscle contractions (dopamine blockade)
- **Anticholinergic** symptoms: dry mouth, constipation, weight gain (acetylcholine blockade)
- **Cognitive Impairment**
- **Tardive Dyskinesia** (TD) – learn AIMS (Abnormal Involuntary Movement Scale)
- **Neuroleptic Malignant Syndrome** (NMS) - “Fever”

Side Effects as a class

- **Akathisia** – Greek for “inability to sit”
  - Feeling of unease
  - Inner restlessness
  - Compulsive need to move
  - Repetitive movements primarily of the legs
  - Linked with suicidal ideation and behavior
  - Difficult to assess as symptoms overlap with mania, psychosis, depression with anxious distress and ADHD
  - Too often akathisia is missed and the medication causing it is increased rather than decreased or discontinued
Neuroleptic Malignant Syndrome (NMS) “Fever”

- Fever – hyperthermia is considered the hallmark of NMS and predicts poor prognosis
- Encephalopathy – abrupt and unexpected confusion and disorientation
- Vital sign instability
- Enzyme elevation – extreme creatinine phosphokinase (CPK) increases caused by rhabdomyolysis
- Rigidity – generalized muscle rigidity described as “lead-pipe”

Neuroleptics Atypicals

- Clozaril (clozapine)
- Seroquel (quetiapine)
- Zyprexa (olanzapine)
- Risperdal (risperidone)
- Geodon (ziprasidone)
- Abilify (aripiprazole)
- Latuda (lurasidone)
- Vraylar (cariprazine)
- Rexulti (brexpiprazole)

Benefits:
- Less akathisia (inner restlessness)
- Less EPS (movement disorder)
- Less Tardive Dyskinesia (irreversible movement disorder)

Class Side Effect:
- Metabolic dysregulation (elevated glucose)
- Dyslipidemia (elevated lipids such as cholesterol)
Side Effects - Atypicals

- **Clozaril:**
  - seizures
  - life threatening decrease in white blood cells
  - myocarditis (inflammation of the heart muscle)

- **Zyprexa:**
  - elevated lipids
  - type 2 diabetes
  - weight gain
  - available tabs, IM, dissolving tabs (Zydis) and in combination with Prozac (Symbyax)

Atypical Antipsychotics

- **Risperdal:**
  - prolactin elevation / gynecomastia in males
  - movement disorders
  - available in tabs, IM (Consta), extended release (Invega)

- **Seroquel:**
  - QT prolongation (heart arrhythmia) in OD
  - elevated lipids
  - weight gain
Atypical Antipsychotics

Third generation atypicals:

- **Geodon:**
  - QT prolongation (fatal cardiac arrhythmia)
  - movement disorders

- **Abilify:**
  - akathisia (which presents as worsening psychosis)
  - recent reports of TD
  - impulse control problems with compulsive gambling, shopping, eating and sexual activities

  - *Medscape Medical News, May 3, 2016*

Atypical Antipsychotics

- **Latuda**
  - Sedation
  - Pregnancy category B (the only category B)

- **Vraylar**
  - Major metabolites accumulate over time
  - Monitor for side effects after several week exposure
  - Low weight gain

- **Rexulti**
  - Monitor for thoughts of suicide and / or increasing depression
  - Incidence of akathisia 9.4% vs 21.2% on Abilify

  - *International Clinical Psychopharmacology, March 9, 2016*
Key Points

- All antipsychotics are effective in controlling psychotic symptoms caused by an excess of dopamine
- All antipsychotics can cause movement disorders by blocking dopamine
- The Atypicals:
  - treat acute mania without any worsening of depression
  - may also have antidepressant effects
    • Abilify approved to augment antidepressants
    • Seroquel and Latuda approved for bipolar depression

Key Points

- Antipsychotics are more effective and better tolerated than the mood stabilizers
- Most effective of these are: risperidone, olanzapine and haldol
- Provide rapid control of acute mania
- Appropriate for adjunct use with mood stabilizers
- Do not use an antidepressant. Consider addition lamotrigine
- Do not forget benefits of ECT (electroconvulsant therapy)
Novel Medications

- **Strattera** (amoxetine) – classified as a SNRI
  - used to treat ADHD/ADD.
  - major side effects: high blood pressure and elevated liver enzymes
  - mechanism of action: inhibits norepinephrine reuptake

- **Provigil** (modafinil) – classified as an anti-narcoleptic
  - used to treat daytime sedation of narcolepsy, obstructive sleep apnea and shift work sleep disturbance
  - non-addictive
  - major side effects: headache, anxiety
  - mechanism of action: inhibits dopamine reuptake

Sleep Medications (New)

- **Ambien** (zolpidem)
  - major side effects: depression, suicidal ideation, aggression, sleep-related behavior (e.g., driving, eating), prolonged impairment
  - mechanism of action: Benzo receptor agonist

- **Lunesta** (eszopiclone)
  - major side effects: same
  - mechanism of action: Benzo receptor agonist

- **Rozerem** (ramelton)
  - major side effects: same but including hallucinations and behavioral disturbances
  - mechanism of action: melatonin receptor agonist
Sleep Medications (New)

- **Sonata** (zaleplon)
  - major side effects: same with amnesia and withdrawal symptoms if abruptly discontinued after prolonged use
  - mechanism of action: Benzo receptor agonist

- **Belsoma** (suvorexant) – 1st in class
  - major side effects: same as above with addition of abnormal dreams, sleep paralysis, hypnogogic hallucinations, and cataplexy symptoms (sudden muscle weakness with full conscious awareness)
  - mechanism of action: suppresses wakefulness as an orexin antagonist

Sleep Medications (Traditional)

- **Benadryl** (diphenhydramine)
  - Advil PM
  - Aleve PM
  - Tylenol PM

- **Vistaril** (hydroxyzine)

- **Melatonin** (hormone which helps regulate sleep and wake cycles)

- **Amitriptyline**
- **Benzodiazepines**
- **Doxepin**
- **Remeron**
- **Seroquel**
- **Thorazine**
- **Trazodone**
Medication Assisted Therapy

- **Naltrexone** - an **opioid antagonist**
  - appears to reduce or eliminate the pleasure associated with alcohol consumption by blocking opiate receptors
  - major side effects: abdominal pain, cramps, nausea, vomiting and an elevation in liver enzymes
  - used for both alcohol and opiate dependency
  - contraindicated with moderate to severe liver impairment

- **Vivitrol** (IM Naltrexone) – monthly injection
  - major side effects: nausea, headache & fatigue
  - significantly less elevation in liver enzymes
  - contraindicated for acute hepatitis or liver failure
  - used for both alcohol and opiate dependency
  - studies showed improved treatment compliance with monthly injection versus daily pill
Medication Assisted Therapy

- **Campral** (acamprosate)
  - approved for the treatment of alcohol abuse
  - mechanism of action obscure.
  - thought to restore balance between **Glutamate** (excitation) and **GABA** (inhibition).
  - hoped to decrease cue-related drinking behavior
  - side effects: nausea, diarrhea

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Medication Assisted Therapy

**Methadone** (dolophine)

- full agonist at the opiate receptor
- designer opiate
- equal potency and duration to morphine
- harm reduction when taken by mouth
- when abused by taking IV, the liver is by-passed, the blood brain barrier is quickly crossed, and a rapid euphoria, or rush, results
Medication Assisted Therapy

- excess Methadone is stored in the liver and time released over 24 hours
- 70 mg daily is considered the blockade dose, preventing withdrawal
- Brain scans since 2000 confirm long-term damage and dysregulation in essential physiological systems

Medication Assisted Therapy

- Methadone
  - Dysregulation in:
    - Response to stress and pain
    - Gastrointestinal function
    - Immune function
    - Neuroendocrine function
    - Endorphins are displaced and cannot carry out their normal role as the body's natural opiates
- Methadone myths include:
  - gets in your bones and "never comes out"
  - harder to kick than Heroin
  - just a substitute for Heroin
Medication Assisted Therapy

- Despite the limitations of Methadone it is the treatment of choice by CSAC for opiate dependent pregnant women:
  - harm reduction
  - close monitoring of pregnancy with daily clinic visits and consultations with obstetrician
  - less stress on the fetus: decreased premature deliveries, safer withdrawal, less time hospitalized

Medication Assisted Therapy

- Buprenorphine (Suboxone / Subutex)
  - a designer opiate
  - acts as a partial agonist at the mu receptor and as an antagonist at the kappa receptor
  - binds to and kicks off any other opiate on the receptor for up to 72 hours
  - prevents other opiates from activating the receptors
  - has a ceiling, or set point, producing a 40-60% effect compared to the 100% effect of Heroin, Oxycontin, Demerol, Morphine, Fentanyl
  - can be abused but euphoria is less
Medication Assisted Therapy

- **Buprenorphine (Suboxone / Subutex)**
  - Suboxone (Buprenorphine / Naloxone) was designed to prevent injection because of the added effect of naloxone
  - Subutex can be injected
  - may not be strong enough for high end Heroin abusers
  - both are being sold on the streets to buy Heroin
  - use for pain management is increasing as a safer alternative to opiates such as Oxycontin

- **Samidorphan**
  - Code name ALKS-33
  - Similar efficacy of Naltrexone but with reduced side effects

Stimulants

- **Amphetamines**: 1887
- Charles Bradley treated ADHD kids with Benzedrine
- **Methylphenidate (Ritalin)**: 1944
  - Marketed for geriatric fatigue and depression
  - Dopamine –norepinephrine reuptake inhibitor
- **Amphetamine Mixed Salts (Adderall)**: 1960
  - Method of action differs from Ritalin
  - Acts as both a presynaptic releasing agent of dopamine and norepinephrine and reuptake inhibitor
Stimulants

- Cylert: 1975
- Modafanil (Provigil): 1998 for narcolepsy
  - Effects last 8-10 hours
  - Abused for hangovers
- Dexmethylphenidate (Focalin): 2001
- Lisdexamfetamine (Vyvanse): 2007
  - Prodrug: inactive drug until metabolized within the body. Less abuse potential

Side Effects

- Most common:
  - Insomnia: 50%+
  - Loss of appetite: 50%+
  - Headaches: 20-40%
  - Nervous habits (tics): <10%
  - Irritability, tearfulness: <10%
  - Psychosis: <3%

Note: Exercise works just as well!
Questions

References

- Bell, S. et al. (2015). Heavy Drinking and Mental Health Problems: Which Comes First. Alcohol Clinical Research (e-pub)
References

- Epocrates Rx: Athenahealth Pub

References