Dual Diagnosis Treatment Services
at
Stanley Street Treatment and Resources

Understanding Psychopharmacology

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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

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Examples

- **Schizophrenia**
  - 47% of patients with Schizophrenia have an alcohol or drug disorder
  - Alcohol & benzodiazepines have a sedating effect and decrease the intensity and volume of auditory hallucinations
  - Cocaine and Methamphetamine (MA) increase hallucinations and increase the likelihood of violent behavior & suicide

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Examples

- **Bipolar Disorders (BPAD)**
  - 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

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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 number has dropped to 8%

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Accurate Assessment is Key

- Substance use both **causes** psychiatric symptoms and **mimic** psychiatric disorders
  - Stimulants (Adderall / Cocaine / Methamphetamine) cause signs and symptoms similar to mania, panic, delirium and delusional disorders
  - Hallucinogens (LSD / Salvia / Psilocybin) cause symptoms similar to psychotic disorders such as Schizophrenia

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Accurate Assessment

- Substance abuse can **induce** the development, **trigger** a 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

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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 antidepressants / antipsychotics

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Pharmacotherapy

- Starts in the brain

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Key Concepts

- Dependence
- Addiction
- Relapse

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Dependence

- Physiological state of ***neuroadaptation*** produced by repeated administration of a drug
- Necessitates continued administration and increasing doses to prevent withdrawal known as ***tolerance***

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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

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Relapse

- **Relapse**
  - Reoccurrence of disease symptoms upon discontinuation of an effective medical treatment
  - Can be in relapse without using:
    - "**Dry Drunk Syndrome**" – includes behaviors and attitudes of the person that have not (yet) changed: dishonesty, isolation, depression, anxiety, poor impulse control and glamorizing alcohol or drug use

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The Chemical Brain

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

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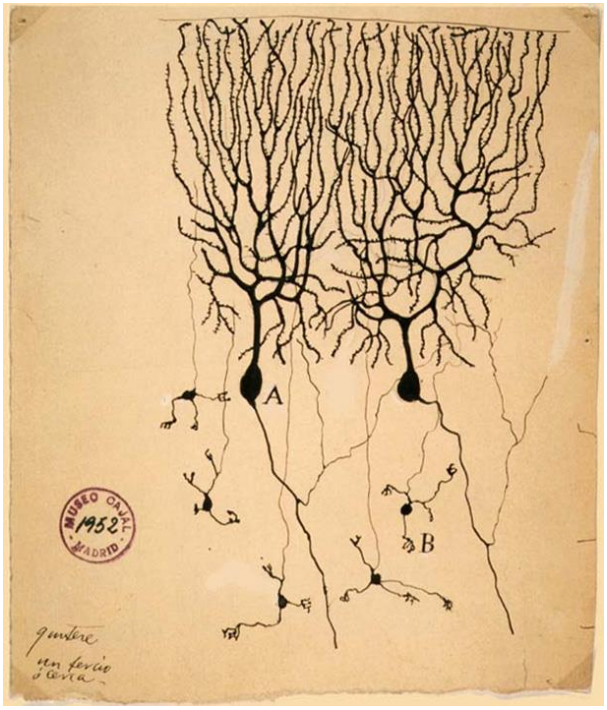

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The Chemical Brain

- 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

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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

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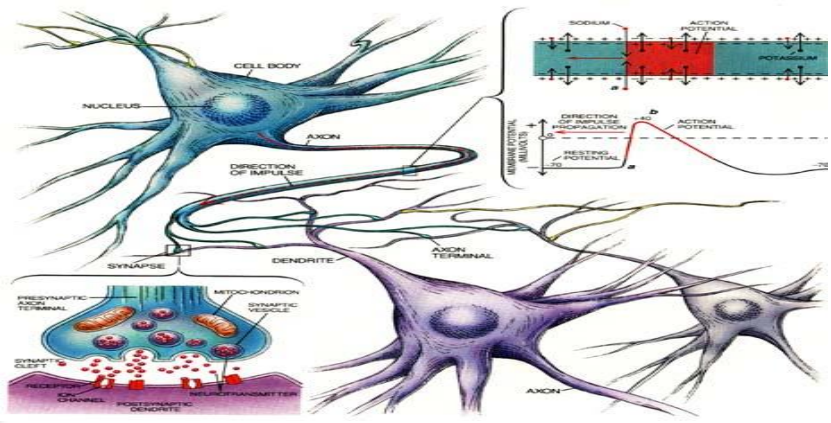
NEURONS



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Receptors

- 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”

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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

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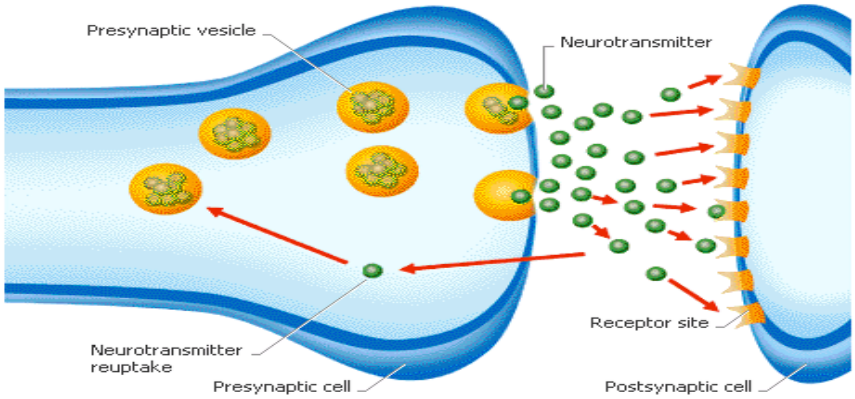

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Receptors

- 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

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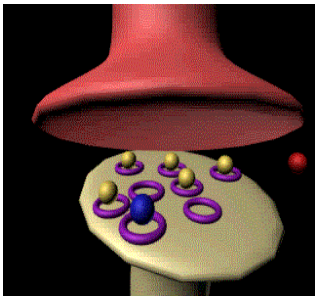
Chemical Brain



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

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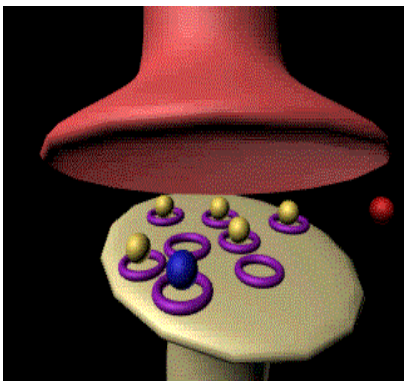
Neurotransmitters



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

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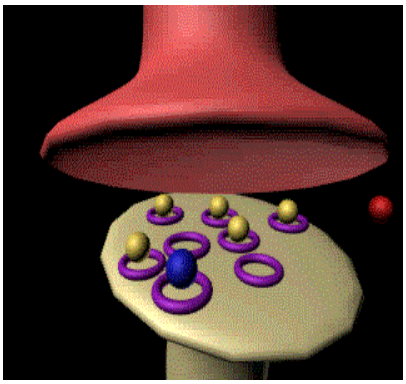
Neurotransmitters



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

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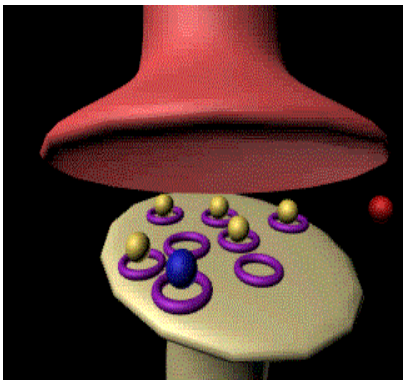
Neurotransmitters



- Classic neurotransmitters include:
  - Serotonin
  - Norepinephrine
  - Dopamine
  - GABA (gamma-amino-butyric acid
  - Glutamic acid
  - Acetylcholine

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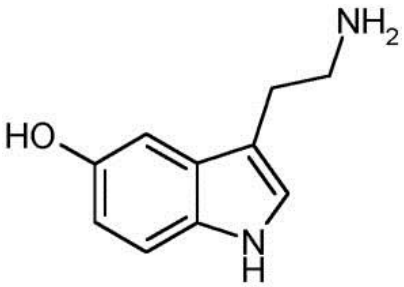
Neurotransmitters



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

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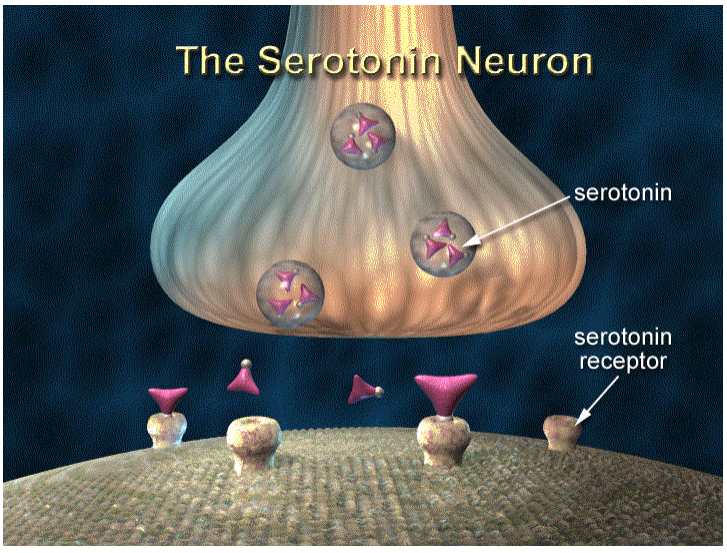

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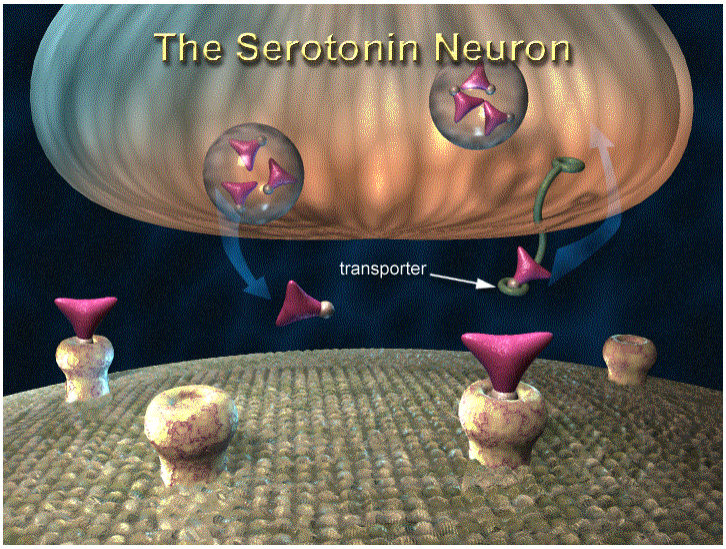

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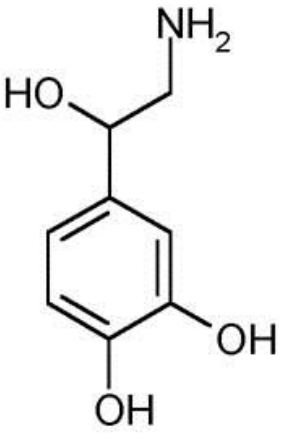
Neurotransmitters



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

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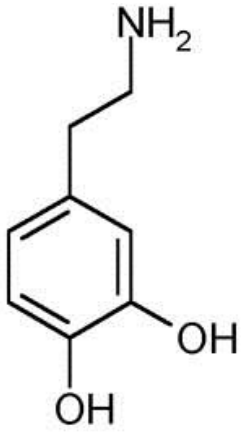
Neurotransmitters

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



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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)

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Monoamine Hypothesis (The Big Bang Theory)

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

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Glutamatergic System

GABA

Glutamate

Acetycholine

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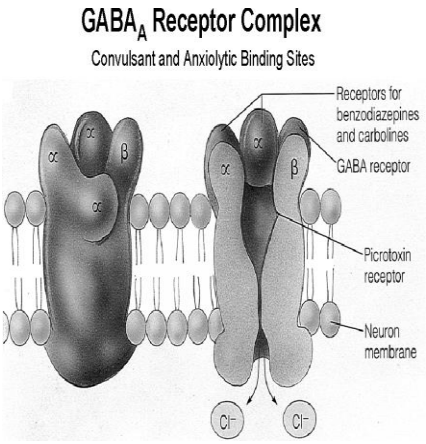
Neurotransmitters

- 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



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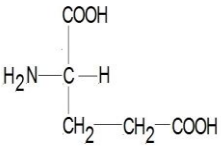
Neurotransmitters

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



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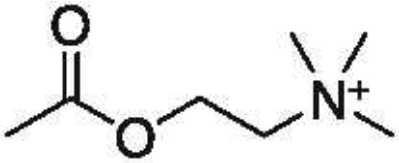
Neurotransmitters

- Acetycholine (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



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Neurotransmitters

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

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Neurotransmitters

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

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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**

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Opioid Peptides

- Primary peptides:
  - Beta **Endorphins**: the body's naturally occurring opiates. Example: Vivitrol blocks the receptors preventing endorphins from working.
  - Others include:
    - Dynorphin
    - Met-enkephalin
    - Leu-enkephalin
    - Kyotophin

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Pathophysiology

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

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Benzodiazepines

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

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Benzodiazepine abuse

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

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Psychostimulants

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

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Psychostimulants

- Methylenedioxymeth-amphetamine (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

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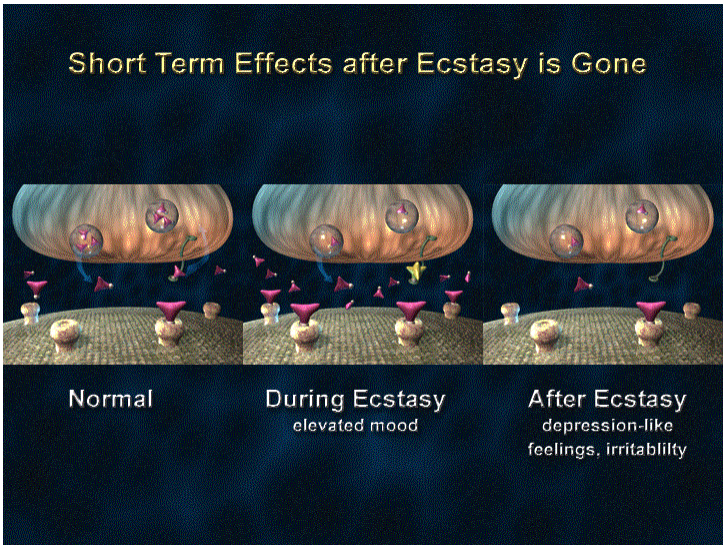

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Psychostimulants

- 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.

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Psychostimulants

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

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Hallucinogens

Hallucinogens:

- Lysergic acid
- PCP
- Ketamine
- Anabolic Steroids

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Hallucinogens

- **Lysergic acid (LSD)**

  Binds to **Serotonin** receptors causing rapid mood swings, delusions and visual hallucinations

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Hallucinogens

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

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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

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Hallucinogens

Ketamine – appears to 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.
- Effects are short-lived, lasting 1-2 weeks after a single dose
- Repeated infusions carry significant risk:
  - Hallucinations, paranoia, dissociation called "trippy" side effects which can last up to 60 minutes
  - Significant abuse potential

CNS Spectrum, December 2017

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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
  - Active ingredient in **oxybate,** approved for cataplexy and narcolepsy

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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

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Anabolic Steroids

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

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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

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Psychotropics

- Classification of Drugs

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Psychopharmacology

"It's better to be lucky than smart."

Stephen M. Stahl, MD, PhD

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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). First MAOI.
  - withdrawn in 1961 related to the high incidence of hepatitis
  - less hepatotoxic MAOI's were developed as the first class of antidepressants

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Antidepressants

Monoamine Oxidase Inhibitors (MAOI's)

- Parnate (tranylcypromine)
- Nardil (phenelzine)
- EMSAM (selegiline)
  - Transdermal patch

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

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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)

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Side effects

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

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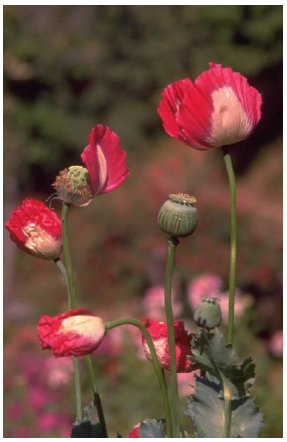
Serotonin Reuptake Inhibitors
SSRI's



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

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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**."

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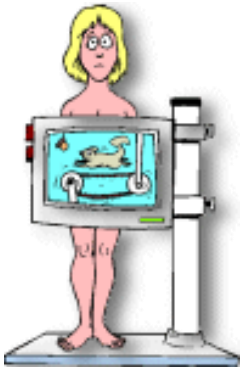
Side effects

- Sexual dysfunction
- Gastrointestinal upset
- Sleep problems
- Emotional numbing
- Discontinuation syndrome
- Serotonin Syndrome
  - "SHIVERS"



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Serotonin Syndrome – "Shivers"

- **S**hivering
- **H**yper reflexes & sudden jerking of muscles
- **I**ncreased temperature
- **V**ital sign instability – elevated heart rate and respirations, labile BP
- **E**ncephalopathy - agitation, confusion, delirium
- **R**estlessness and in coordination
- **S**weating – an autonomic response to excessive serotonin stimulation

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Serotonin and Norepinephrine Reuptake Inhibitors -NSRI's

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

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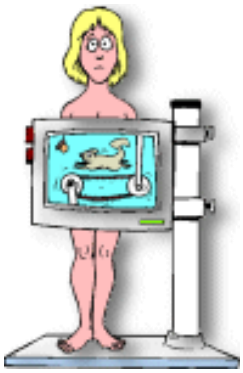
Side effects

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



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Atypical Antidepressants

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

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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

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Trintellix

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

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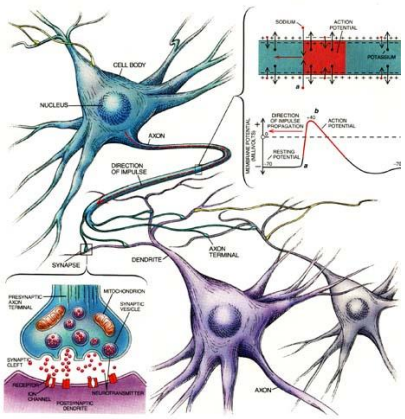
Key Points

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



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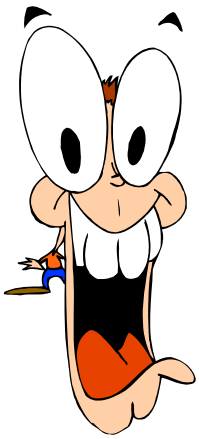
Mood Stabilizers



FDA approved:

- Lithium
- Depakote (valproate)
- Tegretol (carbamazepine)
- Lamictal (lamotrigine)

Non FDA approved:

- Trileptal (oxcarbazepine)
- Topamax (topiramate)
- Neurontin (gabapentin)
- Lyrica (pregabalin)

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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, 2016*

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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

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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

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Side Effects

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

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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 but may trigger mania in some
  - mechanism of action: unknown

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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

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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

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Key Points

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

- **Neurontin (Gabapentin)** 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

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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

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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”

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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

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Neuroleptic Malignant Syndrome (NMS) "Fever"

- **F**ever – hyperthermia is considered the hallmark of NMS and predicts poor prognosis
- **E**ncephalopathy – abrupt and unexpected confusion and disorientation
- **V**ital sign instability
- **E**nzyme elevation – extreme creatinine phosphokinase (CPK) increases caused by rhabdomyolysis
- **R**igidity – generalized muscle rigidity described as "lead-pipe"

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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)

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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**)

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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

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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
  - Available in IM (**Maintena**)
    - *Medscape Medical News, May 3, 2016*

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Atypical Antipsychotics

- **Latuda**
  - Sedation
  - Former 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*

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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

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Key Points

- Antipsychotics are more effective and better tolerated that 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**

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ECT (electroconvulsive therapy)

Evidence is growing to support ECT as first line treatment in:

- Unipolar depression
- Bipolar depression
- Mania
- Catatonia
- Acute psychosis

- It is not barbaric, does not cause brain damage or permanent memory loss
- It will not change one's personality
- It is not a permanent cure

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Other neuromodulations

- Transcranial magnetic stimulation (**TMS**)
- Vagus nerve stimulation (**VNS**)
- Deep brain stimulation (**DBS**)

- **TMS** has made the greatest strides with
  - >1000 centers nationally
  - 7 TMS devices FDA cleared for treating depression
    - *Current Psychiatry, March 2019*

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Botulinum Toxin

- Potent neurotoxic protein
  - Researchers exploring role as adjunctive treatment of depression (first proposed by Charles Darwin in 1872)
  - Based on facial feedback hypothesis: changes in facial expression can influence affect / emotions
  - Manipulation of human facial expression with an expression associated with a particular emotion
  - Also being used to treat facial nerve disorders, GI spasms, chronic pain, headaches and symptoms of ALS (amyotrophic lateral sclerosis)

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Novel Medications

- **Strattera** (amoxetine) – classified as a SNRI
  - used to treat ADHD/ADD.
  - major side effectives: 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

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Sleep Medications (New)

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

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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

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Sleep Medications (Traditional)

- **Benadryl** (diphendyramine)
  - Advil PM
  - Aleve PM
  - Tylenol PM
- Vistaril (hydroxyzine)
- Melatonin (hormone which helps regulate sleep and wake cycles)
- Amitriptyline
- Benzodiazepines
- Doxepin
- Remeron
- Seroquel
- Thorazine
- Trazodone

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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 mod –severe liver impairment

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Medication Assisted Therapy

- **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

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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

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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

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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

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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

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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

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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
- Sublocade
  - IM Suboxone – given monthly
  - Much less abuse potential

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N-acetylcysteine (NAC)

- OTC (over the counter) antioxidant
  - Long been used to treatment APAP (Tylenol) OD
- Under consideration for polysubstance abuse, especially:
  - Cannabis, Cocaine, Methamphetamine and Alcohol
- Removes excess glutamate from the brain
- Side effects are mild and infrequent
  - Nausea, vomiting, diarrhea, sleepiness

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Stimulants

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

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Stimulants

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

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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!

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Pharmacogenomics

- **Genetic testing** to find the optimal treatment for individual patients based upon concept that genes play an important role in drug response
- Practice points:
  - Claims by testing companies may not be supported by evidence
  - Confusion as to how to best use the information
  - FDA recommends that treatment decisions be based on the information provided in the drug labeling
  - Use as a valuable resource
    - *Current Psychiatry, April 2019*

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Questions

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