The Ninja's Guide to PRITE

2022 Study Guide

Loma Linda Department of Psychiatry

15th Edition

WHO WE ARE

Welcome to the fifteenth edition of the Ninja's Guide to PRITE! Loma Linda University Medical Center is located in sunny Southern California about 60 miles east of Los Angeles. A part of the Adventist Health System, we provide patient care in one of the largest non-profit health systems in the nation. Loma Linda's mission is to excel in medical education, global healthcare, and community outreach, all under a central tenant: "To Make Man Whole." At the Loma Linda Department of Psychiatry, our residents are trained in many diverse patient care settings. As an official World Health Organization Collaboration Center, our department funds resident electives in Global Mental Health at locations around the world. Additionally, our residents can participate in national and international disaster relief on the LLU Behavioral Health Trauma Team. We were proud to welcome our first group of Child and Adolescent Psychiatry fellows in the Summer of 2019 and work collaboratively with 3 other residency programs within the region. Our residency didactic education is constantly evolving based upon resident feedback, and our residents have the opportunity to aid in course development. More than anything, our residency fosters an environment where residents and faculty treat each other like family. Our faculty are dedicated to resident education and professional development. We believe in "taking 'No' off the table", encouraging innovative change, and passionately supporting our residents to achieve anything they set their minds to. For over a decade our residents have volunteered their time to create The Ninja's Guide to PRITE at our Annual Ninja PRITE Workshop. We are excited to present this 15th edition with new content contributed directly by our residents.

Dr. Melissa Pereau, Associate Residency Training Director

Created The Ninja's Guide to PRITE in 2007 on her kitchen table, when residents converted 6 years of PRITE exams to a Q&A format. She spent her Chief Resident Year writing and organizing the original guide and for the past decade has continued to edit and update the guide.

Special "Thank You" to **Dr. Gretchen Ascher** (Class of 2023) for this year's contribution to the PRITE 2022 study guide

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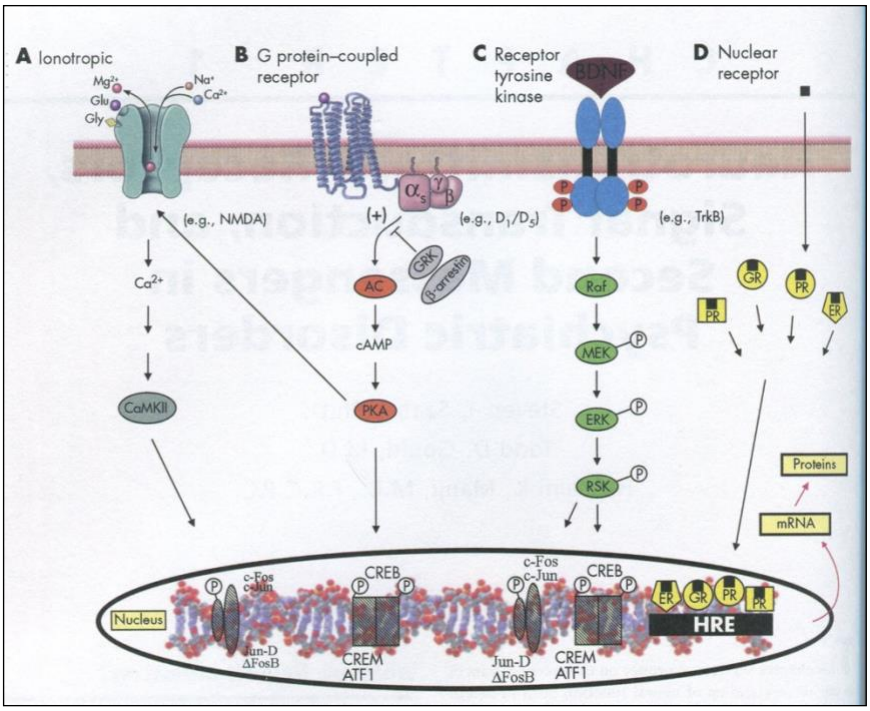
A Ninja's Guide to Receptors, Neurotransmitters, and Signal Transduction

Receptor Basics

Receptors are made up of protein chains that span a membrane, thus having 3 parts: extracellular, transmembrane, and intracellular. The neurotransmitter (NRT) binding site is generally on the transmembrane portion of the receptor. Receptors are categorized by the number of times the protein chain loops within the membrane. Examples: 4 transmembrane regions, 7 transmembrane regions, etc.



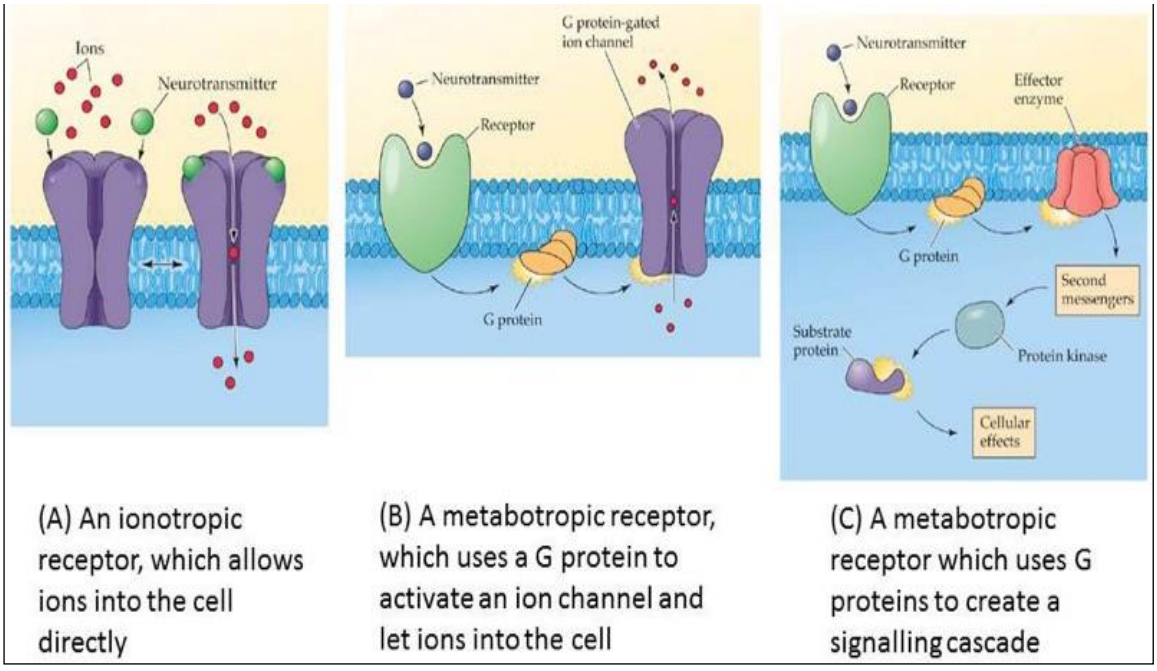
Major Receptor Subtypes

Ionotropic Receptors

Generally, 5 individual receptors combine to make this mega-receptor. The individual receptors that combine are the 4 transmembrane region types (the protein chain loops through the membrane 4x). Thus, one ionotropic receptor is comprised of 5 of the 4 transmembrane receptors. *Action: excitability*. NRT → Na^+ influx (excitation) or Cl^- influx (inhibition) through the receptor channel. This is a FAST response. Examples: NMDA, nicotinic Ach, 5HT-3, and GABA-A receptors.

Metabotropic Receptors

G-Protein Coupled Receptors (GPCRs): often have 7 transmembrane regions and use a second messenger system. While ionotropic receptors are involved in changes in cell excitability, G-Protein receptors directly lead to gene transcription, resulting in widespread changes in the cell. *Action: genetic transcription***.** NRT → binding on external site → receptor transforms → activates 3 G-proteins → activates an enzyme → creates a second messenger (most commonly cAMP or IP_3) → activates a protein kinase → phosphorylates (activates) a transcription factor → binds to an inactive gene to activate it. RNA is then transcribed and makes proteins. This is a SLOW response as genetic changes take much longer to complete than simple electrical changes. Second messengers can, however, also change membrane permeability to ions (change excitability), which is a FAST response. G-Protein receptors constitute 80% of all known receptors in the body. Examples: Ach, catecholamines (NE, Epi, DA), peptides, and serotonin.

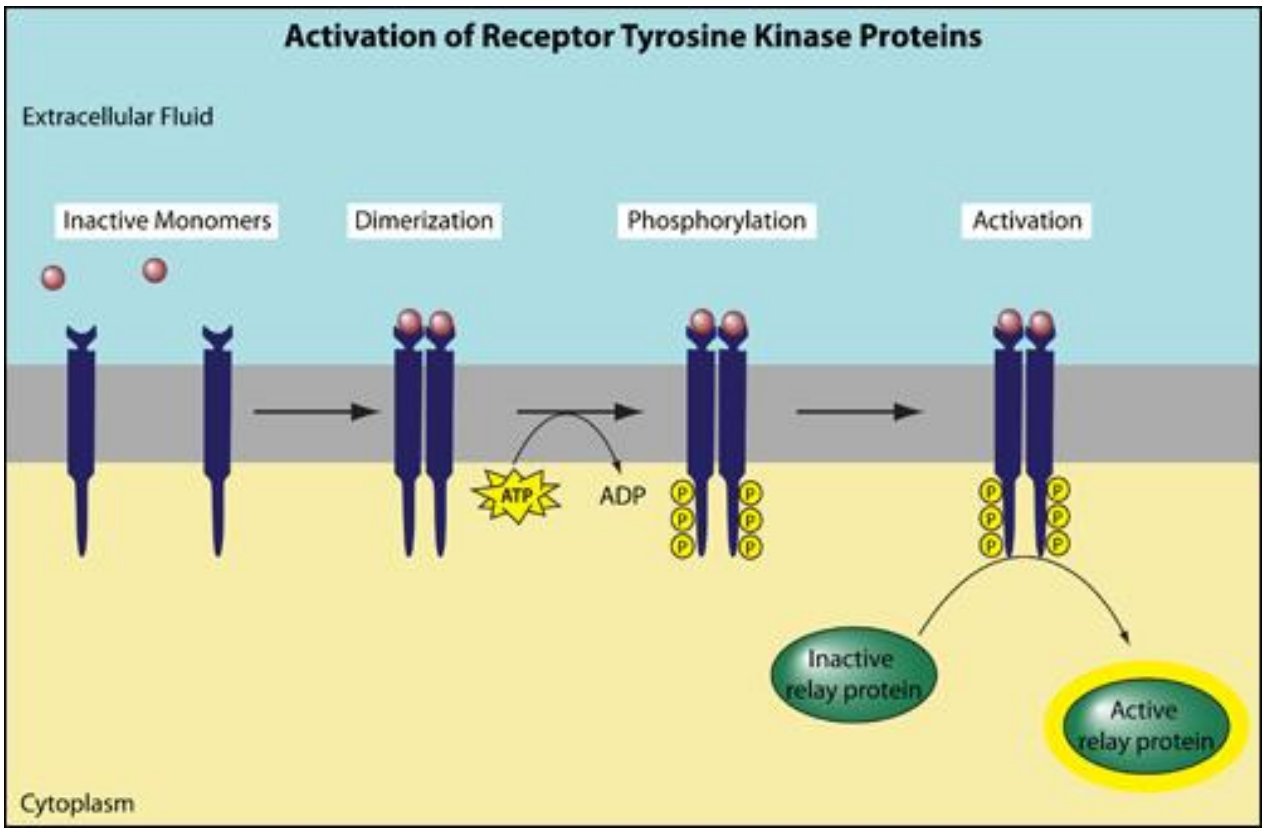


(A) An ionotropic receptor, which allows ions into the cell directly

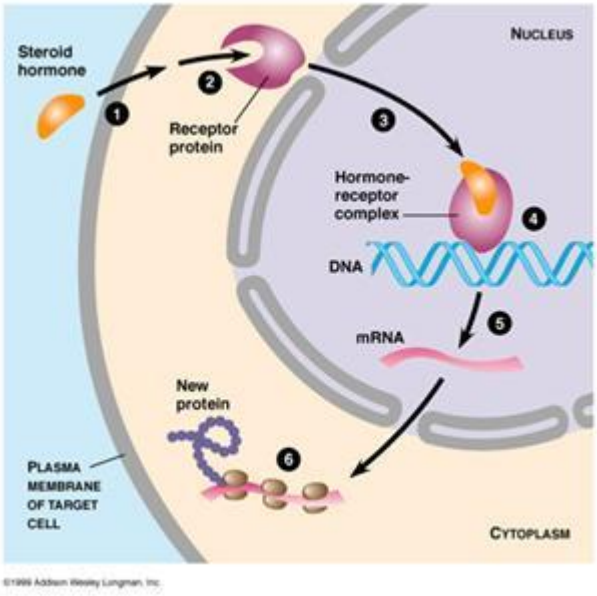
(B) A metabotropic receptor, which uses a G protein to activate an ion channel and let ions into the cell

(C) A metabotropic receptor which uses G proteins to create a signalling cascade

Receptor Tyrosine Kinases: are receptors that are mainly influenced by growth factors and neurotrophic factors, which are involved in axon generation, migration, neural plasticity, and regulation of apoptosis. *Action: synaptic plasticity***.** BDNF (or other neurotrophic factor) → phosphorylation of cytoplasmic tyrosine → activation of enzymes → genetic transcription → synaptic plasticity.



Nuclear Receptors: lipophilic ligands (hormones) pass through the membrane and bind to floating intracellular receptors. Receptor-ligand complex enters the nucleus, binds to hormone-specific regions of DNA and leads to gene transcription.



Miscellaneous Receptor Stuff

Autoreceptors: inhibitory presynaptic GPCRs specific to NRT released

- Somatodendritic autoreceptors: located on cell bodies and dendrites, regulate the presynaptic neuron's *firing rate*. Generally, these receptors are *inhibitory*. Inhibition occurs by opening K^+ channels and reducing cAMP. Example: 5HT-1A autoreceptors decrease 5HT firing rate/amount
- Nerve terminal autoreceptors: decrease the amount of NRT released by closing Ca^{2+} channels. Example: α_2-adrenergic receptors inhibit NE release (clonidine mechanism of action)

Heteroreceptors: are also presynaptic GPCRs, but are NOT specific, and not always inhibitory. Examples: 5HT presynaptic heteroreceptor on DA neuron decreases firing rate/amount of DA released (atypical antipsychotics mechanism of action); NE α_1 presynaptic heteroreceptor on 5HT neuron increases 5HT firing.

Desensitization: a GPCR with chronic agonist activation can be desensitized. In this process, the receptor gets over-phosphorylated → arrestin proteins binding → blockade of G-protein cascade → receptor reset.

Down-regulation: after prolonged desensitization, the GPCR is internalized and degraded. This results in less GPCRs and decreased production of GPCRs at the genetic level. Example: SSRI medications chronically activate 5HT-1A autoreceptors, causing down-regulation, where the autoreceptors are degraded and less are produced. This results in less 5HT-1A autoreceptors → more 5HT → improvement in depression due to changes at the genetic level.

Upregulation: chronic antagonism of GPCR (like antipsychotics on DA neurons) → more receptors on the membrane → increased sensitivity to NRT. Example: Tardive Dyskinesia. Chronic D2 blockade leads to making more D2 receptors (in areas responsible for movement) → more sensitivity to DA → movement looks like *too much* DA (similar to *hyper*kinetic disorders such as tics or chorea). Unlike EPS, anticholinergic medications make TD worse. Why? Anticholinergics decrease Ach and increase DA. EPS is caused by *too little* DA (*hypo*kinetic), so adding DA improves the condition. TD is caused by hypersensitivity to DA from adding too many receptors. Increasing DA with anticholinergic medications only worsens TD. *Thus, chronic agonism leads to diminished receptor production (internalization), while chronic antagonism leads to increased receptor production (externalization).*

Neurotransmitter Overview

Neurotransmitters allow the presynaptic genome to communicate with the postsynaptic genome.

Neurotransmitter Criteria

1. NRTs are synthesized and released from neurons
2. Released from nerve terminals in a chemically or pharmacologically identifiable form
3. Interacts with postsynaptic receptors and brings out same effects as are seen with stimulation of the presynaptic neuron
4. Interaction with the postsynaptic receptor displays a specific pharmacology
5. Actions are terminated by active processes

Three dimensions of neurotransmission

Space: local vs. distant signals

- Anatomically Addressed: presynaptic electrical signal → postsynaptic chemical messenger. This is through direct communication
- Chemically Addressed: NRT diffusion across far distances, binding to receptors based on affinity/compatibility

Time: fast vs. slow-onset signals

- Fast: ion channel receptors change membrane permeability/excitability. Examples: NMDA, GABA, Glutamate
- Slow: 2^{nd} messengers change genetic transmission. Examples: monoamines like NE, DA, 5HT

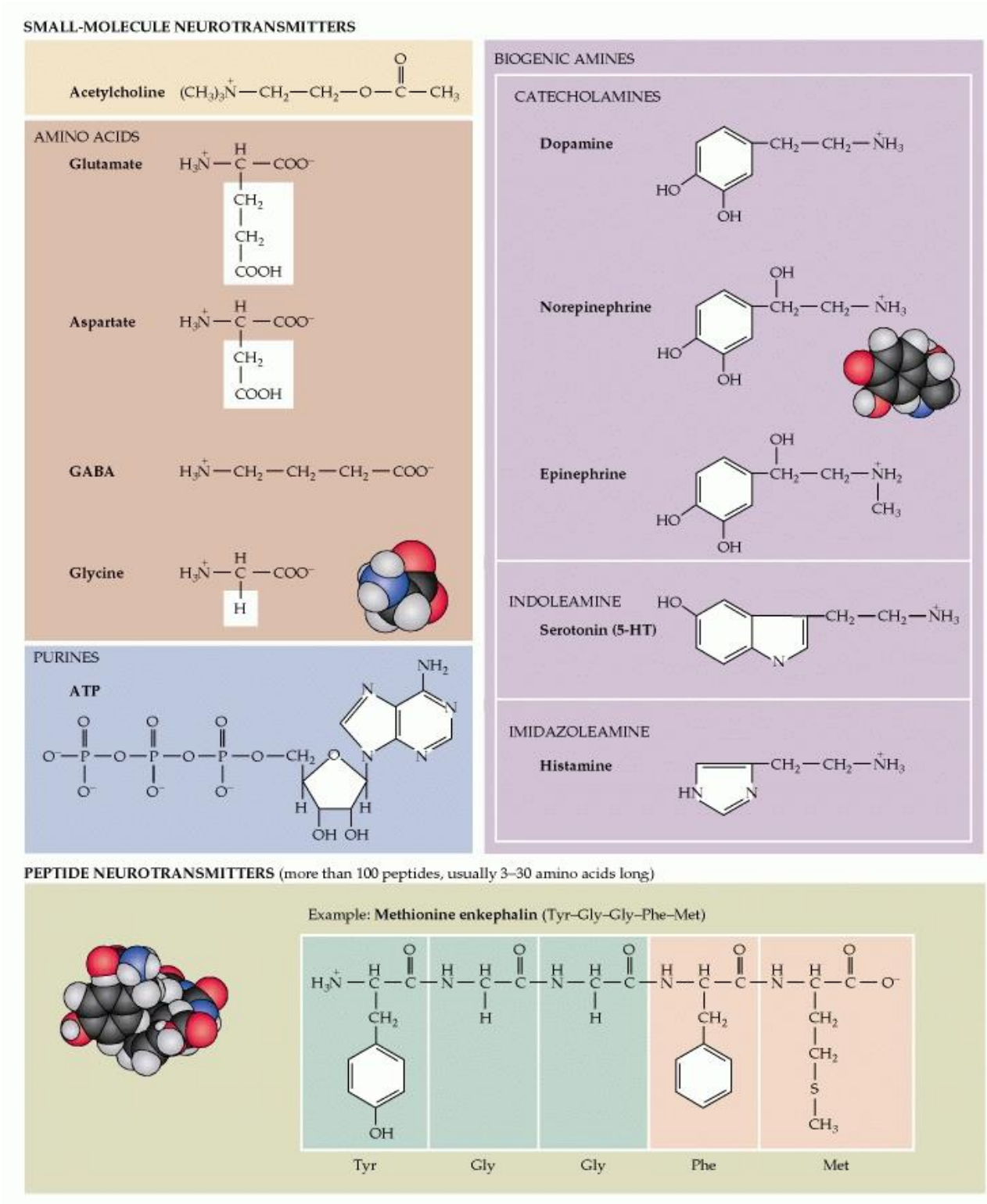
Function: presynaptic electrical impulse → opens Ca^{2+} channels → anchors synaptic vesicles containing NRT to membrane → spills NRT into synaptic cleft

- Monoamine NRTs**:** are packaged up with enzymes which make more NRT, and have transports for NRT reuptake
- Neuropeptide NRTs: do not have reuptake transporters. Here, a chemical NRT binds a receptor and starts a chemical cascade (2^{nd} messenger) or is converted into an electrical signal (ion)

Types of Neurotransmitters

- Amines: monoamines are derived from aromatic amino acids like tyrosine, tryptophan, and phenylalanine. Includes 5HT, DA, NE, E, Melatonin and Histamine. Packaged into vesicles by VMAT for release. Have reuptake transporters
- Cholinergic: Ach
- Amino Acids: Fast acting, GABA, Glycine, Glutamate, Aspartate
- Primary Peptides: ACTH, GH, Oxytocin, Vasopressin, TSH, Prolactin
- Circulating Hormones: Angiotensin, Glucagon, Insulin, Calcitonin, Estrogens, Androgens, Progestins, Thyroid hormones

- Hypothalamic-Releasing Hormones: CRH, GnRH, Somatostatin
- Gut Hormones: CCK, Gastrin, Motilin, Secretin, VIP
- Opioid Peptides: Endorphins and Enkephalins
- Gases: NO, CO

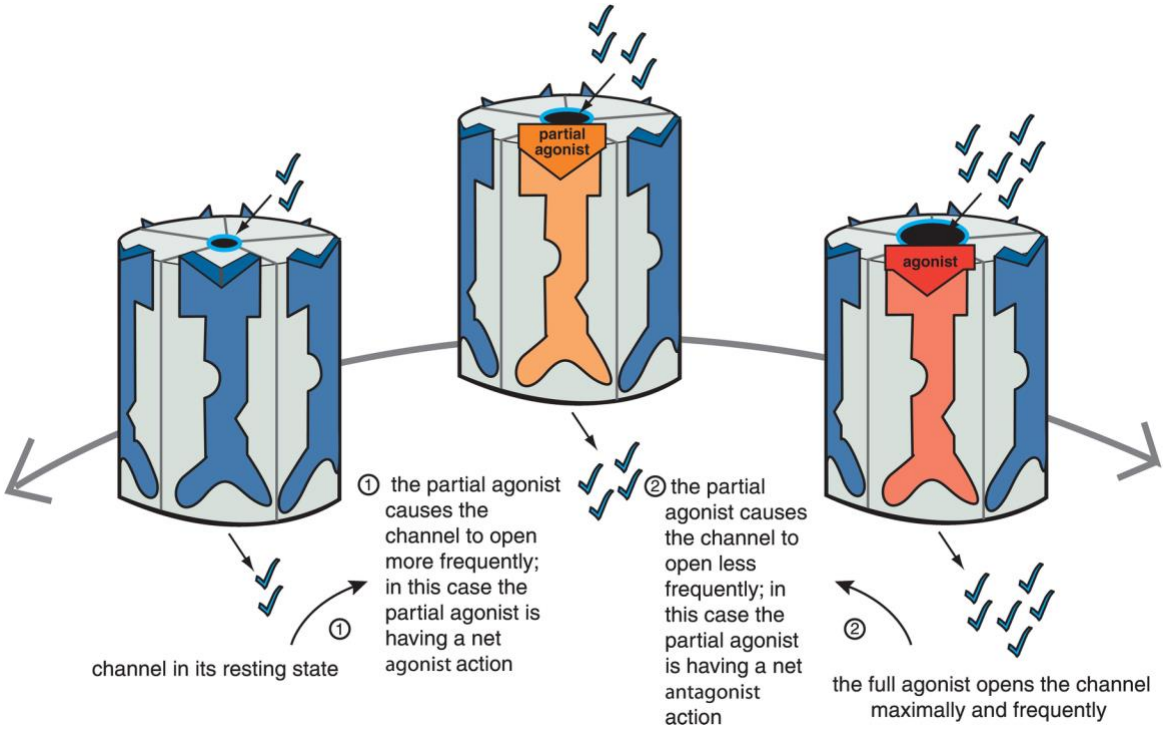

SMALL-MOLECULE NEUROTRANSMITTERS
Acetylcholine
AMINO ACIDS
Glutamate
Aspartate
GABA
Glycine
PURINES
ATP
BIOGENIC AMINES
CATECHOLAMINES
Dopamine
Norepinephrine
Epinephrine
INDOLEAMINE
Serotonin (5-HT)
IMIDAZOLEAMINE
Histamine
PEPTIDE NEUROTRANSMITTERS (more than 100 peptides, usually 3–30 amino acids long)
Example: Methionine enkephalin (Tyr–Gly–Gly–Phe–Met)
Tyr
Gly
Gly
Phe
Met

Neurotransmitter Interaction

- Co-transmitters: neurons with >1 NRT release BOTH simultaneously for combined or interactive effects
- Allosteric Interactions: each receptor has a primary NRT. Allosteric interaction is the effect of a 2nd NRT (or medication) on that receptor. Examples: ETOH has positive allosteric effects on GABA receptor, increasing GABA's action on Cl^- channels. SSRI medications have negative allosteric effects on 5HT reuptake transporter

Neurotransmitter Effects: The Agonist Spectrum

- Full Agonist: drug or NRT that strongly opens ion channels or has 2nd messengers which lead to the greatest effect on gene transcription
- Partial Agonist: has a weaker effect on ion channels or second messenger systems. Alone, it acts as a weak agonist. In the presence of a full agonist, the partial agonist competes and dilutes the agonist's ability (acting *antagonistically*)
- Antagonist: no intrinsic activity of its own. When bound alone, receptor is in a resting state (channels neither open nor closed). In the presence of an agonist, an antagonist works to return the membrane to its resting state. Multiple kinds such as non-competitive, un-competitive
- Inverse Agonist: does the opposite of agonists. Most channels have some intrinsic flux of NRTs, but an inverse agonist stops even that. An antagonist in the presence of an inverse agonist would return a channel to its resting state intrinsic activity



Neurotransmitter Systems

Serotoninergic System

Monoamine (tryptamine) NRT

Projections: From Raphe Nucleus, neurons project widely throughout the CNS

- Frontal Cortex: mood
- Basal Ganglia (5HT-2A/C): repetitive movement and OCD
- Limbic area: anxiety and panic
- Hypothalamus (5HT-3): regulates appetite and eating behavior

Production and Destruction: dietary L-tryptophan → presynaptic 5HT terminals → tryptophan hydroxylase converts to 5-hydroxytryptophan (5HTP) → converted to serotonin (5HT) → packaged into vesicles by a vesicular monoamine transporter (VMAT). Vesicles of 5HT are released from the presynaptic terminal and interact with up to 15 different postsynaptic receptors. Reuptake is via transporters (5HTT) and 5HT is repackaged for re-release or broken down to 5-HIAA by MAO in mitochondria.

Modulation

- Autoreceptors: 5HT-1A (somatodendritic = decrease firing rate) and 5HT-1B,1D (nerve terminal = decrease amount released)
- Heteroreceptors: NE presynaptic α_2 decreases 5HT release. NE presynaptic α_1 receptor in the brainstem *increases* 5HT release

5HT transporters (5HTT): transporters are receptors with 12 transmembrane regions that shuttle large molecules into a cell. They require ATP & Na^+ to function. 5HTTs cotransport 5HT with Na^+ while translocating K^+ across the membrane to the outside of the cell.

5HT Receptors: GPCRs (except 5HT3 = ionotropic)

- 5HT-1A: presynaptic are somatodendritic autoreceptors which decrease 5HT firing by opening K^+. Postsynaptic are associated with the expression of trophic factors, promoting axon arborization. SSRIs enhance hippocampal neurogenesis. 5HT-1A antagonists lead to synaptic losses and play a role in mood disorders
- 5HT-1B & 1D: nerve terminal autoreceptors
- 5HT-2: Chronic SSRIs *downregulate* 5HT-2 receptors. Leads to better 5HT/receptor ratio (serotonin deficit hypothesis)
- 5HT-2A: mainly postsynaptic. Projects to BG to control movement/compulsions. Mesocortical reduces DA, causing apathy and diminished libido. Regulates slow-wave sleep. Stimulation inhibits orgasm/ejaculation. 2A and 2C projection to limbic decreases panic/anxiety
- 5HT-2C: causes weight gain (isolated from histaminic weight gain)

- 5HT-3: ionotropic receptors with FAST synaptic responses. GI effects of SSRIs are due to activation of this receptor system. Anti-emetics *antagonize* 5HT-3 (ondansetron). Projections to hypothalamus may regulate appetite and eating behavior (satiety)
- 5HT-4, 6, 7: GPCRs that activate adenylyl cyclase. 5HT-6 is antagonized by multiple antidepressants and antipsychotics. 5HT-7 is down-regulated by chronic SSRI treatment

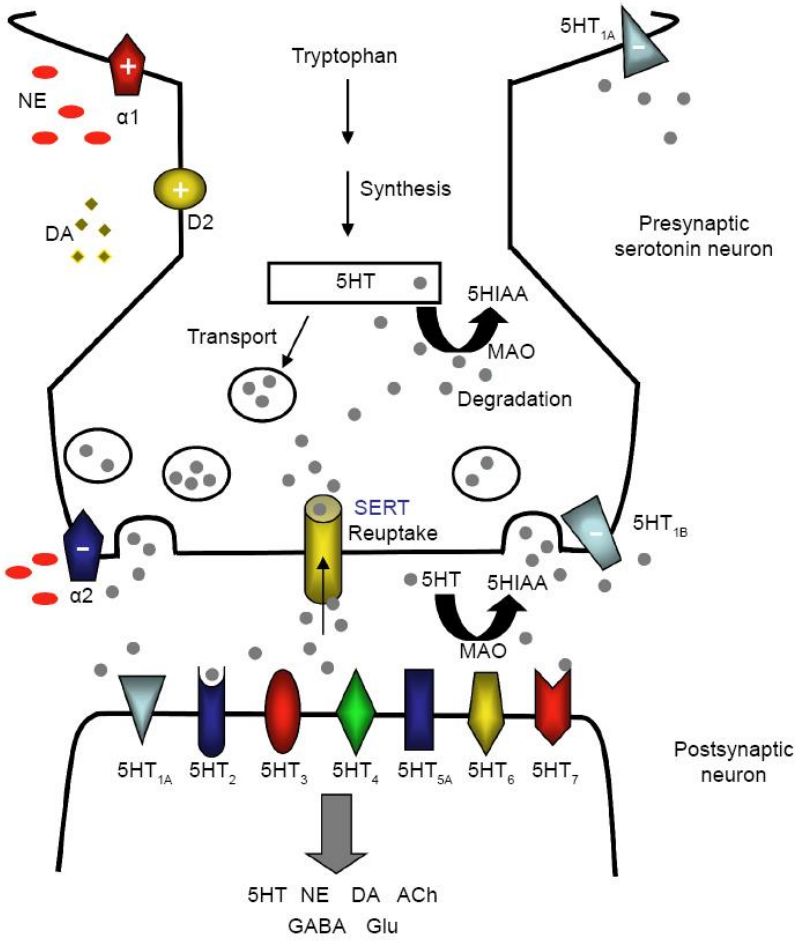


Figure 4 The serotonergic synapse.
Notes: Serotonin (5HT) is produced from tryptophan and packaged into storage vesicles until its release into the synapse. Multiple postsynaptic 5HT receptors interact with 5HT to mediate its signaling and modulate diverse transmitter systems involving 5HT, NE, DA, ACh, GABA, and Glu. Excess 5HT is removed from the synaptic cleft by SERT or degraded to an inactive metabolite 5HIAA by MAO. Presynaptic $5HT_{1A}$ and $5HT_{1B}$ autoreceptors detect the presence of 5HT in the synapse and shut down further 5HT release, while D2-like dopamine receptors and α1- and α2-adrenoceptors positively (+) or negatively (–) influence 5HT transmissions.
Abbreviations: 5HIAA, 5-hydroxyindoleacetic acid; 5HT, 5-hydroxytryptamine or serotonin; ACh, acetylcholine; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; MAO, monoamine oxidase; NE, norepinephrine; SERT, serotonin transporter.

Dopaminergic System

Monoamine (catecholamine) NRT

Projections

- Mesolimbic: ventral tegmental → hypothalamus → limbic, frontal and nucleus accumbens Associated with reward behaviors and addiction. Excess DA = positive symptoms of schizophrenia and aggression
- Mesocortical: ventral tegmental → cortex and limbic area. Associated with cognition and motivation. *Deficiency* of DA = negative symptoms and cognitive issues in schizophrenia. Treatment with typical D2 blocking agents leads to worsening of negative symptoms and cognition in schizophrenia. Thus, *overactive mesolimbic* and *underactive mesocortical* DA pathways create the pathology of schizophrenia
- Nigrostriatal: reticular formation and substantia nigra → caudate nucleus and putamen. Deficiency of DA = Parkinsonian symptoms (rigidity, bradykinesia, tremor), akathisia, and dystonia. Excess DA = chorea, dyskinesia, and tics
- Tuberoinfundibular: hypothalamus → anterior pituitary → *inhibition* of PRL release. DA blockade = elevated PRL (galactorrhea, amenorrhea, sexual dysfunction)

Production and Destruction: L-tyrosine → enters presynaptic terminals → tyrosine hydroxylase converts to L-DOPA → converted to DA (by the same decarboxylase that converts 5HTP to 5HT) → packaged into vesicles by VMAT → release into synaptic cleft. Reuptake is via a dopamine transporter (DAT) into the presynaptic neuron. DA is either repackaged or broken down to dihydroxyphenylalanine or HVA by MAO. Examples: bupropion and sertraline inhibit DAT.

DA Transporters: like other MAO pumps, is Na^+/K^+. Amphetamines reverse the direction of the transporter to *release* DA and cocaine blocks the reuptake. In the medial frontal cortex, DA is taken up by the NE and 5HT reuptake transporter. This may be a mechanism for how NE/5HT reuptake-inhibiting antidepressants may also increase DA in frontal cortex (two-and-a-half mechanism hypothesis).

DA Receptors: GPCR. Two subtypes/families exist, D1 (D1 and D5: stimulate adenylyl cyclase) and D2 (D2, 3, 4: inhibit adenylyl cyclase)

- D1, 5: Frontal cortex is almost completely D1 (cognitive functioning) vs. D5 in limbic areas and associated with *memory consolidation*
- D2: presynaptic autoreceptors are both somatodendritic (reduce firing rate by opening K^+ channels) and nerve terminal (reduce amount NRT released by closing Ca^{2+} channels). Post-synaptically, D2 receptors are found in high density in the striatum and nucleus accumbens, and in lower density throughout the cortex
- D3: primarily located in the limbic system, is an important target for antipsychotics. May interact with BDNF
- D4: highest density in midbrain, amygdala and frontal cortex with minimal presence in the striatum. Clozaril has high affinity for this receptor, and has minimal EPS due to limited striatal DA blockade. This receptor may be associated with thrill-seeking behavior and ADHD

Areas of Highest Receptor Density

- D1: Frontal cortex (mesocortical)
- D2: Striatum, nucleus accumbens (nigrostriatal, mesolimbic)
- D3: amygdala, hippocampus (mesolimbic)
- D4: amygdala, some frontal cortex (mesolimbic)
- D5: amygdala, hippocampus (mesolimbic)

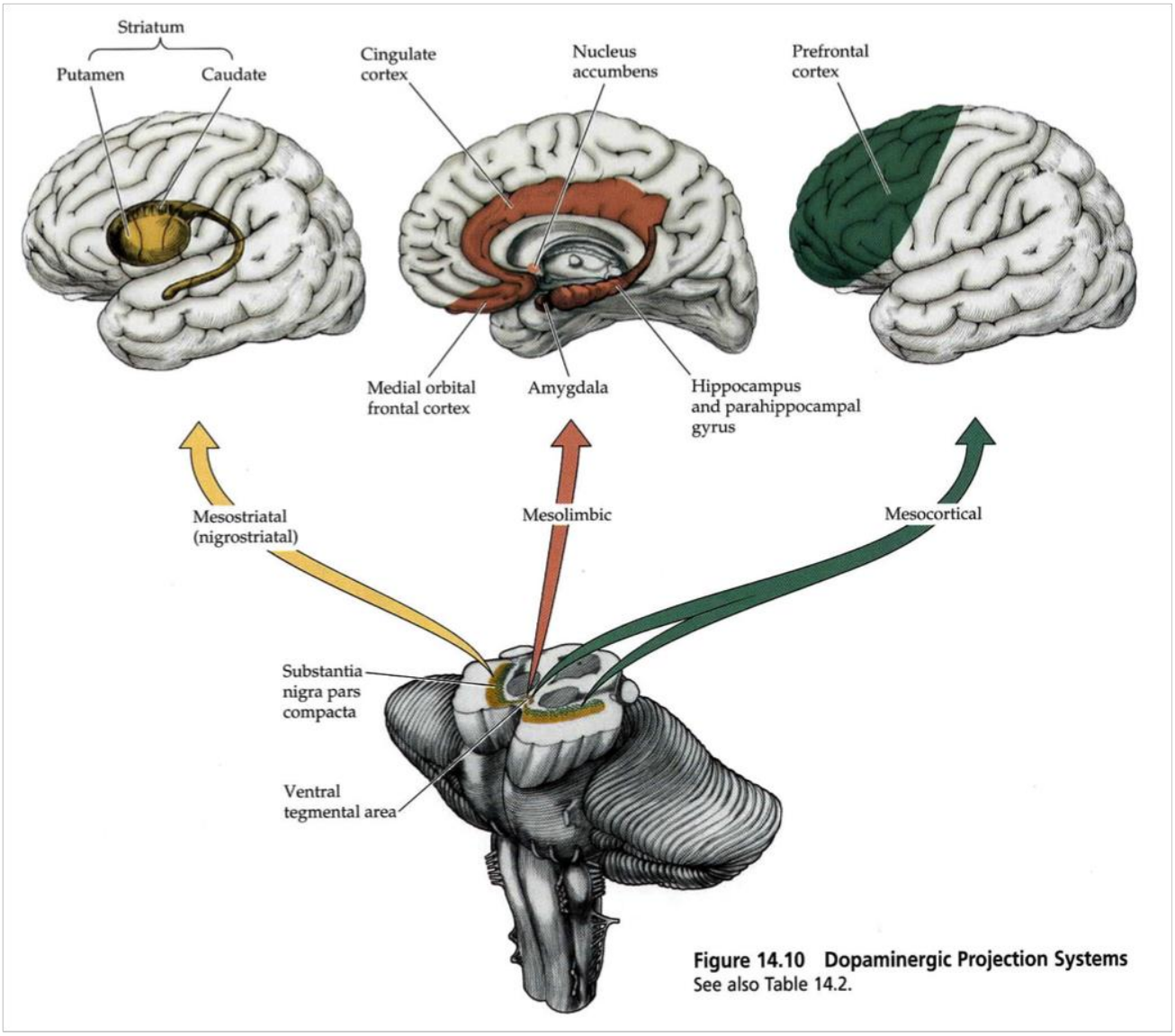
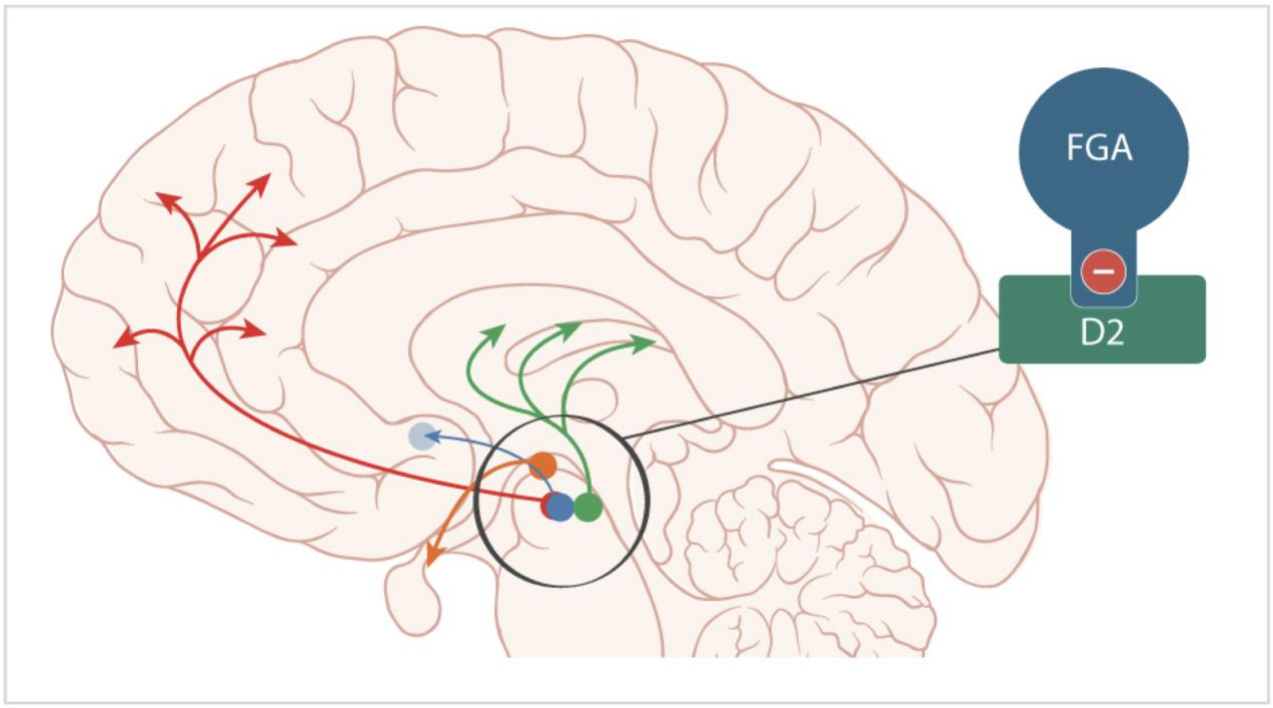


Figure 14.10 Dopaminergic Projection Systems
See also Table 14.2.

First Generation Antipsychotics Are D_2 Antagonists



Mesocortical Pathway
Nigrostriatal Pathway
Mesolimbic Pathway
Tuberoinfundibular Pathway

PSYCHOPHARMACOLOGY INSTITUTE

Noradrenergic System

Monoamine (catecholamine) NRT

Projections: from the Locus Coeruleus (LC)

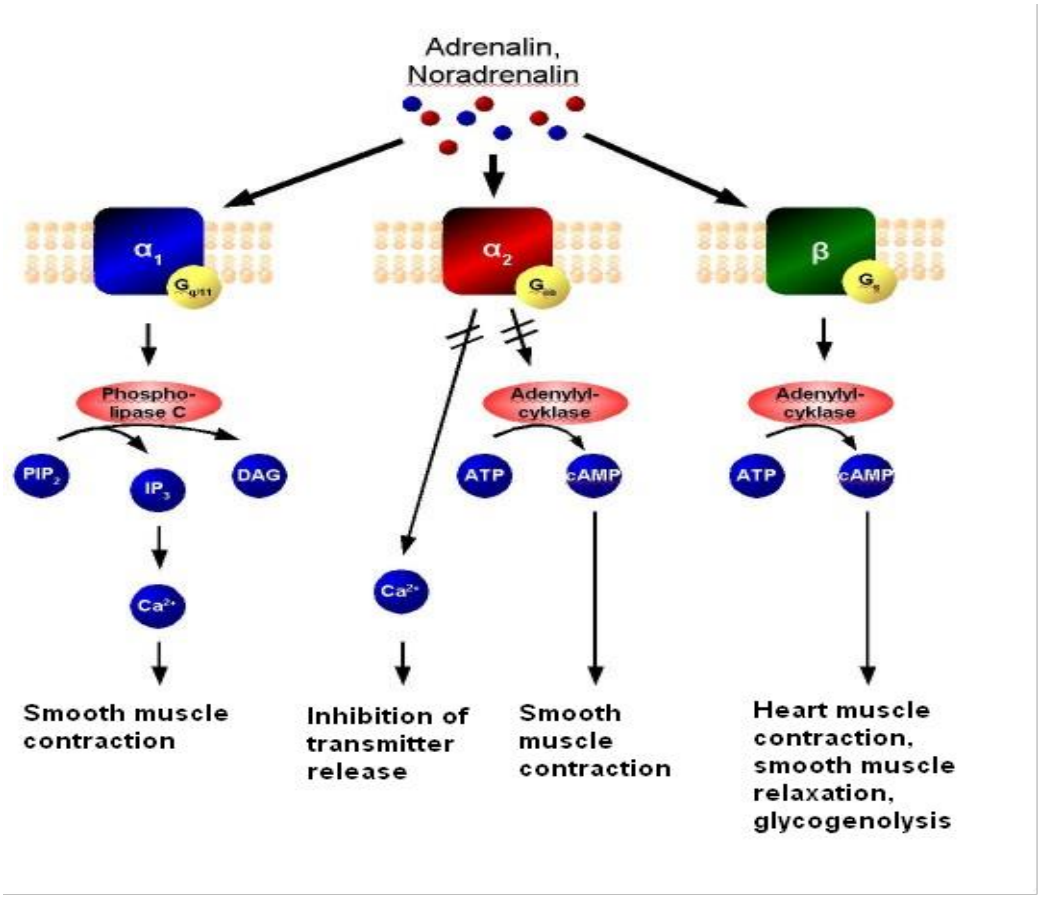
- Frontal Cortex: mood
- Prefrontal Cortex: attention
- Limbic: emotions, energy, fatigue, and pmr/a
- Cerebellum: regulates motor movements and tremor
- Peripheral: cardiovascular and sympathetic systems

Production and Destruction: DA→ DA β-hydroxylase (DBH) → NE. DA neurons lack DBH and cannot synthesize NE. Packaged in vesicles by VMAT and released. Has NE transporter for reuptake (is not specific to NE, can accept other monoamines). COMT metabolizes to normetanephrine, which is metabolized to MHPG by MAO.

Modulation: presynaptic α_2 autoreceptors. Yohimbine antagonizes both somatodendritic and nerve terminal α_2 autoreceptors (increased NE firing rate/release). Clonidine is an α_2 agonist (decreases firing rate/release of NE). Prazosin is an α_1 inverse agonist used to treat PTSD. SSRIs down-regulate NE transporters. Less transporters → less reuptake → more NE.

Receptors: GPCR. α_1, α_2 and β receptors

- α_1: postsynaptic, primarily. α_1 heteroreceptor on presynaptic 5HT neurons *increase* 5HT in the brainstem
- α_2: the only presynaptic NE autoreceptors. Also act as heteroreceptors for 5HT (inhibit release). Postsynaptic in frontal cortex are associated with cognition and focus
- β_1: modulate mood in the frontal cortex; the most effective antidepressants down-regulate these receptors. β antagonists may help treat PTSD due to role in regulating emotional memories
- β_3: not in CNS, but are located in brown fat, leading to lipolysis and thermogenesis. Selective β_3 receptor agonists in future may be developed for treatment of obesity



DISTRIBUTION AND PHYSIOLOGIC EFFECTS OF DIFFERENT ADRENERGIC RECEPTORS

TISSUE	RECEPTOR TYPE	EFFECT
Blood vessels	α_1 and α_2	Constriction
	β_2	Dilatation
Heart	β_1	Tachycardia; increased contractility
	α_1	Increased contractility
Bronchi	β_2	Relaxation
Thrombocytes	α_2	Aggregation
Kidneys	α_1 and α_2	Vasoconstriction
	β_1 and β_2	Renin release; inhibition tubular sodium reabsorption
Adipocytes	α_2	Inhibition lipolysis
	β_1, β_2, and β_3 (?)	Lipolysis

Cholinergic System

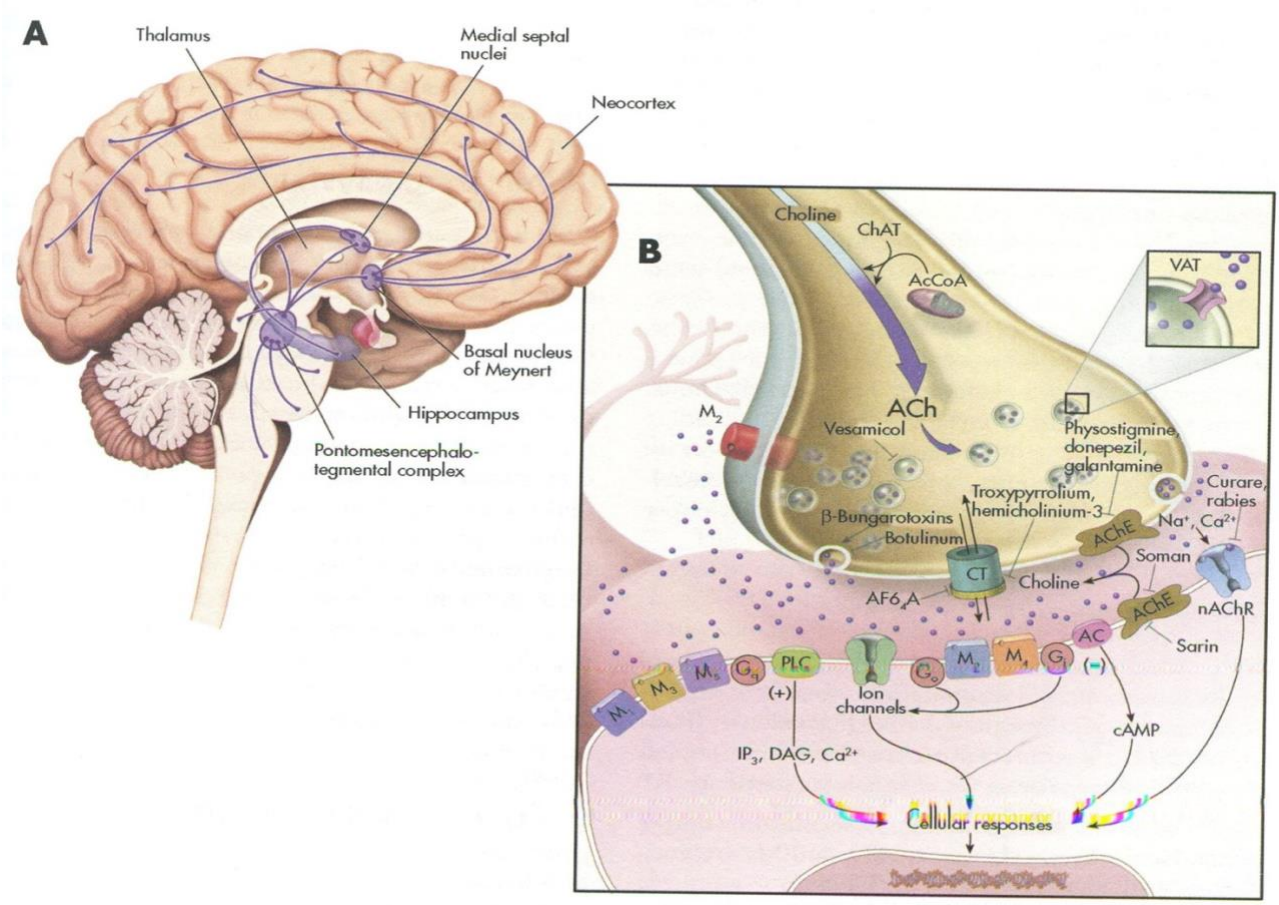
Projections: from hippocampus, basal nucleus of Meynart, medial septal nuclei, and other midbrain area. Associated with formation of memory, cognition, learning and attention. Pathology involved in Alzheimer's Dementia.

Production and Destruction: choline crosses the BBB → transported into presynaptic terminals (requires ATP) → converted to Ach through donation of acetyl group from acetyl coenzyme A → secretory vesicles → release. Direct breakdown occurs in the synaptic cleft by acetylcholinesterase. Free choline is transported back into presynaptic neuron for repackaging or enzymatic degradation.

Modulation: autoreceptors are present on presynaptic neurons. Botulism prevents presynaptic Ach vesicle release. Antibodies against presynaptic Ca^{2+} channels cause decreased Ach release (Lambert Eaton). IgG antibodies to the postsynaptic Ach nicotinic receptor leads to paralysis (MG). Centrally, changes to Ach transmission lead to problems with memory, concentration, and cognition.

Receptors: muscarinic (autonomic functions and learning/memory/behavior) and nicotinic (peripheral muscular activity)

- M1: may be associated with dementia. It is the most abundant receptor in the cortex and hippocampus, is postsynaptic on pyramidal neurons, and has important signaling roles in enhancing Glutamate transmission via NMDA receptors. Is related to learning and memory
- M2: primary autoreceptor in cortical structures. Peripherally is parasympathetic to heart. Antagonist = atropine
- M3: parasympathetic to smooth muscles (including vasodilation), pupil, glands, and GI. Associated with atypical antipsychotic insulin resistance and weight gain through M3 blockade
- M4: most abundant receptor in striatum, is affected in Alzheimer's Dementia. Is a site for research, as M1/M4 agonists have shown improvement in cognitive and behavioral symptoms in both Alzheimer's and schizophrenia
- Nicotinic: receptors are ionotropic with multiple subunits. Two types, neuronal and muscle. Neuronal nAch receptors are primarily presynaptic and modulate Ach, 5HT, Glu, DA, and NE neurotransmission. Schizophrenics have abnormal nAch receptors, leading to cognitive deficits. Additionally, schizophrenics have abnormal expression and function of the α_7 nicotinic receptor, which is involved in filtering auditory information. High rate of cigarette use may be an attempt to correct nAch abnormalities



Glutamatergic System

Amino acid NRT

Effects: excitation and neuromodulation (pruning). In the presence of Glu, an action potential is more likely to occur. Glu and aspartate are the two-major excitatory amino acids of the CNS. Associated with synaptic plasticity, learning, and memory. Is also a potent neuronal excitotoxin, with Ca^{2+} influx into cells leading to cell death.

Production and Destruction: unlike monoamines, Glu and aspartate don't pass the BBB. Produced locally by enzymes in neurons and glial cells. Glu is mainly synthesized from glucose (glucose → α-ketoglutarate → transaminated to glutamate by GABA-T in neurons). Glu is released by Ca^{2+} dependent exocytosis → crosses synaptic cleft → binds excitatory receptors including ionotropic receptors (NMDA), GPCR metabotropic receptors (mGluR), or autoreceptors (mGluR-2,3). Reuptake is through transporters on presynaptic neuron and astrocytes. Astrocyte loss is associated with excess Glu signaling, leading to cytotoxicity and mood disorders.

Modulation: growth factors such as glial-derived neurotrophic factor (GDNF) and S100-β (modulated by 5HT-1A) influence Glu neurons and synapse formation.

Receptors

- AMPA: Ionotropic receptor. When stimulated by Glu, produces a fast-excitatory signal, depolarizing the membrane. Paired with NMDA, AMPA's membrane depolarization leads to dislodging Mg blocking the NMDA receptor. AMPA helps activate NMDA
- Kainate: shares similar properties with AMPA
- NMDA: Ionotropic ligand gated (needs glutamate to open it) AND voltage gated (needs AMPA to depolarize the cell). *Ok, so this is a complicated one***.** Opening an NMDA receptor requires: AMPA to depolarize the membrane to dislodge NMDA Mg^{2+} blockade, 2 molecules of glycine (co-agonist) to bind to NMDA NR1 subunit, 2 molecules of Glu (ligand) to bind to NMDA NR2 subunit. The result is influx of Ca^{2+}, leading to a cascade involving protein kinases and gene transcription. Antagonists include PCP, ketamine, amantadine, and memantine. Neurodegenerative diseases such as Huntington's and Alzheimer's, are associated with excitotoxicity. Medications such as memantine may reduce symptoms or slow progression of these illnesses. Clozapine enhances the NMDA receptor activity. *NMDA modulators (including glycine agonists, such as D-serine) and glycine reuptake inhibitors (sarcosine) improve cognition and reduce negative symptoms in schizophrenics receiving antipsychotic*
- Metabotropic Glutamate Receptors (mGluR): GPCRs with 3 types. The mGluR subgroup I preferentially interacts with the G protein α subunit → activates IP3/Ca^{2+} and DAG (diacylglycerol)/PKC cascades. Groups II and III inhibit adenylyl cyclase and regulate ion channels; they also negatively modulate glutamate and GABA as presynaptic autoreceptors/heteroreceptors. This action may be anxiolytic, antipsychotic, and neuroprotective, offering a mechanism for new medications

Sending a signal (an NMDA receptor shopping list)

- Active neighbor AMPA receptor
- Post synaptic depolarization (Na^{+} influx) by AMPA
- Mg^{2+} removed
- 2 Glycine co-agonists (NRT1)
- 2 Glutamate ligands (NRT2)

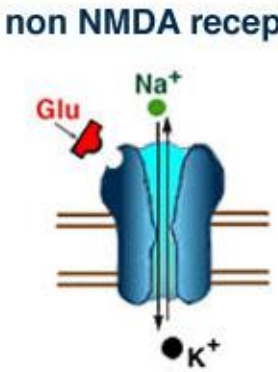


Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

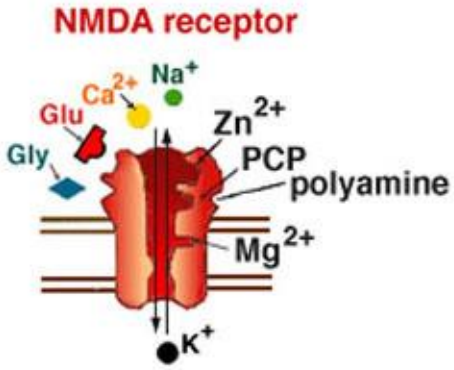
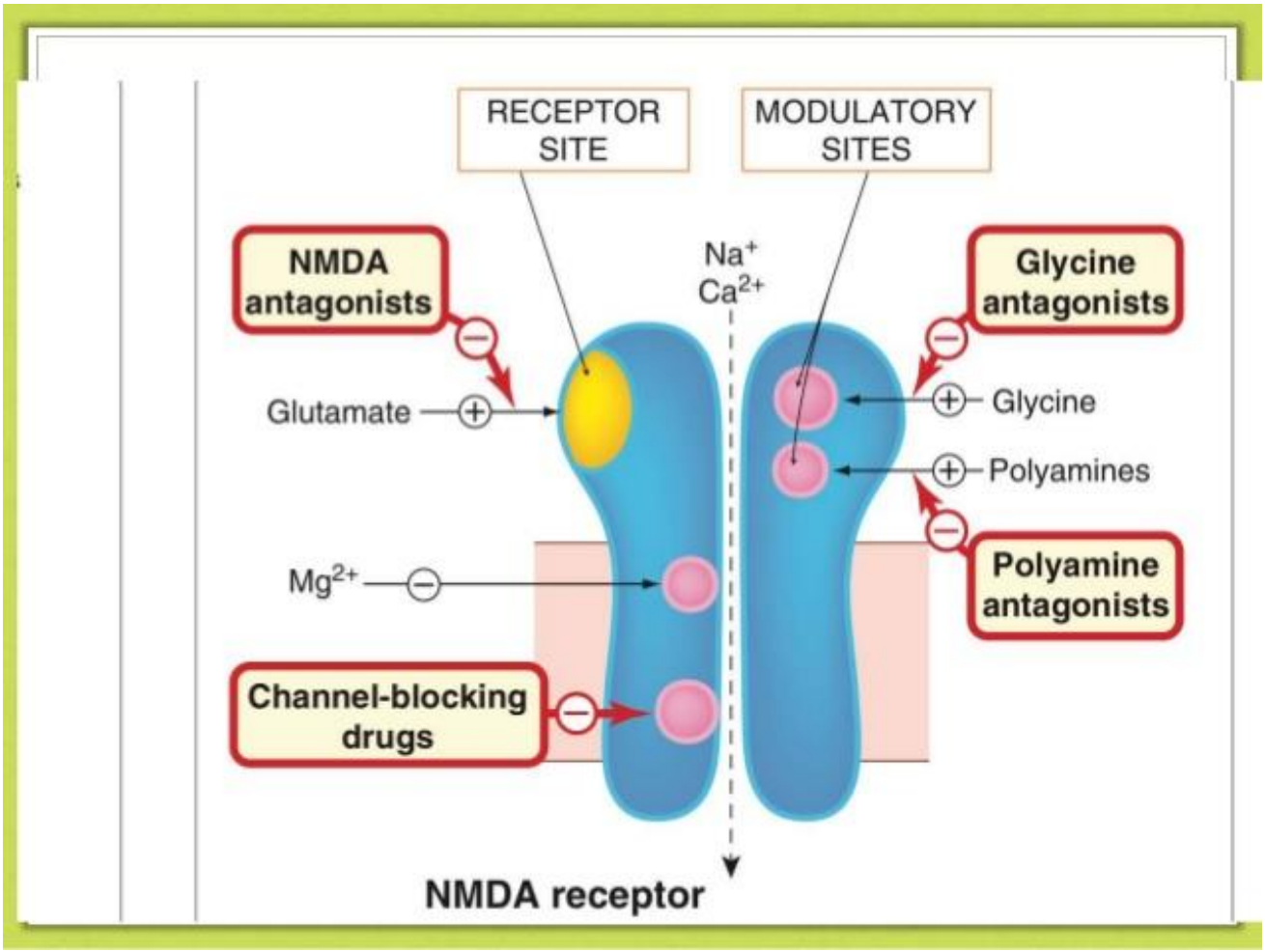
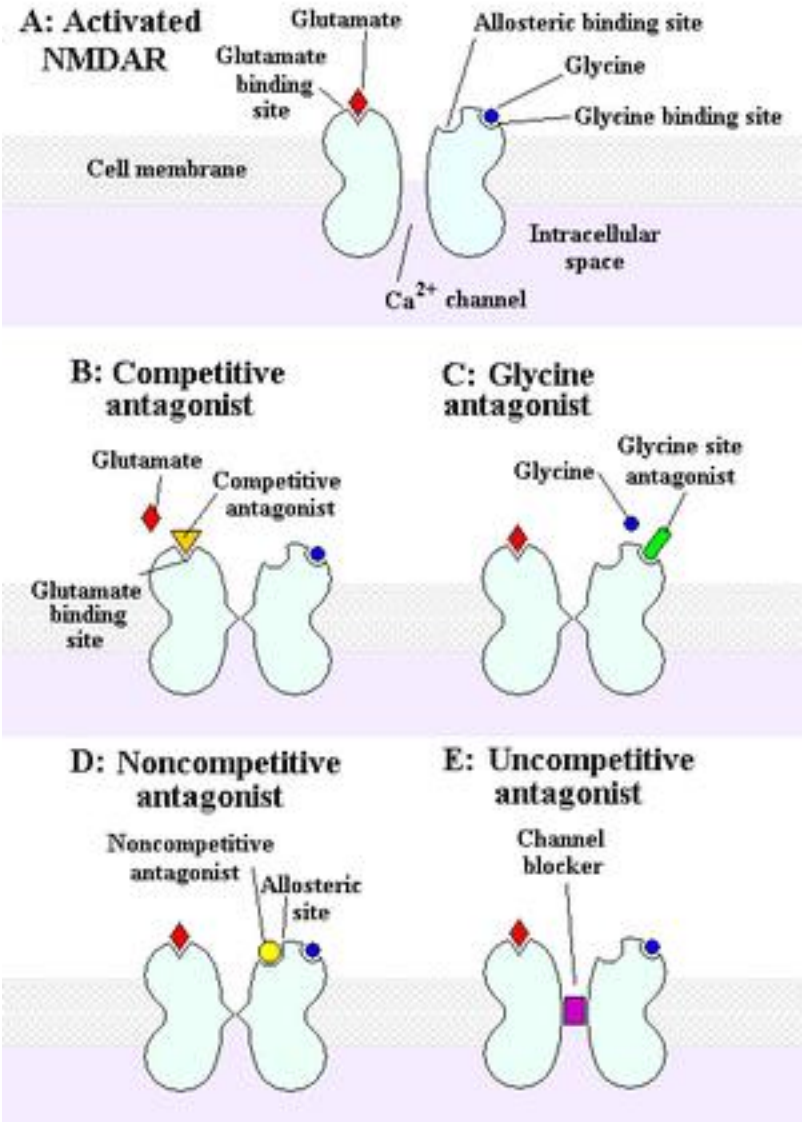


Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).


RECEPTOR SITE
MODULATORY SITES
NMDA antagonists
Na+
Ca2+
Glycine antagonists
Glutamate
Glycine
Polyamines
Mg2+
Polyamine antagonists
Channel-blocking drugs
NMDA receptor



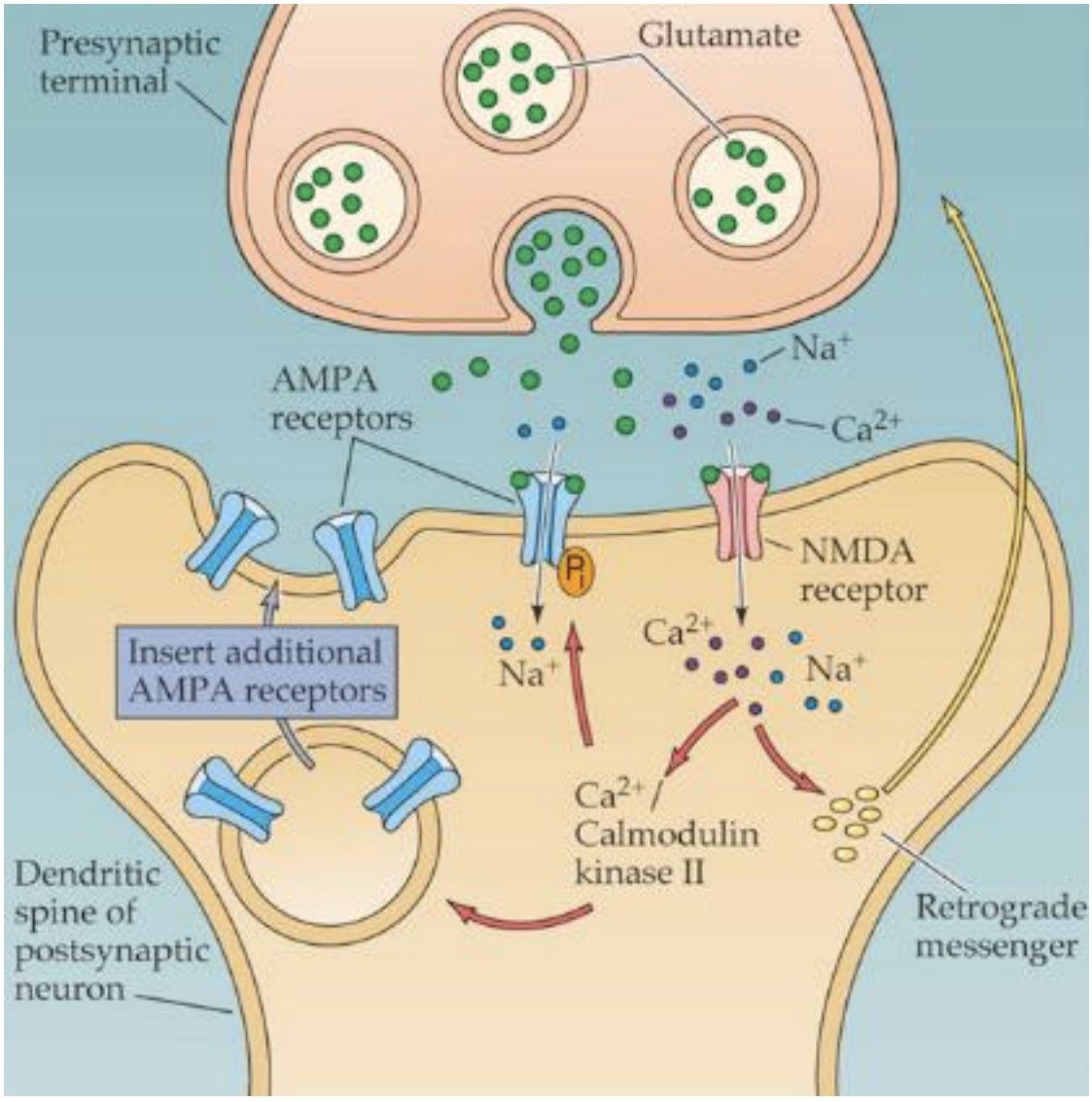
Four different types of inhibition of the NMDA receptor

Synaptic Plasticity: refers to the ability for synapses to strengthen or weaken over time. This is not solely about chronic agonism or antagonism, but has more to do with *signal strength*. In the 1800s, neurobiologists discovered that the formation of new memories did not require the generation of new neurons. This led to the idea that through repetition, connections strengthened, and long-term changes occurred. Medications can then be used to erase or treat pathological stimulation states.

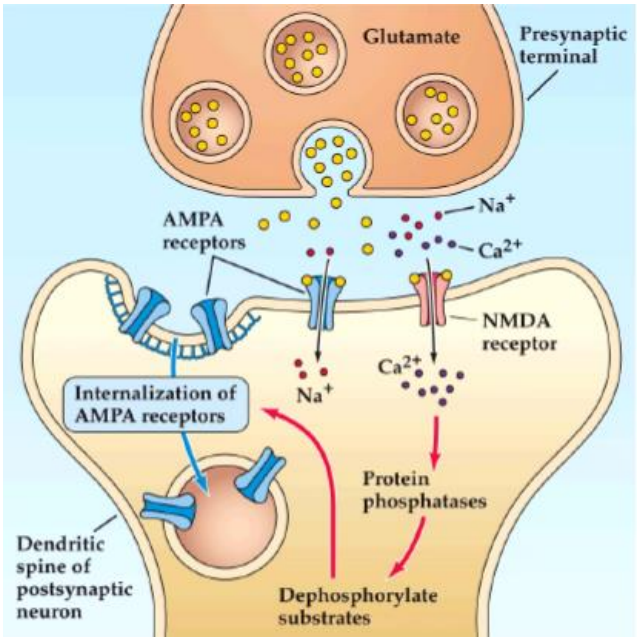
- Long Term Potentiation: *survival of the fittest.* Synapses with strong depolarization and large Ca^{2+} influx end up making more receptors and strengthening signal transmission

- Long Term Depression: *culling the herd.* LTP must be matched with balance—there is not enough room/energy for unlimited synapses. When some synapses strengthen, others weaken. Synapses with weak depolarization make less receptors and the overall synapse weakens. Induction of LTP and LTD in the hippocampus are associated with learning and memory, and are dependent on NMDA receptor activation

Excitotoxicity: excessive Glu signaling leads to excess intracellular Ca^{2+}, disrupting the cellular skeleton and mitochondria, causing cell death. This process is involved in the pathology of spinal cord injury, stroke, TBI, and neurodegenerative diseases.



Growth of dendritic spines in Long Term Potentiation due to increased synaptic firing. Use leads to production, insertion, and phosphorylation of AMPA receptors



Decrease in side of dendritic spines in Long Term Depression due to underutilization of synapse. Decreased use leads to less AMPA receptors density by dephosphorylation and eventual internalization

Glycine

Amino acid NRT

Production: Two pathways

1. serine-*trans*-hydroxymethylase reversibly transforms serine into glycine (folate dependent reaction)
2. D-glycerate dehydrogenase produces glycine from glyoxylate.

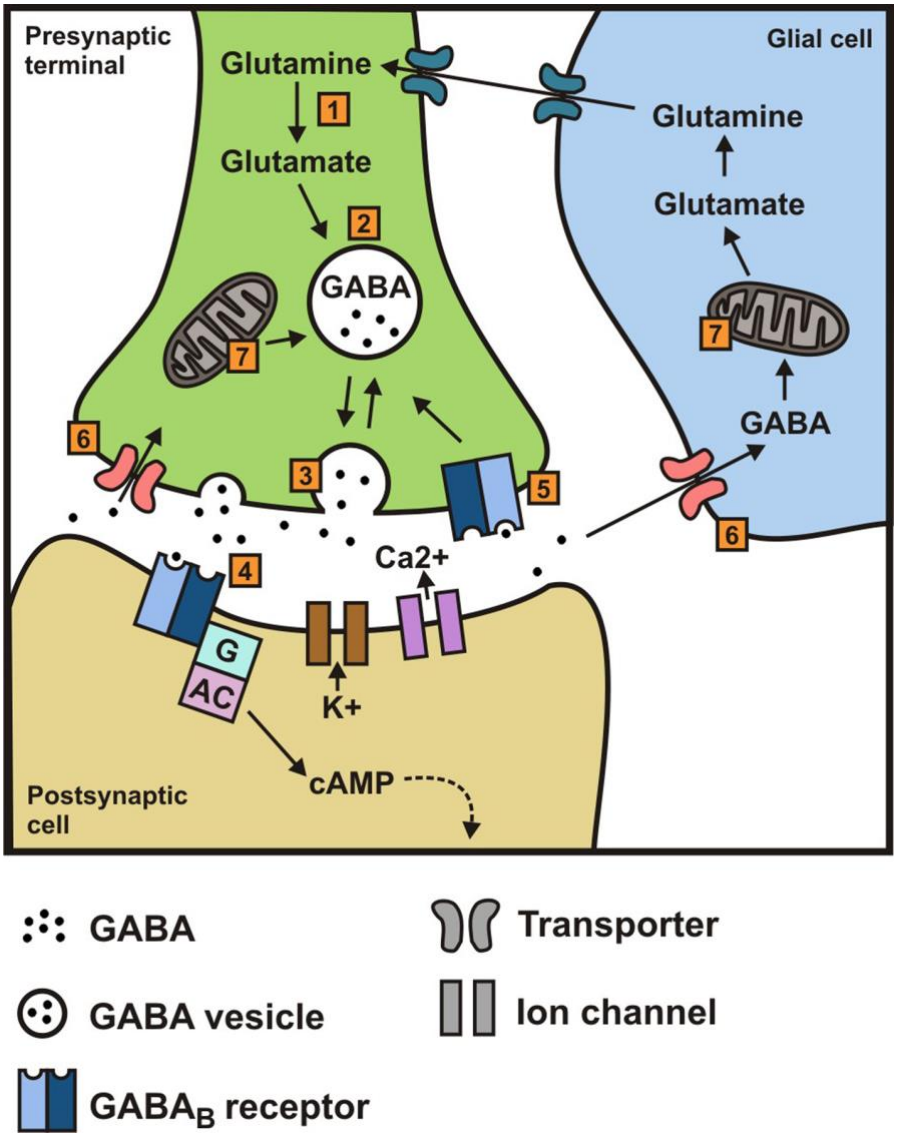
Functions: higher concentrations in the brain stem and spinal cord. Augments the NMDA receptor opening in response to glutamate.

GABAergic System

Amino acid NRT

Effects: located throughout the brain in high concentrations, is the chief inhibitory neurotransmitter in the CNS. GABA-A has sites for allosteric modulation by alcohol, benzodiazepines (BZD), barbiturates, and non-benzodiazepine sedative hypnotics like Ambien.

Production and Destruction: synthesized in the brain from Glutamate. Glu → decarboxylated by glutamic acid decarboxylase to GABA. After release, has reuptake transporter → repackaged and metabolized via GABA transaminase to α-ketoglutarate → reconverted back to Glu and even GABA again (*GABA shunt*).



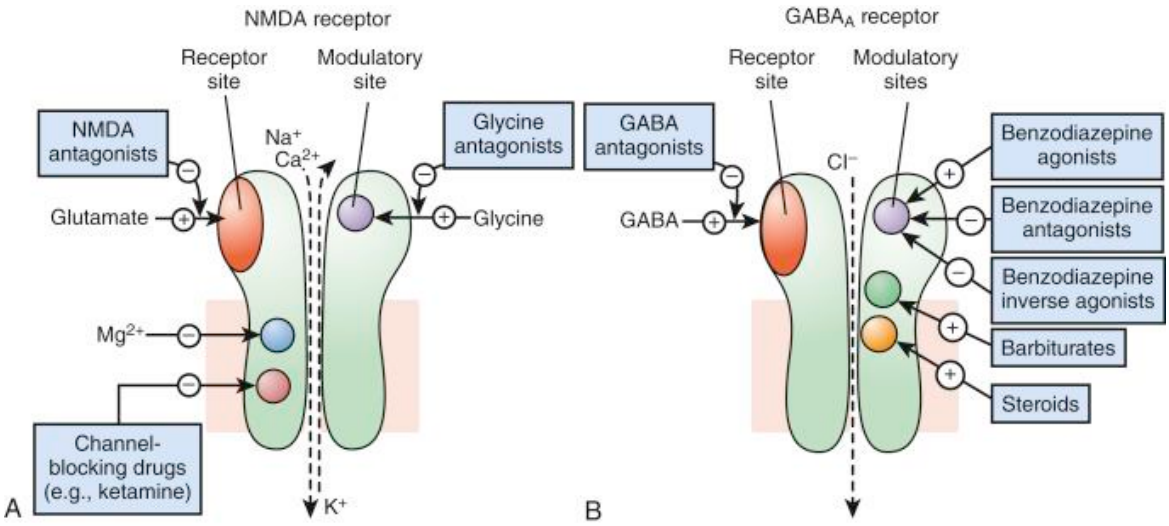
GABA Shunt

1. Glutamate decarboxylase (GAD)
2. transport and storage of GABA
3. release of GABA by exocytosis
4. binding to $GABA_B$ receptors and subsequent downstream effects mediated via a G protein and/or cAMP to K^+ and Ca^{2+} channels
5. binding to presynaptic receptors
6. reuptake in presynaptic terminal and uptake by glia
7. transamination of GABA to α-ketoglutarate (catalyzed by GABA transaminase, GABA-T), thereby regenerating glutamate and glutamine; glial glutamine then re-enters the neuron

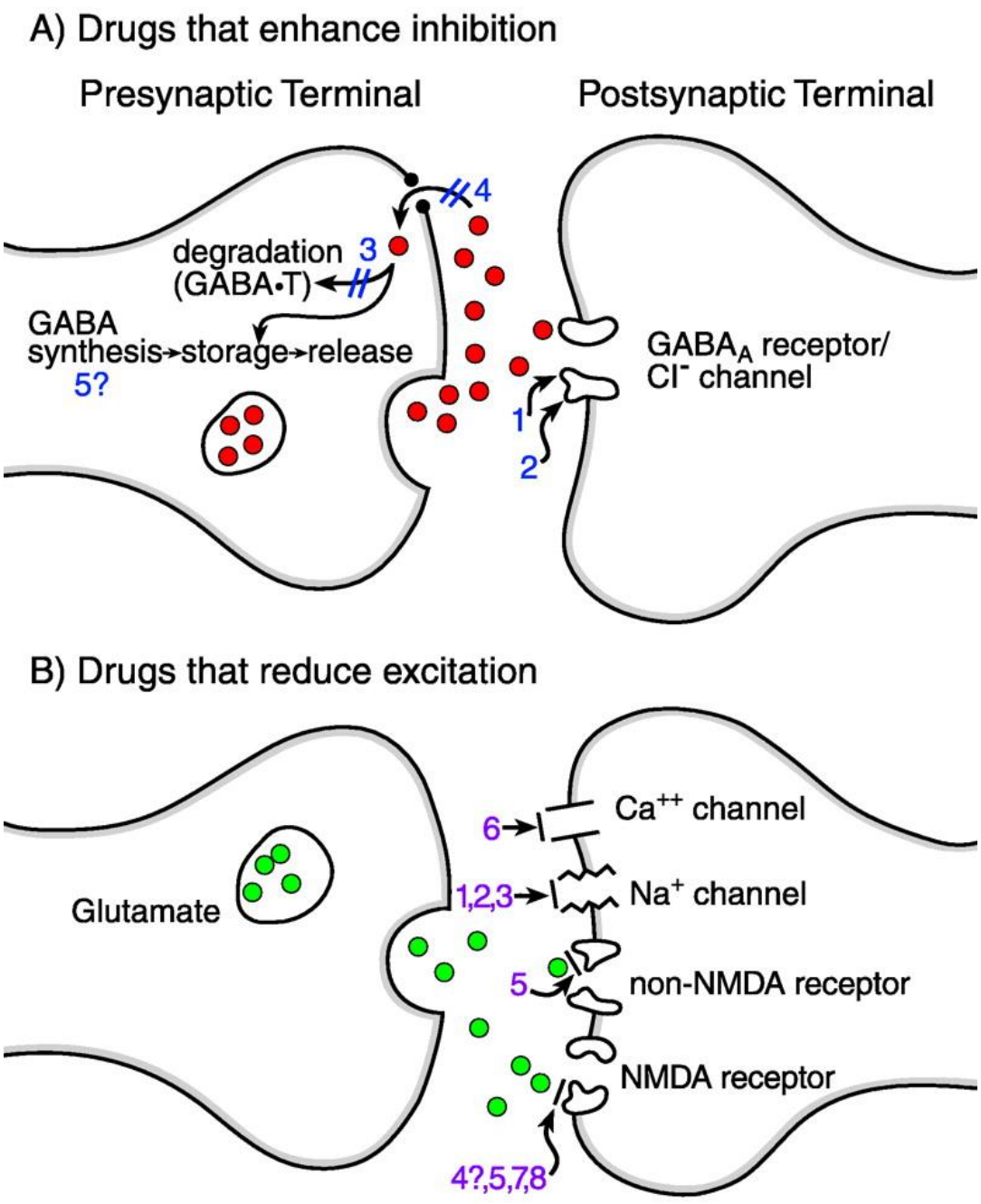
Agonist spectrum: GABA functions to open Cl^- channels and hyperpolarize/inhibit the cell. GABA-A receptor is *allosterically modulated* by many substances which have no intrinsic GABA activity of their own. These substances increase the action of GABA at the receptor. Positive agonists include BZD, barbiturates, and alcohol. Inverse agonists, conversely, would create the opposite effect of GABA (anxiety provoking). Antagonists (like flumazenil) serve to knock agonists off the receptor, returning it to resting state. Partial agonists may have less sedation and dependency than full agonists.

Receptors: GABA-A (ionotropic) and GABA-B (GPCR)

- GABA-A: ionotropic transmembrane Cl^- channel that is opened on receptor activation, and results in hyperpolarization of the neuron (suppressed excitability). Has 5 classes of polypeptide subunits (α, β, δ, ε, γ). Benzodiazepines binding to the α_1 subunit results in sedation, while binding to the α_2 subunit is anxiolytic. Possible drug design: α_2-specific ligand, resulting in anxiolysis without SE profile
- GABA-B: GPCRs that inhibit adenylyl cyclase, open K^+ channels, and close Ca^{2+} channels. Also function as autoreceptors. No allosteric modulation of this receptor. Is not closely linked to anxiety disorders or anxiolytics



Actions of Antiepileptic Drugs



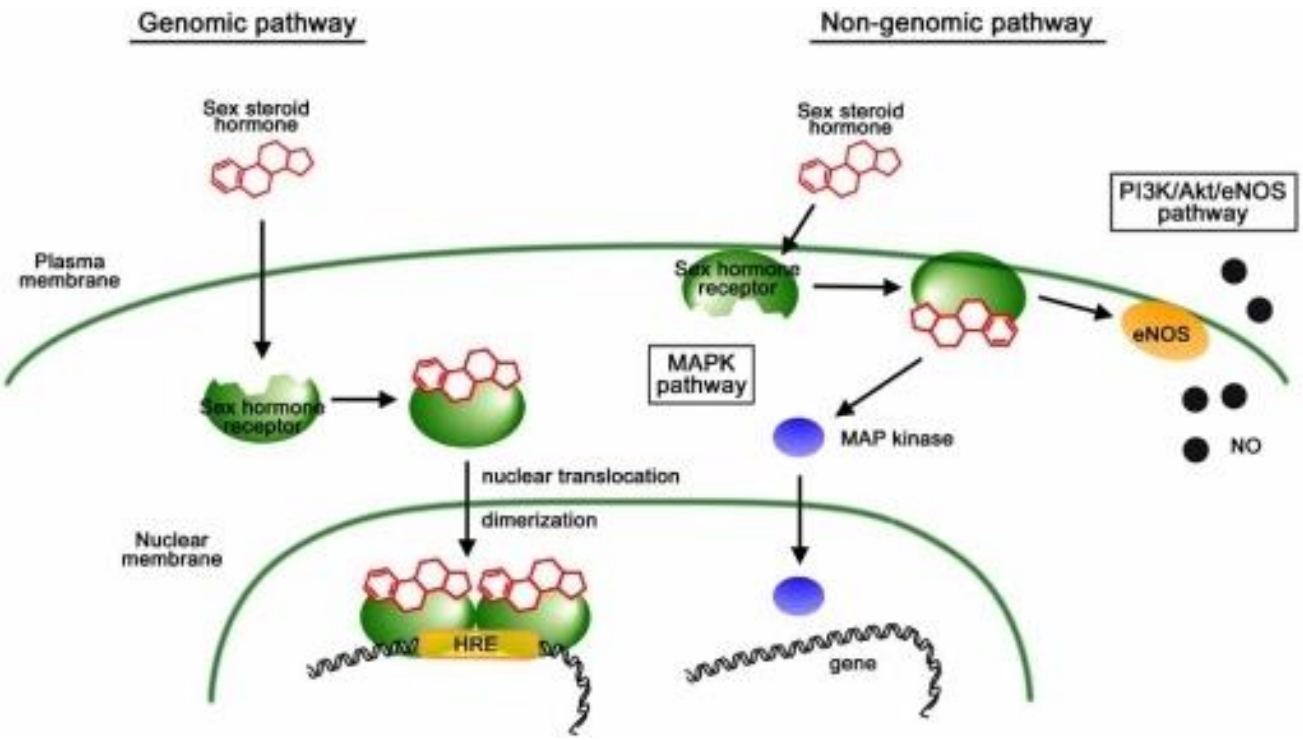
A) Drugs that enhance inhibition
1. phenobarbital
2. benzodiazepines
3. vigbatrin
4. tiagabine
5. gabapentin

B) Drugs that reduce excitation
1. phenytoin
2. carbamazepine
3. lamotrigine
4. felbamate
5. topiramate
6. ethosuximide
7. ketamine
8. Mg^{++}

Nuclear Hormones

Mechanism: lipophilic hormones are able to permeate the neuron membrane and bind to an intracellular receptor. This receptor-ligand complex passes into the nucleus and binds to hormone-specific DNA sequences, leading to gene transcription. Nuclear receptors are regulated by accessory proteins that serve as *nuclear receptor coregulators*, which either activate transcription factors (coactivators) or inhibit transcription factors (corepressors).

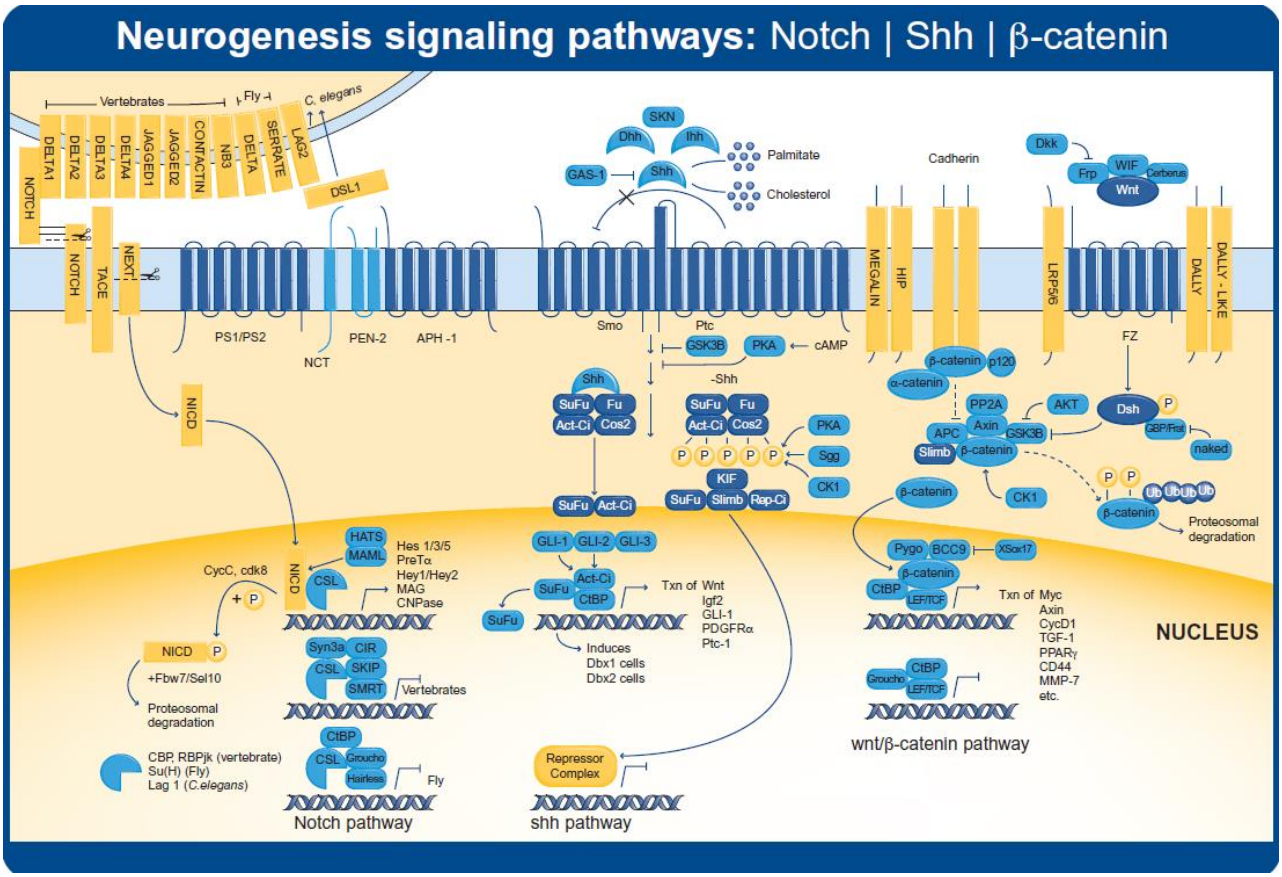
Non-genomic Effects: steroid hormones are also involved in modulating receptors, channels, and second messengers. Estrogen rapidly inhibits Ca^{2+} channels in neurons. There is crosstalk between nuclear receptors and GPCRs, thus gonadal steroids can modulate monoaminergic neuron receptors. *Neuroactive steroids* can both interact with their nuclear receptor, and alter neuron excitability by interacting with other receptors. Many neuroactive steroids can allosterically enhance GABA-A. Thus, a number of neuroactive steroids possess sleep enhancing, anticonvulsant, anxiolytic, and neuroprotective properties. Finally, neuroactive steroids play a role in psychiatric symptoms during pregnancy and the postpartum period.



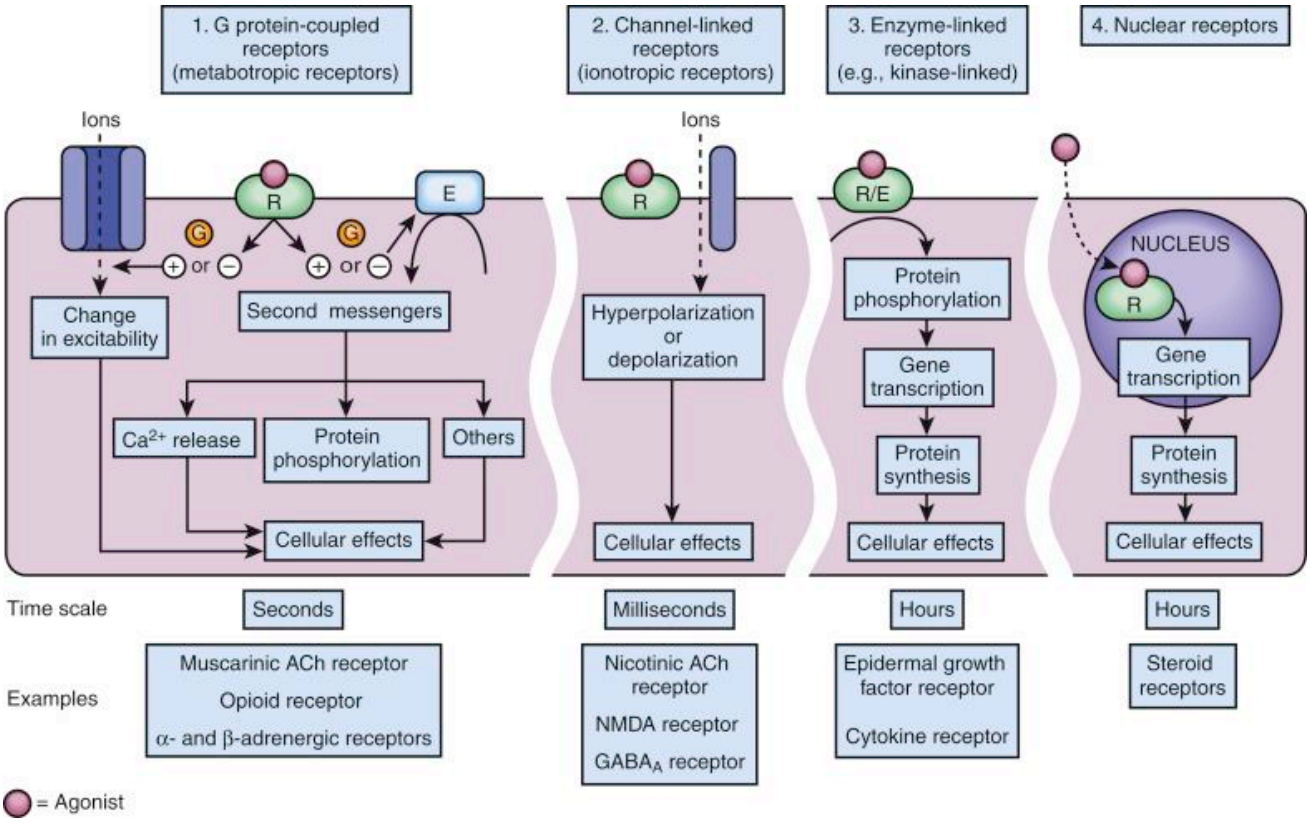
Signal Transduction Pathways

Signal transduction is the result of neuroactive molecules binding with receptors, leading to stimulation or attenuation of cellular signaling pathways. This stimulation vs. attenuation is the result of type of receptor, location in CNS, and activity of other nearby signaling pathways in the cell. Signals can converge onto one pathway or diverge into multiple pathways. Activation of signal pathways leads to gene transcription and activity of proteins (ion channels).

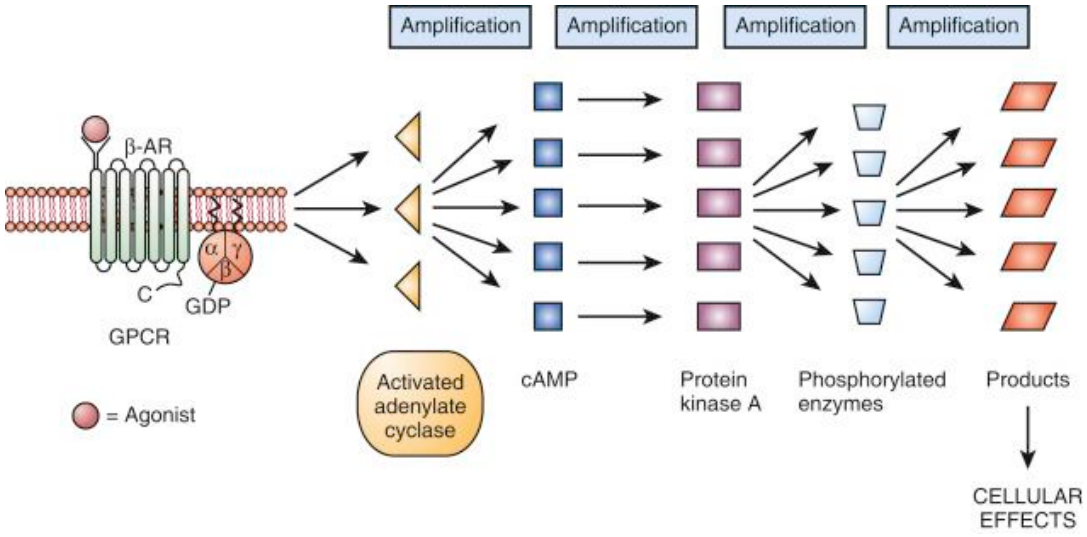
This guide will provide a BASIC overview of a few important signal transduction pathways. At NO time will things get this complicated:



Pathways Overview



Signal Amplification



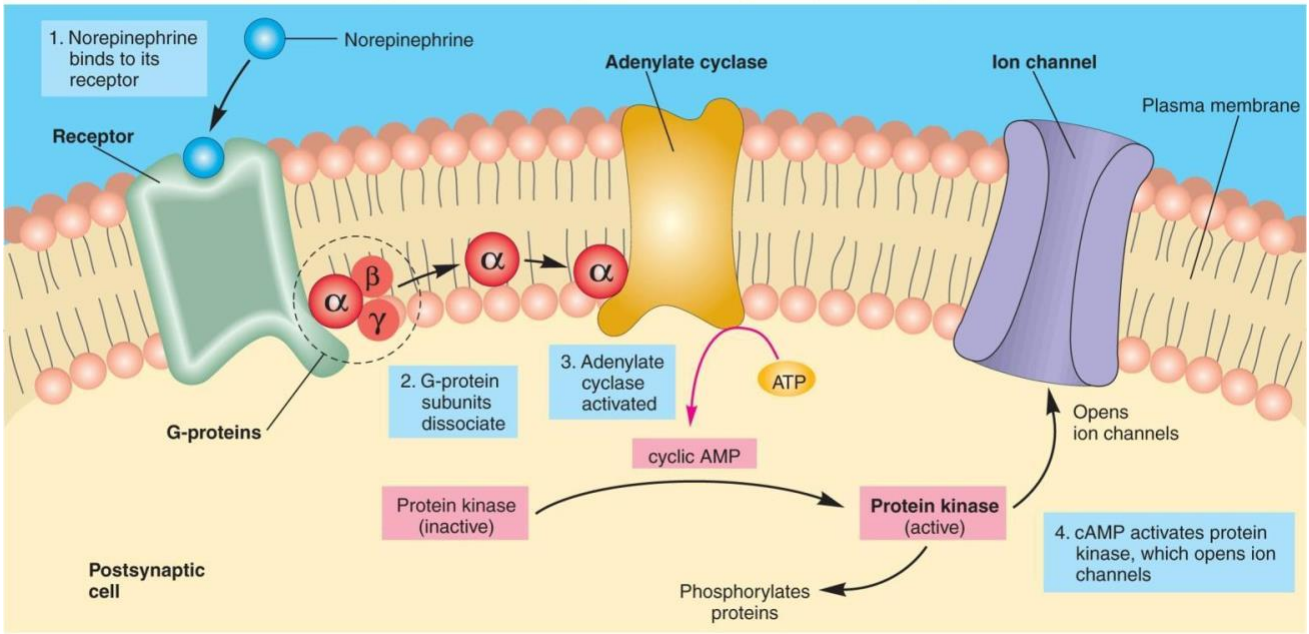
G proteins

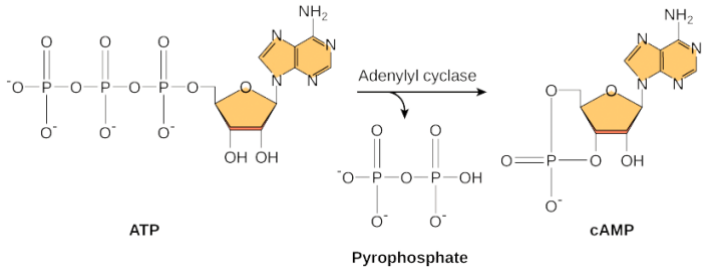
Membrane bound "molecular switches" inside cells, turning pathways off and on.

Function: G proteins *amplify signals* and form a complex information processing network in the plasma membrane. They interact and integrate signals from multiple receptors. Abnormalities in G protein signaling cascades are likely related to human disease.

Subtypes: G proteins are composed of a heterotrimer of α, β, and γ. The β and γ subunits pretty much serve to anchor the α subunit to the membrane. The α subunit can stimulate adenylyl cyclase (Gαs), inhibit adenylyl cyclase (Gαi), activate PLC (phospholipase C) (Gαq), or regulate G protein signaling.

Example Pathway: ligand binds receptor → activates Gαs → activates enzyme adenylyl cyclase → converts ATP to cAMP. From there, cAMP activates a protein kinase → phosphorylates a transcription factor → genetic transcription. This may lead to increased expression of BDNF, generation of more receptors, and many other intracellular processes.



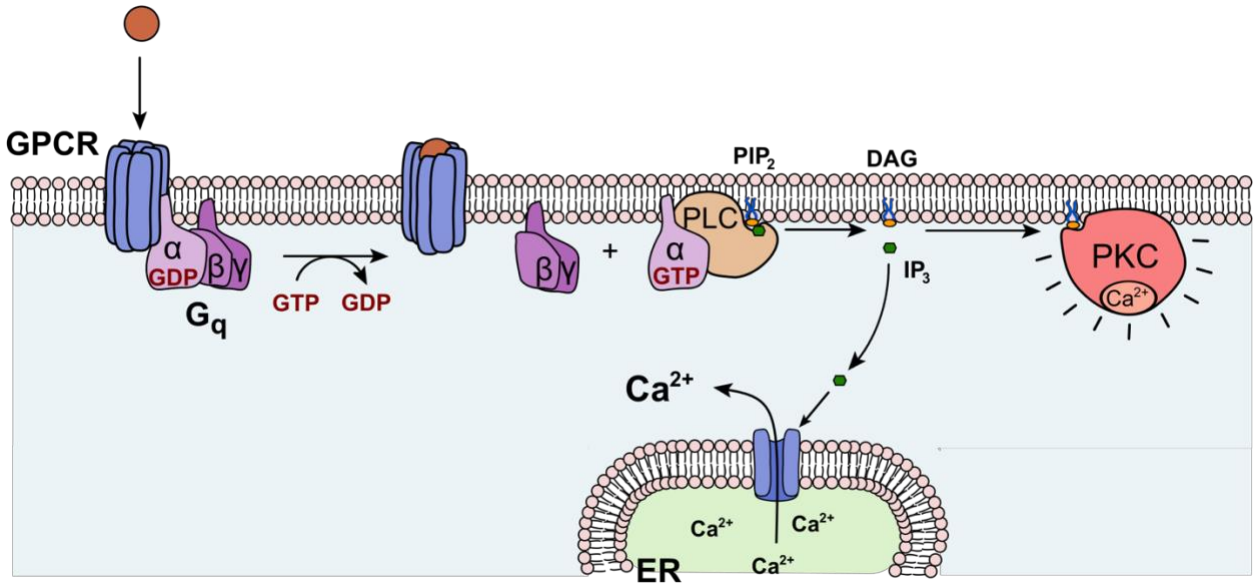


Protein Kinase C (PKC):

Kinases are enzymes which transfer phosphate groups from ATP to substrates. Phosphorylation leads to enhancement or inhibition of the substrate. Common substrates in signal transduction include enzymes, transcription factors, and receptors.

Production: ligand → binds GPCR → activation of Gα subunit → binds to and activates phospholipase C → cleaves PIP2 phospholipid to the second messengers IP_3 and DAG. DAG activates PKC. Most PKC isoforms are Ca^{2+} dependent.

Function and Pathology: PKC is associated with helping maintain the cytoskeleton (related to neural plasticity) and regulating NRT release through regulation of Ca^{2+} influx and coordinating interaction between vesicles and Ca^{2+}. Postmortem evaluations of PKC show elevated PKC isoforms in bipolar patients.



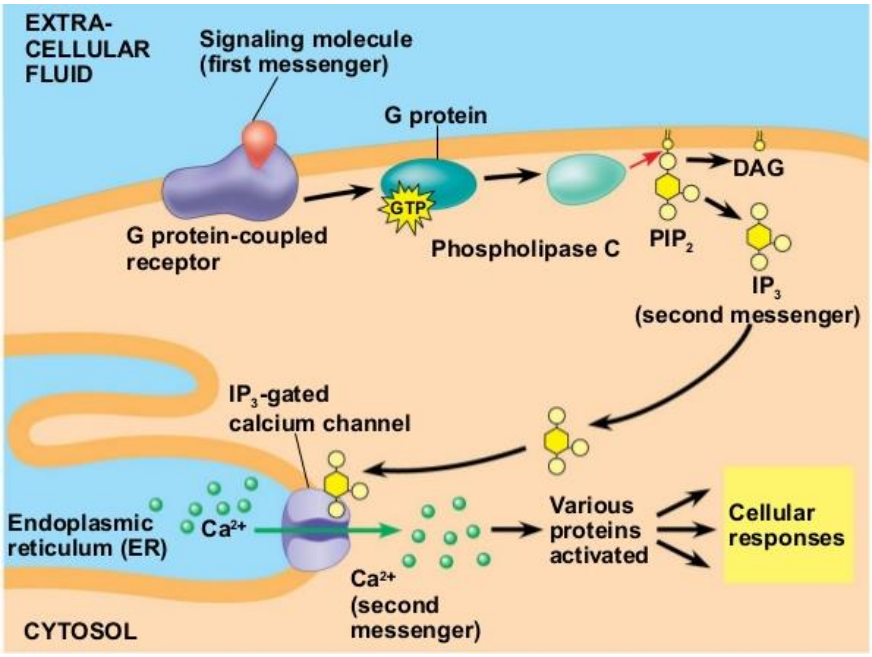
Phosphoinositide

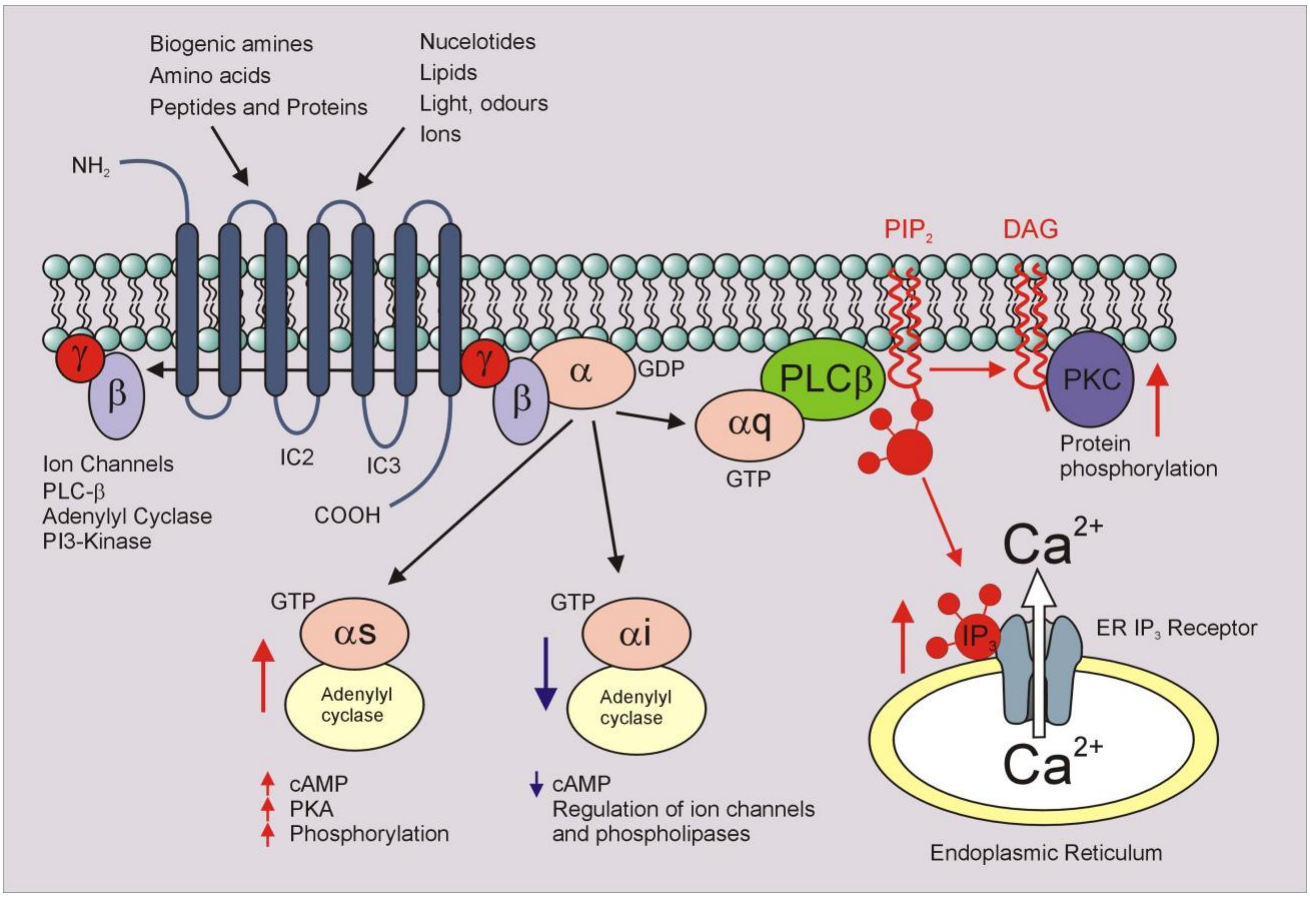
Inositol phospholipids are components of the cell membrane. In addition, they play a role in receptor-mediated signal transduction pathways. They are involved in cell division, secretion, excitability, and neuronal responsiveness.

Production: ligand → binds GPCR → activation of Gα subunit → binds to and activates phospholipase C (PLC) → cleaves the phospholipid PIP_2 to the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG).

Second Messengers

- IP_3: binds to an intracellular IP_3 receptor and facilitates release of intracellular/endoplasmic reticulum stores of Ca^{2+}. The Ca^{2+} interacts with proteins called calmodulins, which activate protein kinases. These calmodulin-dependent protein kinases lead to changes in signal molecules, ion channels, apoptosis, scaffolding, and transcription molecules. IP_3 is metabolized by inositol monophosphatase (IMPase) to PIP_2. PIP_2 can then be recycled back to IP3 and DAG. Inhibition of IMPase leads to depletion in recycled IP3 and DAG. *Lithium inhibits IMPase* to decrease the symptoms of acute mania (downstream effects on protein kinase C [PKC])
- DAG: activates PKC through binding to a regulatory site on PKC and increasing Ca^{2+} affinity. PKC is involved in activating transcription factors and is involved in the arachidonic acid pathway to form prostaglandins and thromboxanes, which mediate transynaptic and intracellular responses





Calcium

Functions: $Ca^{2+}$is mobilized from intracellular stores (endoplasmic reticulum, released by IP_3) or enters the cell via plasma membrane ion channels (e.g., NMDA). Ca^{2+} leads to activation of enzymes, signaling cascades, and cell death. Proteins bind to $Ca2^{+}$, including calcium pumps, calmodulin, PKC and phospholipase A_2. Elevated intracellular Ca^{2+} can lead to excessive activation of some systems and inhibition of others.

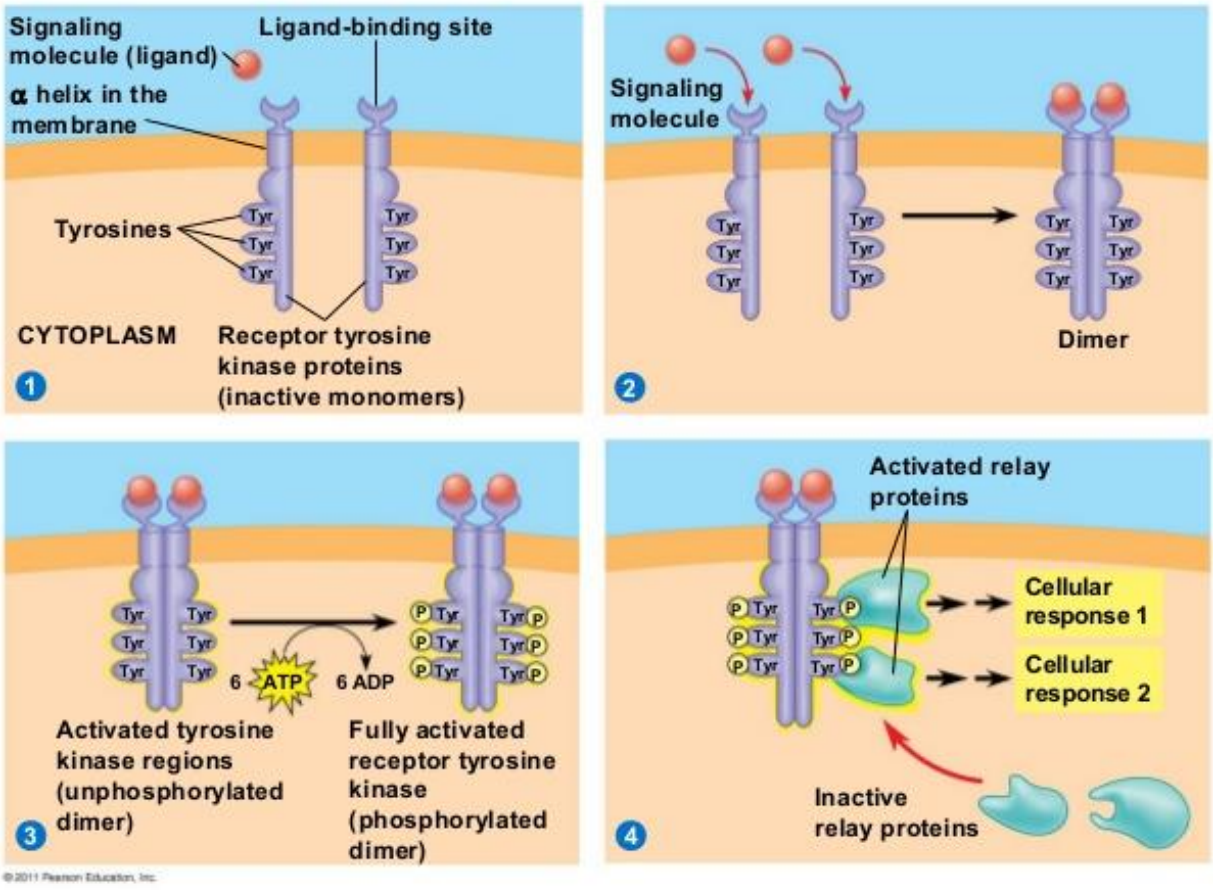
Neurotrophic Receptor Signaling Cascades

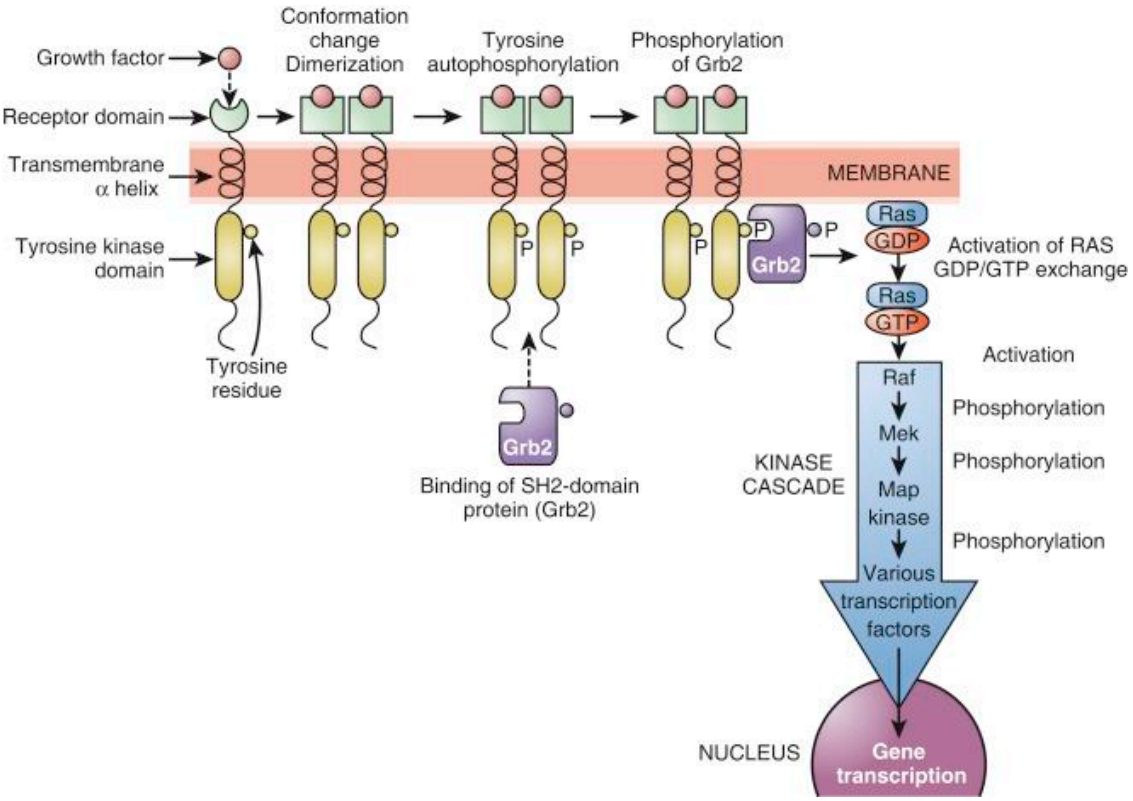
MAP-Kinase (mitogen-activated protein kinase) Signaling Pathway: involved in associative learning, classical conditioning, spatial memory, and LTP. A neurotrophic factor (like BDNF) binds to Trk (tyrosine receptor kinase), leading to phosphorylation of Trk. GTP is used to activate Ras, a small GTP-binding protein.

Functions of Ras

- Activates the phosphoinositol-3-kinase (PI3K) system: deactivates glycogen synthase kinase-3 (GSK-3), which is pro-apoptotic. *GSK-3 is the only kinase to be directly inhibited by Lithium*. Inactivation of GSK-3 blocks apoptosis and activates transcription factors
- Activates a cascade of kinases: results in gene transcription of anti-apoptotic factors and BDNF. This pathway also phosphorylates an apoptotic protein, deactivating it

Figure 11.7c




Growth factor
Receptor domain
Transmembrane α helix
Tyrosine kinase domain
Tyrosine residue
Conformation change Dimerization
Tyrosine autophosphorylation
Phosphorylation of Grb2
MEMBRANE
P
Grb2
Binding of SH2-domain protein (Grb2)
Ras
GDP
Activation of RAS GDP/GTP exchange
Ras
GTP
Activation
Raf
Phosphorylation
Mek
Phosphorylation
KINASE CASCADE
Map kinase
Phosphorylation
Various transcription factors
NUCLEUS
Gene transcription

Some Recommended Textbooks to Pick Up

Textbook of Psychopharmacology. 5th ed. Schatzberg AF and Nemeroff CB. (2017) Washington, D.C., American Psychiatric Publishing.

Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. Stahl, SM (2008). Cambridge, UK, Cambridge University Press

Essential Psychopharmacology: The Prescriber's Guide. 6th ed. Stahl SM. (2008) Cambridge, UK, Cambridge University Press

Drug Metabolism in Psychiatry: A Clinical Guide. Third ed. Daniel J. Carlat, MD

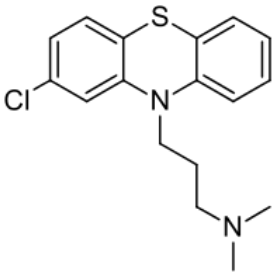
Kaufman's Clinical Neurology for Psychiatrists. 8th ed. (Major Problems in Neurology). David Myland Kaufman MD; Howard L. Geyer; Mark J Milstein MD. (2016) Elsevier

A NINJA'S GUIDE TO PSYCHOPHARMACOLOGY

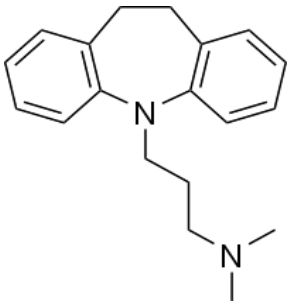
Antipsychotics

Typical Antipsychotics

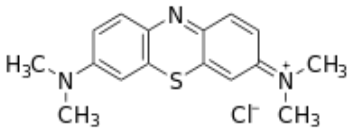
Phenothiazines are compounds derived from the original parent drug, methylene blue. This chemical is used in histologic staining, analytic chemistry, and as an antimalarial medication (as early as 1891). During WW2 methylene blue's use as an antimalarial due to lack of access in the Pacific tropics and side effects of turning urine green and sclera blue. The antihistamine properties of methylene blue were found to be helpful as anesthetic agents. In 1951, French surgeon Laborit asked a pharmaceutical company to create a specialized phenothiazine to reduce post-surgical psychosis. This medication was chlorpromazine. Shortly thereafter, the medication was used serendipitously in psychiatric patients to reduce psychosis. Through further research and development, a similar structure, imipramine was created. This medication was one of the first antidepressants.



Chlorpromazine



Imipramine



Methylene Blue

Indications: schizophrenia (improves positive symptoms, may worsen negative symptoms), acute mania, MDD with psychosis, hemiballismus, hiccups, Tourette's. High potency antipsychotics are better used in patients with psychosis due to tumor/organic causes. As they decrease seizure threshold, use with caution in ETOH detox. Low potency antipsychotics should be avoided in the elderly and medically ill due to multiple anticholinergic and cardiac side effects. Avoid use in 1st trimester (especially chlorpromazine); 2nd and 3rd trimester are safer. Contraindicated in cardiac patients, acute angle glaucoma, and patients with a history of TD.

Mechanism of Action: blockade of D2 receptors

- Mesocortical/mesolimbic: diminishes psychosis

- Tuberoinfundibular: increases PRL (DA decreases PRL; DA blockade increases PRL)
- Nigrostriatal: basal ganglia and caudate. Movement disorders including EPS, PD, tremor

Drug Interactions and P450: typicals are metabolized by 2D6 and 3A4, thus are increased in the presence of Prozac, Paxil and Luvox. They are reduced by coadministration with Tegretol. Antacids decrease the absorption of typicals. Anticholinergic delirium is possible in the presence of anticholinergic medications, low potency typical and TCA coadministration. Typicals increase blood concentrations of valproic acid. Cigarettes decrease blood concentrations of typical. Thus, if a patient is stabilized on a specific dose of a typical and quits smoking there is risk for EPS and other side effects.

Overview of Side Effects: EPS and non-EPS (anticholinergic, cardiac, sedation, etc). High potency antipsychotics have greater affinity for D2 receptors and have less spillover into other systems (muscarinic, cholinergic). As a result, the more prevalent symptoms are nigrostriatal. The term "extrapyramidal" refers to motor symptoms outside of those from motor cortex medullary pyramids spinal cord muscles. The extrapyramidal system works to modulate motor control through the reticular formation, nigrostriatal pathway, cerebellum, vestibular system, and anterior horn cells. EPS involves abnormal coordination of movement, including akathisia, akinesia, pseudoparkinson symptoms, and acute dystonia (muscle spasms).

Categories

- High Potency: fluphenazine (Prolixin), haloperidol (Haldol), thiothixine (Navane), trifluoperazine (Stellazine)
- Medium Potency: perfenazine (Trilafon), molindone (Moban), loxipine (Loxitane)
- Low Potency: chlorpromazine (Thorazine), thioridazine (Mellaril)

Extrapyramidal Side Effects (More Common in High Potency)

- Pseudoparkinson: bradykinesia, rigidity, masked face, cogwheeling, tremor. Women are 2x more likely. Treat with anticholinergics, Benadryl, or amantadine
- Dystonia: muscle spasms of jaw, tongue, eyes. Laryngospasms possible. More common in young males. Treat with anticholinergics or Benadryl
- Akathisia: pacing, restlessness, described as feeling the urge to move around or having "crawling" sensation under skin. Treated with propranolol, BZD, or clonidine
- Tardive Dyskinesia: occur about 6 months after initiation of the medication. Is related to increased sensitivity to DA due to receptor changes. Thus, appears to be closer to a movement disorder that occurs due to excess DA despite presence of DA blocking medication. Presents with abnormal muscular jerking of limbs, trunk and periorbital. Increases with stress. More common in older females. Treat by decreasing the medication or discontinuing. Anticholinergics worsen TD
- Neuroleptic Malignant Syndrome: fever, muscle rigidity, autonomic symptoms, increased CPK and acute mental status change. More common in males. Can be lethal. Treat with cooling, dantrolene or bromocriptine, and discontinue the inciting medication

Non-EPS Side Effects (More Common in Low Potency)

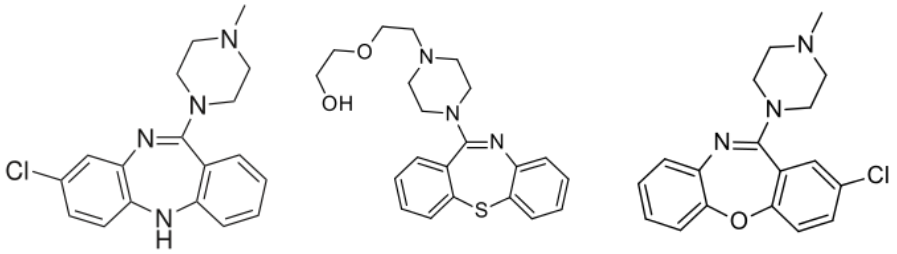
- Alpha Blockade: orthostatic hypotension
- Anticholinergic: dry mouth (treat with sugarless gum), constipation, sore throat, urinary retention (treat with bethanechol), blurred vision, confusion
- Antihistamine: weight gain and sedation
- Endocrine: prolactin causes sexual side effects like erectile dysfunction, priapism, increased time to ejaculation, gynecomastia, impotence, and anorgasmia
- Hepatic: jaundice and elevated LFTs (less severe than with atypicals)
- Cardiac: arrhythmia and prolonged QTc
- Hematologic: agranulocytosis (monitor for fever, sore throat)
- Neurologic: epilepsy due to lowered seizure threshold
- Dermatologic: skin discoloration and photosensitivity in chlorpromazine
- Opthomologic: retinitis pigmentosa and blindness in thioridazine

Choosing Between Typicals

- Cardiac patients: avoid low potency, especially thioridazine (Mellaril)
- Elderly: avoid low potency due to anticholinergic confusion
- Weight gain: molindone (Moban) and loxipine (Loxitane) have the least weight gain. High potency has less weight gain. Currently molindone is off the market due to lack of high volume clinical use
- Sexual side effects: most common in thioridazine (Mellaril)
- Sleep: chlorpromazine is a sedating typical and is a good choice for aiding sleep in a patient with mania or psychosis
- Mood: loxipine (Loxitane) has mild 5HT antagonism, making it similar to atypical. Additionally, it is metabolized to the TCA amoxepine. It is useful when a patient cannot get quetiapine or aripiprazole due to cost. DA blockade is similar to quetiapine and the mood component is like aripiprazole. Additionally, Stahl notes the use of loxipine for the augmentation of schizophrenia management with an atypical antipsychotic
- Compliance: Haloperidol has a depot formulation that lasts 3-4 weeks to ensure compliance. Fluphenazine (Prolixin) has a depot formulation that lasts 2 weeks. *Always do an oral test dose before giving a depot injection due to risk of irreversible EPS once depot is given*. Consider avoiding fluphenazine depot in med-naïve young muscular males due to EPS risk
- Dysphagia: Haloperidol has a liquid formulation to aid in ease of administration and an IV formulation. Reminder that IV formulations are much higher potency due to lack of first pass in the liver. Thus, start with lower doses than would use in PO or even IM (2-5mg IV)

Atypical (Second Generation) Antipsychotics

Due to the prevalence of EPS with typical antipsychotics, the atypicals were created. If excessive DA blockade leads to EPS, then less severe DA blockade would cause less EPS. The best way found to modulate the amount of DA blockade was through 5HT. Normally, serotonin binds to 5HT receptors on DA neurons and inhibits DA release. By blocking these 5HT receptors, DA release is not inhibited. The combination of DA receptor blockade plus 5HT blockade (less inhibition) leads to a net increase in free DA compared with straight DA blockade in the typicals. Thus, the atypicals have less EPS. Additionally, they better treat the negative symptoms of schizophrenia than the typicals do. However, the atypicals appear to have more metabolic side effects (weight gain, diabetes) than the typicals do due to effects on other receptors. Additionally, the atypicals may have more liver effects and leukopenia than the typicals do. The majority of the atypicals are also approved by the FDA for treating bipolar mania and monotherapy for bipolar disorder.



Clozapine **Quetiapine** **Loxapine**

Clozapine (derived from imipramine, a dibenzazepine) is a dibenzoxazepine. Other dibenzoxazepines are quetiapine and loxapine. These medications all improve mood in addition to psychosis.

Risperidone (Risperdal): the first atypical to become generic, thus lower cost. In addition to mania and psychosis, it is approved for the treatment of aggression and self-injurious behavior in autistic children. It can be used in children with tic disorders (consider also using haloperidol) or impulsive/disruptive behaviors. Half-life is 20 hours; thus once-daily dosing is fine. Equivalent to haloperidol in D2 binding affinity with less incidence of EPS when kept below 6 mg per day. Minimal alpha and muscarinic affinity. Has an active metabolite that is formed by 2D6, thus inhibiting 2D6 (paroxetine, fluoxetine) leads to less efficacy of risperidone. Has most prolactin increase of all antipsychotics. Watch for pedal edema and increased LFTs. Weight gain is #3 after clozapine and olanzapine. Formulation includes pill, dissolving M-Tabs, and Risperdal Consta (depot preparation lasting 2 weeks, but need oral risperidone x3 weeks after start Consta. Useful in severe OCD, impulse control issues, and body dysmorphic symptoms.

Paliperidone (Invega): the isolated active metabolite of risperidone (i.e., risperidone is converted to Paliperidone in the liver normally), which may be a better choice in hepatically impaired patients. While it is considered to have less side effects than risperidone, paliperidone has more QTc prolongation and requires lower dosing in renal impaired patients (as it is excreted unchanged through the kidneys). It exists as an immediate release and a delayed release medication (avoid in gastric bypass) and also occurs in a depot formulation (Sustenna). Sustenna requires no continued oral dosing once the depot is given. Injection into deltoid has nearly 30% higher plasma concentration that gluteal. Most likely is a "me too" drug with no major benefit over risperidone, but depot formulation has best evidence for avoiding hospital readmission.

Olanzapine (Zyprexa): half-life averages 31 hours, leading to once-daily dosing is fine. Metabolized by 1A2, thus fluvoxamine, cimetidine, and ciprofloxacin increase olanzapine concentrations (inhibitors of 1A2), while carbamazepine reduces olanzapine. Weight gain and metabolic side effects are common (#2 after clozapine). Can be very sedating and alcohol coadministration leads to an increased olanzapine absorption by 25%, worsening sedation. Became generic in late 2011. Studies show best oral adherence despite SEs. Formulation includes pill, dissolving Zydis tabs, IM, and depot Relprevv (injections q 2-4 weeks), however it requires monitoring due to Post-Injection Delirium/Sedation Syndrome.

Quetiapine (Seroquel): half-life is 7 hours, thus BID or TID dosing is recommended. While it has less EPS than other atypicals, it is sedating and has weight gain. Is used off label for the management of anxiety, PTSD and sleep. Has orthostatic hypotension commonly. Has an XR formulation with equivalent bioavailability. Dilantin increases Quetiapine's clearance 5-fold, thus consider higher dosing in patients on Dilantin. Weight gain appears to be somewhat dose dependent. If using it for sleep, once exceeding 200mg consider changing to another medication for sleep, like Trazodone, Vistaril or Doxepin. Additionally, because the weight gain is metabolic in origin, telling the patient that the medication will cause weight gain due to appetite increase alone is inaccurate. It is important to have the patient monitor their weight while on most of the atypicals.

Ziprasidone (Geodon): half-life is 5-10 hours, thus BID dosing needed. Bioavailability doubles when taken with food, preferably a 500-calorie meal. Due to 5HT1A agonism and SSRI/SNRI properties, it has some benefit in treating or augmenting depression treatment. Has less weight gain and EPS than other atypicals. Common side effects include sedation and QTc prolongation (more than other atypicals). Ziprasidone has BID dosing and exists as a capsule (cannot be broken in half), liquid, and IM. While ziprasidone is not a highly potent atypical, it is useful in treating MDD with psychosis.

Clozapine (Clozaril): likely the most effective antipsychotic. Half-life of 12 hours. Considered to have higher affinity for limbic than striatal areas, compared with atypicals. Is metabolized primarily by 1A2 (increased in presence of fluvoxamine or ciprofloxacin). Side effects include severe sedation, weight gain, sialorrhea, agranulocytosis, QTc prolongation, and requires weekly blood draws for 6 months to monitor the ANC. Dosing is held if WBC <3000 or granulocytes <1500. Additionally, this medication is only dispensed at certain pharmacies and requires proof of labs to dispense. There is a national clozapine registry where all patients on the medication are followed and their labs reported. In order to start clozapine, the patient's information must be given to the registry and pretreatment labs must be normal (lipids, CBC with ANC, Chem 13 and EKG). The risk of agranulocytosis is <1% in the first year of treatment with clozapine. The risk of TD is incredibly low and it is the best treatment for psychosis that has not responded to other agents. It occurs in pill and dissolving tablet formulations and is BID dosing. Dosing starts at 25mg BID and can increase by 25mg per day maximum. Sialorrhea may respond to clonidine. Like risperidone, is generic. Lithium can be used to raise the ANC in order to help with clozapine titration. A simple dosing of 600 mg at night of Li can help improve the ANC enough to start or continue clozapine.

Aripiprazole (Abilify): unlike the other atypicals, is a D2 partial agonist, competing with endogenous DA (both postsynaptic and presynaptic) and binds less robustly. This is considered to be modulation of the DA receptor rather than blockade. The net result is diminished DA activity in the limbic system (which is elevated in schizophrenia) and increased DA activity in the frontal and prefrontal areas (which is considered low in schizophrenia). In addition to mania and psychosis, it is indicated for augmentation of depression treatment. The half-life is about 75 hours; thus once-daily dosing is fine. Metabolized by 3A4 and 2D6. Is a strong 5HT2C agonist (unlike the other atypicals), which means less weight gain. It is also a strong 5HT-7 antagonist, improving mood. Side effects include akathisia, orthostatic hypotension (alpha blockade), nausea/GI effects, somnolence or insomnia.

Asenapine (Saphris): like clozapine, has higher affinity for D3 and D4 receptors than D2 receptors. It has minimal anticholinergic side effects. Is associated with akathisia, dizziness, sedation, and weight gain (histamine affinity). Metabolized by 1A2 and is dosed BID in a sublingual formulation. The patient may not eat or drink for 10 minutes after dosing. Preliminary drug company data reports results from 1,500 patients but there is paucity of published data on actual efficacy (the main published study only evaluated 174 patients). Thus, asenapine has weight gain, sedation, must be dosed sublingually, and is very expensive. There is limited published data on the efficacy on this medication as compared with other atypicals.

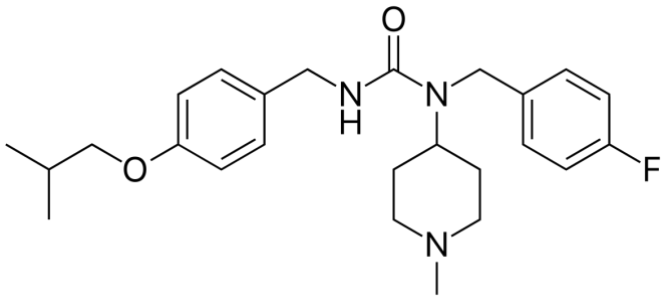
Iloperidone (Fanapt): not structurally related to any other atypicals. Has mixed D2 and 5HT2 antagonism with low affinity for histamine and muscarinic receptors. Metabolized by 2D6 and 3A4 and the half-life varies between 18-37 hours based on the strength of 2D6 enzymes (longer half-life in poor metabolizers). Avoid in hepatic impairment. Prolongs QT interval as much as ziprasidone. It is also associated with orthostatic hypotension (alpha blockade), dizziness, and somnolence. Iloperidone has minimal weight gain. Prolactin is increased in over 25% of patients. Due to risk of orthostatic hypotension, dosing must be gradual over 4 days in BID scheduling. Considering that this medication was first in trials in 1998 and took over 10 years to be released after moving between multiple drug companies, likely due to subpar efficacy results. The bottom line: this medication is similar to ziprasidone in QTc prolongation with less akathisia but more weight gain. It must be titrated slowly due to orthostatic hypotension and many studies do not show it to be any better than existing atypicals.

Lurasidone (Latuda): strong D2/5HT2 antagonist with minimal histamine interaction (thus low weight gain). It does have sedation, which may be related to strong 5HT-7 antagonism (see below). Metabolized by 3A4. There are only four 6-week trials of this medication submitted to the FDA, thus the clinical data is limited. One study suggested that it upregulates BDNF in the prefrontal cortex, suggesting that the medication may be "pro-cognitive." Has once-daily dosing, but must be taken with food to be absorbed. Minimal weight gain, no QTc issues. EPS is equivalent to other atypicals. Further data on lurasidone efficacy will show if this medication is a "me too" medication.

A note on 5HT-7: some of the new antipsychotics are boasting 5HT-7 antagonism. While not fully understood, the 5HT-7 receptor may be associated with depression. Medications that block 5HT-7 improve depression. Additionally, they may improve hippocampus-mediated actions, like memory. Many of the atypicals (risperidone, ziprasidone) are potent 5HT-7 antagonists.

Newer Antipsychotics

Nuplazid (pimavanserin)



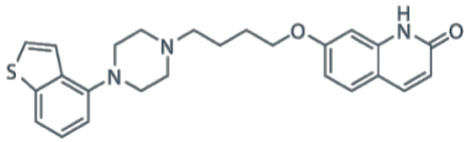
Indication: FDA approved in 2016 for psychosis within the context of Parkinson's Disease. Unlike other antipsychotics, Nuplazid reduces hallucinations without worsening parkinsonism

Dosing: recommended 34 mg once daily with or without food, no titration needed. No dose adjustment of carbidopa/levodopa is required

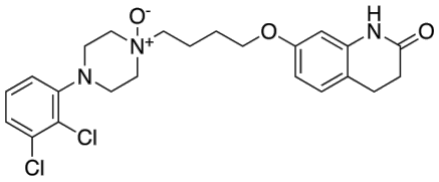
Profile: non-dopaminergic atypical antipsychotic, inverse agonist and antagonist activity at serotonin 5HT2A receptor. While traditionally we think of treatment of hallucinations by D2 blockade, in PD this mechanism substantially worsens the underlying movement disorder. Placebo-controlled trials support the use of clozapine (at a miniscule dose of 6.25-75 mg/day) to treat PD psychosis (PDP). A dose that low is not expected to do much DA blockade, and another mechanism has been proposed. Clozapine blocks 5HT2A receptors, reducing PDP. Wait, 5HT2A receptors? Consider that the mechanism for LSD induced hallucinations is through cortical 5HT pathways. Pimavanserin works as an antagonist and inverse agonist specifically at 5HT2A receptors. There is minimal binding at 5HT2C and no appreciable affinity for 5HT2B, dopaminergic (including D2), muscarinic, histaminergic, or adrenergic receptors.Pimavanserin is highly protein bound (~95%) in human plasma. Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5.

Side Effects: Nausea (7%), Constipation (4%), Peripheral edema (7%), confusional state (6%), possible QTc prolongation

Rexulti (brexpiprazole)



Brexpiprazole



Aripiprazole

Indication: schizophrenia and adjunctive treatment for depression

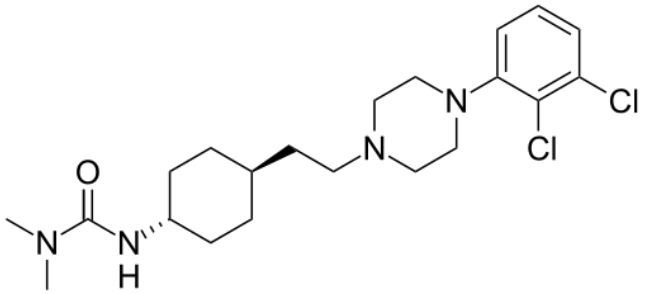
Dosing: start at 0.5mg-1mg once daily and titrate. For schizophrenia: 2–4 mg once daily. For depression: 2 mg once daily. Can be taken with or without food.

Profile: related to aripiprazole, is also a D2 partial agonist, along the agonism spectrum. It is closer to the antagonist end than aripiprazole. Is also a partial agonist at serotonin 1A receptors (improve mood and cognition). Acts as a 5HT-2A receptor antagonist (see Nuplazid). Also potentiates nerve growth factor. Metabolized primarily by CYP450 2D6 and CYP450 3A4.

Side effects: weight gain and dose-dependent akathisia. Others include upper respiratory infection, nasopharyngitis, somnolence, tremor, fatigue, headache, hyperglycemia, theoretical risk of tardive dyskinesia, NMS (rare), seizures (rare)

Pregnancy: In animal studies, brexpiprazole did not demonstrate teratogenicity. There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester. In the newborn, symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding.

Vralyar (cariprazine)



Indication: schizophrenia and bipolar 1- manic/mixed episodes

Dosing: starting dose 1.5 mg, max 6 mg per day for both BMD and Schizophrenia. Has the longest half-life of the atypical antipsychotics, half-life of 2-4 days with an active metabolite that has a half-life of 1-3 weeks.

Profile: D2 partial agonist like aripiprazole and brexpripazole, unique high affinity for D3 receptors. D3 agonism is associated with wakefulness, thus partial agonism is associated with the treatment of mania. Additionally, effects at D3 may be precognitive and diminish negative symptoms of schizophrenia. Also has high affinity for the serotonin 1A (partial agonist) and moderate affinity for the serotonin 2A receptor (antagonist). Metabolized by CYP450 3A4.

Side effects: akathisia, EPS, may cause dose-dependent weight gain, GI symptoms (N/V), sedation

Mood Stabilizers

The basic mechanism of action of the mood stabilizers is to enhance the actions of GABA and reduce the actions of glutamate. In this way, both seizures and mood swings are controlled. Additionally, mood stabilizers can be used to aid in the treatment of anxiety for similar reasons. Lithium is the first known mood stabilizer, and is mechanistically different from the others in that it does not also treat seizures.

Regarding historic serendipity, lithium was first used in the 1800s for the treatment of gout. It was known to help dissolve urate, a particle initially blamed for mania and psychosis. Around 1900 lithium was abandoned for the treatment of mania and was not rediscovered until 1949 by Australian psychiatrist Henry Cade. Due to understanding that disorders such as thyrotoxicosis could be detected by metabolites in urine, Cade examined manic patients ' urine for detectable particles related to mania. His study focused on injecting guinea pigs with manic patient urine to see if behavioral disturbance occurred. Long story short, the guinea pigs he was injecting with manic patients ' urine kept dying so he decided to add lithium to the urine to help break down urate. Ultimately, he discovered that lithium alone led to calming of mania.

The FDA did not approve the use of lithium for the treatment of mania until 1970. Strangely, in the 1930s - 50s if you wanted to have access to lithium, it was most easily found as a common replacement for table salt in patients with heart disease OR in 7-UP. Seriously. Originally labeled as "Bib-Label Lithiated Lemon-Lime Soda," 7-UP containing lithium was marketed specifically as a hangover cure.

Valproic Acid was first synthesized in 1882 from valerian as a solvent for organic compound that was believed to be inert metabolically. By the 1960s it was discovered that medications that had long been considered anticonvulsant had no ability to prevent seizures and that the valproic acid solvent had been the active treatment.

Lithium

Indications: approved for acute and maintenance treatment of mania in addition to adjunctive treatment for depression. It is less useful in rapid cycling or mixed episodes than valproic acid (VPA). Additionally, data shows reduction in risk of suicide in patients treated with lithium. It can be used in pregnancy and although it has a risk of Ebstein's abnormality when used in the first trimester, this risk is relatively minimal (general population: 1/20,000; Li: 1/1,100, or 0.1%). This risk reduces after the first trimester and must be considered against a 5% risk of neural tube defect with VPA and the risk of danger to the patient and fetus if mania continues untreated. Thus, after the first trimester, lithium is the mood stabilizer of choice for mania in pregnancy.

Profile: it does not bind to proteins, is not metabolized, and is excreted in the kidneys. Half-life is 18 to 24 hours with steady state reached in about 5 days. Dosing should start at 300 mg BID or TID and plasma trough drawn after 5 days of continuous dosing. Formulation includes immediate release lithium carbonate, 450 mg extended release tabs (Eskalith), and liquid lithium citrate. Therapeutic level aims for 0.8-1.2 and can be dosed BID or TID (or once daily with Eskalith). Prior to starting lithium, baseline CBC, Chem 13 (including renal function), TSH, EKG and HCG should be done.

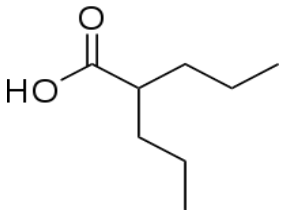
Side effects: include nausea/vomiting, sedation, weight gain, tremor (treat with propranolol), hypothyroidism (15% female, 4% male; If lithium is helpful, consider use of levothyroxine to treat hypothyroidism), renal tubular damage, bradycardia, AV block, sexual dysfunction (due to increased 5HT), alopecia, acne and neurologic symptoms including confusion, coma, stupor, and death in the case of toxicity. Regarding renal symptoms, lithium is associated with Nephrogenic Diabetes Insipidus where lithium antagonizes the effects of ADH in the distal kidney. The symptoms include polyuria and polydipsia and ultimate renal failure if not resolved. The primary treatment is discontinuation of treatment or addition of HCTZ (thiazide diuretic). This is counterintuitive as thiazides are diuretics and should increase water loss. It is postulated that lithium causes the distal kidney aquaporins to be downregulated and lose sensitivity to ADH. Thiazides, in addition to effects on Na in the proximal kidney, increase expression of distal aquaporins, thus reversing the effects of lithium (Loffing et al). Because HCTZ decreases NA reabsorption, it ultimately leads to increased lithium absorption (a positive ion) and can be associated with lithium toxicity. Thus, lithium coadministered with HCTZ must be decreased in dose.

Drug Interactions: lithium toxicity is more common in the presence of NSAIDs, diuretics, ACE- Inhibitors, hyponatremia, and dehydration. Treat lithium toxicity with dialysis, gastric lavage or kayexalate, not charcoal. Caffeine is known to decrease lithium by enhancing its renal clearance. Stopping caffeine leads to worse lithium tremor from higher plasma concentration. Lithium combined with SSRIs can cause serotonin syndrome.

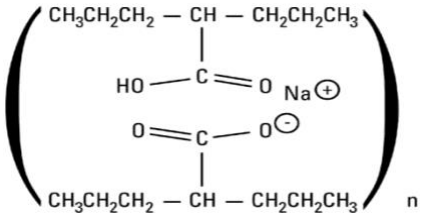
Valproic Acid

Indications: acute mania (including rapid cycling and mixed episodes), mania secondary to traumatic brain injury and organic issues, aggression and impulsivity, migraines, general epilepsy. *Lithium is better at treating depression and suicidality while VPA is better at treating more severe forms of Bipolar Disorder.* Additionally, the elderly may tolerate VPA better due to less cognitive and renal effects.

Profile: highly protein bound with unbound drug crossing the blood brain barrier. Half-life is 10 to 16 hours. Metabolism is primarily by glucuronidation with some oxidative metabolism (producing an active metabolite) and minimal P450 metabolism on VPA. Valproic acid (Depakene) is combined with a second identical molecule and Na to form divalproex sodium (Depakote) which is available as an enteric coated tablet to minimize GI side effects. Depakote also exists in "sprinkle" formulation (it is neither colorful nor tasty—a total letdown), a once- daily Extended Release Formulation (with up to 30% less bioavailability), and IV formulation.
Depakene is available in tablet and liquid formulation. Dosing is generally BID or TID and trough levels are drawn 3 days after continuous dosing. Therapeutic levels are considered between 50-200 for the prevention of seizures, with many side effects starting after crossing 100.



Valproic Acid



Divalproex Sodium

Side Effects: nausea/vomiting, pancreatitis, elevated LFTs, liver failure, tremor, sedation, neutropenia, thrombocytopenia, hair loss, weight gain, polycystic ovarian syndrome, neural tube defect in pregnancy. Overall, the list of side effects is longer and worse with lithium than with VPA.

Drug-Drug Interactions: protein bound drugs displace VPA, making it more toxic/cross BBB more readily. This includes interaction with aspirin, carbamazepine, and diazepam. Lithium plus VPA has increased risk of tremor. Antipsychotics plus VPA have more combined sedation (the same is true for alcohol). Regarding VPA and oxidation in the liver, VPA will increase carbamazepine, diazepam, amitriptyline, and Phenobarbital. VPA *decreases* phenytoin and desipramine. VPA may augment anticoagulants and should be monitored closely. Fluoxetine may *increase* VPA levels. Most importantly, VPA decreases glucuronidation of lamotrigine leading to doubled levels and high risk for Stevens-Johnson syndrome.

Carbamazepine (Tegretol)

Indications: structurally similar to imipramine, carbamazepine (CBZ) was intended initially as an antidepressant. In the late 1960s it was recognized as treatment for trigeminal neuralgia and temporal lobe epilepsy (complex partial seizures). Is considered second-line treatment for acute mania after lithium and VPA. It can also be used in refractory depression and to treat aggression. It should be avoided in pregnancy due to craniofacial abnormalities and spina bifida.

Profile: the average half-life is 26 hours and it is better absorbed with food. CBZ induces (helps) P450 enzyme 3A4. This means that any medications taken with CBZ that require 3A4 to break them down will have decreased dose. Example: warfarin is broken down by 3A4. If taken with CBZ, 3A4 action is increased and warfarin is broken down more than expected. This can lead to loss of warfarin effect (increased blood clotting—i.e., bad). Additionally, CBZ is also broken down by 3A4. With chronic administration of CBZ, the half-life diminishes to 12 hours due to induction of its own metabolism by 3A4 (auto induction). Thus after 3-5 weeks, 3A4 breakdown of CBZ increases, requiring increased dosing and can lead to unpredictable blood levels of CBZ during this time due to autoinduction. After initial processing in the liver, CBZ has an *active epoxide metabolite* that is the stronger form of the medication. This active metabolite is associated with better anticonvulsant properties and likely more side effects than related medication oxcarbazepine (see next section). Whereas lithium and VPA work to increase GABA and decrease glutamate, CBZ works more on inactivating Na channels to stop depolarization.

Due to irregular absorption, CBZ needs to be taken TID, even with food. An XR formulation exists that can be taken just once or twice per day. Generally dosing starts at 200 mg BID and increases by 200 mg every 2 to 3 days. The target dose is 1,200 mg per day and blood levels are often unreliable due to the epoxide metabolite not being the focus of drug monitoring (detects both parent and metabolite indiscriminately) and the risk of autoinduction.

Side Effects: mild nausea, sedation, vertigo, and diplopia are the most common and are dose dependent with diminishing side effects over time as the drug diminishes with autoinduction. Weight gain is minimal. More seriously, it can cause aplastic anemia or agranulocytosis that is not dose dependent in 1/125,000. Benign leukopenia is seen in up to 2% of patients and does not correlate with more serious side effects. Monitor for fever, sore throat, rash, petechiae, bruising and easy bleeding. Additionally, CBZ can cause hepatitis with elevated LFTs. Up to 15% of patients on CBZ develop a benign maculopapular rash in the first 3 weeks of treatment. The concern is the risk of toxic epidermal necrolysis and Steven Johnson's, which also may present with a rash. Stopping CBZ removes the rash and in patients with significant response to the medication may be re-trialed on CBZ as long as rash was the only presenting symptom (no malaise, oral lesions, flu symptoms). CBZ can create symptoms opposite of lithium with hyponatremia and water loading (similar to SIADH), but cannot correct abnormalities in lithium use. Before starting CBZ, CBC, Chem 13 including renal function, and HCG are needed.

Drug-Drug Interactions: due to CYP3A4 induction, it reduces the concentrations of many drugs, including antipsychotics (haloperidol, clozapine, olanzapine, aripiprazole, quetiapine), TCAs (amitriptyline, clomipramine, desipramine, doxepin, imipramine), benzodiazepines (alprazolam, clonazepam), seizure meds/mood stabilizers (lamotrigine, VPA, phenytoin, ethosuximide) and others (warfarin, Tylenol, methadone, doxycycline, oral contraceptives). Medications that inhibit 3A4 cause CBZ toxicity, including fluoxetine, fluvoxamine, cimetidine, verapamil, diltiazem, gemfibrozil, and grapefruit juice. CBZ is diminished by phenytoin and ETOH (3A4 inducers). When combined with VPA, CBZ is displaced from plasma proteins, leading to increased risk of toxicity. Generally, on tests, when asked about CBZ, the correct answer is that it decreases the dose of whatever medication administered with.

Oxcarbazepine (Trileptal)

Indications: approved for treatment of epilepsy, Novartis pled guilty in September 2010 for marketing oxcarbazepine for the treatment of trigeminal neuralgia and Bipolar Disorder without approval or sufficient data.

Profile: unlike CBZ, absorption is rapid and does not require food. The active metabolite is a monohydroxide with a half-life of 9 hours. In trials, dosing was started at 300 mg at night and increased to a total of 1,200 mg per day in BID dosing.

Side Effects: sedation, nausea, dizziness, vertigo are common. Does not have the serious side effects of CBZ. Hyponatremia can occur in 3% of patients and must be monitored closely initially as it may not present with symptoms and can lead to seizures and confusion.

Drug-Drug Interactions: minimal compared with CBZ. May induce 3A4 mildly, thus avoid use of oral contraceptives as primary form of birth control. Phenytoin and ETOH will decrease the dose of oxcarbazepine.

Lamotrigine (Lamictal)

Indications: helpful in reducing depressive episodes in maintenance treatment of Bipolar Disorder, partial epilepsy and Lennox-Gastaut seizures. Other reports using lamotrigine for aggression in Rhett's disorder, Alzheimer's and in mentally retarded patients. There is no data to show that it can manage either acute bipolar depression or mania.

Profile: initially developed as a folate antagonist (elevated folate induces seizures), was noted to block Na voltage channels like CBZ/Trileptal. Additionally, it inhibits 5HT reuptake to increase 5HT concentrations. Half-life is 25 hours and has 98% bioavailability. Lamotrigine is mainly metabolized by glucuronidation in the liver. Due to a varied rate of absorption, BID dosing is recommended. No efficacy has been seen in doses above 200 mg for the treatment of bipolar disorder. Alone, it is dosed 25 mg a day for 2 weeks, then 50 mg a day for 2 weeks then 100mg a day by week 4. When given with CBZ (induces/decreases lamotrigine), the above dosing schedule is doubled (i.e. start with 50 mg per day). When coadministered with VPA (increases lamotrigine), the dosing schedule is changed to 25 mg given every other day for 2 weeks, then 25 mg per day for 2 weeks, then 50 mg by week four to increase by 25 mg per week. Lamotrigine exists in an orally dissolving tablet (ODT) and in chewable tablets.

Side Effects: overall is well-tolerated. Minimal sedation or weight gain. Mild dizziness and nausea are possible. Some data shows that taking lamotrigine after 5pm leads to disruption of stage 3 sleep (restorative sleep and where most parasomnias occur). The main concern is rash associated with Steven Johnson's syndrome. About 8% of patients on lamotrigine develop a benign maculopapular rash within the first 4 months of treatment. The risk of a serious rash is about 0.08%. Despite this low rate, the presence of *any* rash should lead to discontinuation of the medication. Treatment with concomitant VPA and treatment in patients under age 16 is associated with higher risk of serious rash.

Drug-Drug Interactions: as mentioned, VPA increases lamotrigine concentrations and should be monitored closely or avoided. CBZ, phenytoin, and Phenobarbital decrease lamotrigine by up to 50%. In the presence of oral contraceptives, lamotrigine itself may be decreased, but not the reverse.

Gabapentin (Neurontin)

Legal: discussion should begin here. Over 90% of prescribed Neurontin is off-label use. Seriously. Additionally, Pfizer was fined $430 MILLION in criminal fines related to illegal marketing of the medication for off-label use in 2004. After paying that, continued off-label use and marketing led to a Kaiser Permanente suit for an additional $141 MILLION in March, 2010. Thus, gabapentin has been marketed for Bipolar Disorder, migraines, fibromyalgia, sleep, anxiety, diabetic neuropathy, and HIV neuropathy. The FDA has only ever approved gabapentin for add-on therapy for the treatment of seizures. Just a side note about Pfizer, in September 2009 the United States Department of Justice forced Pfizer to plead guilty to the largest criminal penalty ever imposed in American history: $2.3 BILLION in civil and criminal charges for illegal marketing of four medications, including Geodon and Lyrica.

Indications: add on therapy for treatment of seizures. Other off-label uses are above.

Profile: unbound by proteins and is not appreciably metabolized. Eliminated renally. Increases GABA and 5HT. Dosing is usually started at 100 mg TID and gradually increased for a total of 2,700 mg per day. Exists as capsules 100, 300, and 400 mg as well as 600 and 800 mg tablets (useful in gastric bypass). Dosage is decreased in patients with impaired renal function. Bioavailability diminishes by 20% when given with antacids.

Side Effects: somnolence, ataxia, diplopia, and dizziness. Side effects are dose dependent.

Pregabalin: has 6x the GABA binding affinity of gabapentin, is the first medication ever approved by the FDA specifically for the treatment of fibromyalgia. Standard dosing is 50 mg BID or TID and comes in capsules or strawberry flavored syrup. Has the ability to potentiate benzodiazepines and opiates and is a Schedule V drug.

Topiramate (Topamax)

Indications: antiepileptic, migraines, smoking cessation (especially in alcoholics), tremor, bulimia and binge eating, some studies show decreased self-mutilatory behavior in borderline personality disorder, management of anxiety

Profile: is renally excreted 70% and needs to be decreased in dose in patients with renal issues. Half-life 24 hours. Increases cerebral GABA. Dosing begins at 25 mg at bedtime and gradually increases to BID dosing.

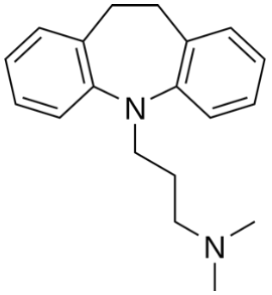
Side Effects: paresthesia, *especially numbness and tingling in fingertips and peripheral extremities*. Sometimes improved by QHS dosing), weight loss, sedation, dizziness, word-finding difficulties. Generally, above 100 mg this is seen. Patients call it "dopamax." Lowers serum bicarbonate through carbonic anhydrase inhibition (causing cardiac arrhythmias and renal stones in 1.5%).

Drug-Drug Interactions: increases phenytoin and VPA levels. CBZ and phenytoin decrease topiramate levels. Avoid with other medications that are carbonic anhydrase inhibitors (acetazolamide/Diamox-glaucoma, altitude sickness, pseudotumor cerebri).

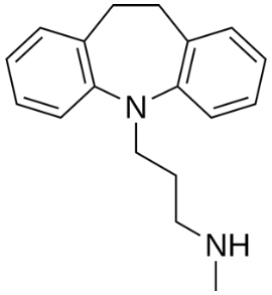
Antidepressants

TCAs

Structurally related to the typical antipsychotic chlorpromazine, imipramine was initially designed as a medication to manage schizophrenia. However, it was noted that the new medication in exacerbated mania (up to 25% of patients with pre-existing Bipolar Disorder will have mania or hypomania when on imipramine). After this was discovered, imipramine was used in the late 1950s as an antidepressant. Many of the TCAs are structurally related to imipramine, which is initially derived from the antihistamine methylene blue. The term "tricyclic" and "tetracyclic" refers to the 3 and 4 rings in the chemical structures of these medications.



Imipramine



Desipramine

TCA basics: the three ringed TCAs are divided into tertiary and secondary amines. Tertiary amines have high affinity for blocking 5HT reuptake. Secondary amines have high affinity for blocking NE reuptake. Interestingly, tertiary amines are metabolized to secondary amines in the liver. Thus, a person taking the tertiary TCA amitriptyline is getting a medication that is strongly serotonergic yet still somewhat noradrenergic. In this way, the CAs serve as the first SNRIs.

Tertiary and Secondary Amine Tricyclic Antidepressants

Medications	Initial/Max Dose	Comments	Adverse Effects
Tertiary Amine TCAs			
Amitriptyline (Elavil)	25-75 mg/200 mg daily	5HT > NE	Orthostatic hypotension, drowsiness, weight gain, anticholinergic, QT prolongation (in overdose)
Amoxapine (Asendin)	50 mg bid/400 mg daily	5HT = NE, weak DA	
Clomipramine (Anafranil)	25 mg/250 mg daily	5HT > NE	
Doxepin (Sinequan)	50-75 mg/300 mg daily	5HT = NE; highly sedating	
Imipramine (Tofranil)	50-100 mg/200 mg daily	5HT = NE	
Secondary Amine TCAs			
Desipramine (Norpramin)	100-200 mg/300 mg daily	NE > 5HT; metabolite of imipramine	Same as above, but with more drowsiness, somnolence, and weight gain than tertiary
Maprotiline (Ludiomil)	25 mg tid/225 mg daily	NE > 5HT	
Nortriptyline (Pamelor)	25-50 mg/150 mg daily	NE > 5HT; metabolite of amitriptyline	

DA: dopamine; 5HT: serotonin; max: maximum; NE: norepinephrine; TCA: tricyclic antidepressant. Source: References 4, 10.

Indications: MDD (but are more likely to induce mania than SSRIs), Panic Disorder with Agoraphobia (imipramine is best), Generalized Anxiety Disorder (especially imipramine and doxepin), OCD (clomipramine is FDA approved), and chronic pain and migraine (amitriptyline is used most for this). Imipramine can be used to treat childhood enuresis but due to reports of sudden death in children and adolescents, TCAs should be avoided in this population if possible.

Profiles: in addition to inhibiting reuptake of 5HT and NE, TCAs can antagonize muscarinic acetylcholine, histamine, and alpha 1 and 2 receptors. Additionally, Na and Ca channels can be blocked, leading to cardiac side effects. TCAs are more likely to cause anticholinergic side effects than SSRIs but are less *likely* to cause sexual side effects, weight gain, and sleep disturbance than SSRIs.

- Clomipramine: most serotonergic
- Amitriptyline: most anticholinergic and alpha
- Desipramine: most noradrenergic, low anticholinergic
- Nortriptyline: low anticholinergic
- Doxepin: most antihistamine
- Protriptyline: closest to nortriptyline but may be more noradrenergic

Pharmacokinetics: absorption in small intestine is rapid. Half-lives vary from 10-70 hours with most TCAs able to be given once-daily. Nortriptyline and doxepin exist in liquid solutions.

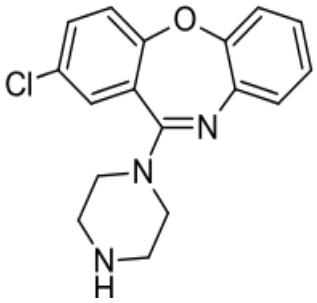
Metabolism: hepatic metabolism focuses primarily on demethylation and hydroxylation. The tertiary TCAs are demethylated by 2C19 and other enzymes, leading to the formation of secondary TCAs. Example: clomipramine → desmethylclomipramine, a secondary TCA. In the case of amitriptyline and imipramine, they are converted to the secondary TCAs nortriptyline and desipramine. Secondary amines are active compounds that are hydroxylated in the liver to active hydroxymetabolites. Due to the multiple metabolites floating around and the high variability from person to person (think: different enzyme numbers and functionality), most of the TCAs cannot be measured in serum reliably. The main TCAs that are associated with a reliable serum level that correlates to therapeutic response are desipramine, nortriptyline, and imipramine. For nortriptyline, plasma levels between 50-150 are more effective than levels below or above. This is called a curvilinear therapeutic window. In the presence of 2D6 inhibitors, TCAs can raise to toxic levels (fluoxetine, paroxetine, sertraline, cimetidine).

Side Effects

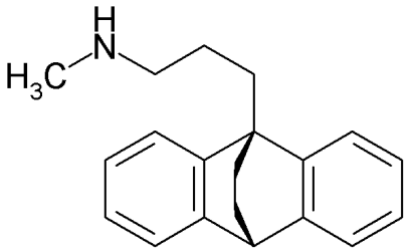
- CNS: delirium due to anticholinergic and antihistamine effects, especially with amitriptyline. Increased risk of seizures, up to 2% with clomipramine
- Anticholinergic: dry mouth, blurred vision, constipation, urinary retention. Symptoms may be reversed with bethanechol. Amitriptyline and clomipramine are most common. Avoid in narrow-angle glaucoma (is fine in chronic open-angle glaucoma)
- Antihistamine: doxepin is most potent (but still less than mirtazapine and olanzapine)
- Cardiovascular: orthostatic hypotension due to alpha 1 blockade is present with many TCAs. Least with nortriptyline. As a class, the TCAs have type I antiarrhythmic qualities with QTc prolongation and should be avoided in cardiac patients
- Hepatic: increased LFTs are associated with imipramine and desipramine. Generally associated with AST>>ALT. Acute hepatitis can be fatal and may be seen in 0.1% of patients
- Overdose: death occurs as the result of cardiac arrhythmia. After acetaminophen, TCAs are the most lethal cause of OD in the US, with amitriptyline deaths exceeding total fatalities of all TCAs combined. Today, OD on SSRIs is 4.5x more common than TCAs. However, the rates of deaths of SSRIs in OD (1.5 deaths/1,000 OD) are much lower than TCAs (8.5 deaths/1,000 OD)

Tetracyclic Antidepressants

Similar to the TCAs, the tetracyclics bind to 5HT and NE transporters to prevent reuptake. Amoxapine is considered by some to be a tricyclic antidepressant as it structurally has 3 rings with a fourth ring as a side group.



Amoxapine



Maprotiline

Amoxapine (Asendin): derived from mid-potency antipsychotic, loxapine. Amoxapine increases 5HT, NE, and blocks DA. It is the only TCA/tetracyclic with both antidepressant and antipsychotic properties. Has an active metabolite. Half-life is 8 hours, but the active metabolite has a half-life of >30 hours. May have TD and may have greater risk of seizures than other TCAs.

Maprotiline (Ludiomil): greatly differs from the others in that it lacks 5HT reuptake inhibition and primarily acts to inhibit NE reuptake. Is a strong antihistamine, thus is sedating. Is less anticholinergic and alpha blocking than amitriptyline. Half-life is 30-60 hours.

Monoamine Oxidase Inhibitors

In the 1950s an antituberculosis drug, isoniazid (INH), was found to have antidepressant properties. Ultimately, INH showed quick resistance to active TB and is generally used in prevention and augmentation of treatment today. Additionally, INH has no MAO inhibition. Isoniazid was altered (simple addition of N-isopropyl group) to create iproniazid (Euphozid) and approved for the treatment of depression in 1958. This medication *was* an MAOI, and was the first antidepressant ever marketed, beating imipramine narrowly. Three years later in 1961 it was removed from the market due to hepatotoxicity. This medication paved the way for other MAOIs which were used steadily until the advent of the SSRIs. The second-line status of the MAOIs currently is related to safety and side effect profile, not efficacy. Currently, MAOIs available include phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate), rasagiline (Azilect), moclobemide (Manerix) and selegiline (Eldepryl). In 2006, a transdermal delivery of selegiline for the treatment of parkinsonism was introduced.

Review of MAO: these enzymes are found on the outer mitochondrial membranes, where they degrade monoamine neurotransmitters (NE, 5HT, DA, Epi, Tyramine). MAOI medications act in the CNS, the GI system, the liver, and the sympathetic nervous system. MAO-A breaks down NE, 5HT, and Epinephrine. DA and tyramine are broken down by MAO-A and MAO-B.

Monoamine Oxidase Inhibitors

Medications	Initial/Max Dose	Comments	Adverse Effects
Isocarboxazid (Marplan)	10 mg bid/60 mg daily	Dietary restrictions: no foods containing tyramine (e.g., beer, wine, aged cheese, soy sauce, bananas, smoked meat)	HTN crisis: palpitations, chest pain, muscle rigidity; 5HT syndrome: nausea, sedation, diaphoresis, confusion, HTN
Phenelzine (Nardil)	15 mg tid/90 mg daily		
Selegiline (Emsam)[a]	6 mg/12 mg (24-h transdermal patch)		
Tranylcypromine (Parnate)	30 mg/60 mg (divided doses)		

[a] Selective monoamine oxidase B inhibitor. 5HT: serotonin; HTN: hypertension; max: maximum.

Indications: MDD, some data may show that phenelzine may better treat atypical depression (hypersomnia and hyperphagia) than TCAs, may treat depression in Bipolar Disorder better than TCAs with less hypomania/mania, anxiety, phobias, pain, migraines, depression associated with TBI. Tranylcypromine was included in the STAR*D trials as an effective option in treatment-resistant depression.

Profile: phenelzine, tranylcypromine, and isocarboxazid have half-lives ranging from 2-3 hours but have tissue half-lives with longer times. They irreversibly inactivate MAOIs, thus the effect can last up to 2 weeks, even with a single dose. Moclobemide is a reversible MAO-A inhibitor, and has less side effects and less dietary restrictions. It is not approved for use in the United States at this time. Selegiline, phenelzine, and tranylcypromine are structurally related to amphetamines, thus have stimulant effects in the brain.

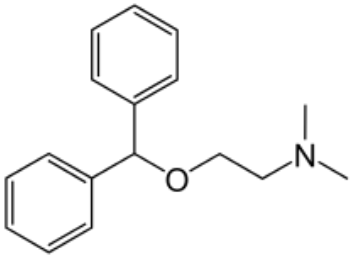
Side Effects: orthostatic hypotension, insomnia, weight gain, paresthesia (possibly from pyridoxine deficiency), and induction of mania. When switching from an irreversible MAOI to another antidepressant, it is important to give a 14-day washout period due to loss of MAO.

Dietary Effects: first noted as headaches, seen more commonly in tranylcypromine and less in phenelzine. Tyramine, present in many foods, is usually broken down by MAO. In the presence of MAOIs, it is not broken down, leading to hypertensive crisis and other symptoms. Symptoms may include hypertension, sweating, chills, headache, nausea, pyrexia, dilated pupils, stiff neck, and restlessness. This can progress to alteration of consciousness, fever, cerebral hemorrhage, and death (0.02%). Treatment with Ca^{2+} channel blocker, nifedipine, is helpful. Foods to avoid include cheese (except cream cheese), fava beans, overripe fruit, sherry, sauerkraut, MSG, picked foods, red wine, and to use caffeine, coffee, chocolate, tea, and beer in moderation.

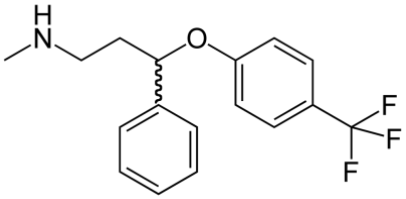
Selegiline (Emsam, L-deprenyl, Eldepryl): an irreversible MAO-B inhibitor used primarily to treat Parkinson's as an adjunct to L-Dopa treatment. Intestinal tyramine interactions with MAO-B are much less than MAO-A and as a result, selegiline requires less food restrictions. Side effects of nausea and lightheadedness are minimal. Due to being metabolized to L-methamphetamine, the medication will have a positive UDS. In addition to a regular tablet, it exists as an orally dissolving tab and a transdermal patch that delivers a steady 6 mg per 24 hours, marketed under the name EMSAM for the treatment of depression. The theory behind selegiline for depression is related to studies from the 1960s where the D-isomer of selegiline (D-deprenyl) showed strong antidepressant properties when high doses of selegiline were used. NE and DA increases were noted with the isomer. In recent trials using oral selegiline for the treatment of depression, required high doses led to a loss of selectivity for MAO-B, thus having affinity for MAO-B and intestinal MAO-A, leading to tyramine interactions. The transdermal patch was a strategy created to bypass the intestinal MAO-A responsible for tyramine reactions. Results for the treatment of depression with the patch are mixed, with some studies showing efficacy and some showing no benefit over placebo.

Selective Serotonin Reuptake Inhibitors (SSRIs)

In 1970, Eli Lilly and Company began research on 3-Phenoxy-3-phenylpropylamine, a structure similar to diphenhydramine (known at the time to have some antidepressant properties). Over the next 2 years, many derivatives of this compound were creating, ultimately leading to the discovery of fluoxetine. The medication entered the market in 1986. Lilly researchers published a paper entitled "Prozac, the first selective serotonin reuptake inhibitor and an antidepressant drug." For the next 20 years, Eli Lilly strongly marketed Prozac into popular culture as the first SSRI. In actuality, the first SSRI was zimelidine (now banned for causing Guillain-Barre syndrome and other sometimes fatal side effects). Interestingly, fluvoxamine entered the market 2 years prior to fluoxetine but it was not approved for treatment of depression. Thus, "Prozac, the first SSRI" continues in public knowledge despite the inaccuracy ("Prozac, the first SSRI marketed in the USA" would be accurate).



Diphenhydramine (Benadryl)



Fluoxetine (Prozac)

Indications: MDD (all except fluvoxamine are approved by the FDA for MDD), depression in pregnancy and postpartum depression (over 70% of patients with MDD relapse into depression upon diminishing or discontinuing their SSRI during pregnancy. Studies following children exposed to fluoxetine in utero show no related decreases in IQ, language, or behavioral issues), depression in the elderly (avoid paroxetine due to anticholinergic), OCD (fluvoxamine, paroxetine, sertraline, and fluoxetine are FDA approved. Use higher doses than used in MDD), panic disorder (paroxetine, sertraline), PTSD, GAD, Bulimia Nervosa (fluoxetine, generally over 60 mg), Anorexia (less dropout from treatment and better treatment of comorbid disorders with fluoxetine), Premenstrual Dysphoric Disorder (Eli Lilly marketed fluoxetine as Sarafem in the early 1990s as the patent for Prozac expired. Literally pink and purple fluoxetine capsule with a new logo. In trials, sertraline and fluoxetine work equally well). In children, the FDA has approved fluoxetine for the treatment of depression and fluoxetine, fluvoxamine, and sertraline for the treatment of OCD.

Black Box: in 2004, the FDA issued a black box warning for the use of SSRIs in patients under the age of 24. This was based upon meta-analyses that showed increased risk of suicidal thoughts and behaviors, in addition to aggression and hostility in children treated with SSRIs. While not issued in the treatment of the adults, the black box is well-known to many patients and is a subject of concern in the general public. All depressed patients should be closely monitored in the first 1-2 weeks of SSRI treatment.

Pharmacokinetics: see the second chart below for the half-lives of the various SSRIs. Regarding CYP interaction, fluvoxamine has the most interaction with 1A2, 2C, and 3A inhibition (with minimal 2D6 inhibition). Fluoxetine and paroxetine are the strongest 2D6 inhibitors, with sertraline having moderate inhibition.

Inhibitory Effect of SSRIs on CYP-450 Isoenzymes

	CYP-450 Isoenzymes				
Agent	**CYP-1A2**	**CYP-2C9**	**CYP-2C19**	**CYP-2D6**	**CYP-3A4**
Citalopram	0	0	0	+	0
Fluoxetine	+	++	+/++	+++	+/++
Fluvoxamine	+++	++	+++	+	++
Mirtazapine	0	0	0	+	0
Nefazodone	0	0	0	+	+++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+	+/++	+
Venlafaxine	0	0	0	+	+

SSRI: selective serotonin reuptake inhibitor; CYP: cytochrome P; 0: minimal/no inhibition; +: mild inhibition; ++: moderate inhibition; +++: potent inhibition.

Selective Serotonin Reuptake Inhibitors

Medications	Initial/Max Dose	Comments	Adverse Effects
Citalopram (Celexa)	20 mg/60 mg daily (40 mg max effective)	$t_{1/2}$ = 35 h; weak CYP2D6 inhibitor; anxiety symptoms significantly improved compared to other SSRIs	Weight gain, insomnia, tremors, prolonged QT interval, dizziness, constipation, dry mouth, nausea, lightheadedness, syncope, confusion, agitation, sexual dysfunction
Escitalopram (Lexapro)	10 mg/20 mg daily (10 mg max effective)	$t_{1/2}$ = 35 h; most potent SSRI; like citalopram, fewer drug interactions	
Fluoxetine (Prozac)	20 mg/80 mg daily	Long $t_{1/2}$ = 7-15 days; active metabolite norfluoxetine; potent CYP2D6 inhibitor = drug interactions; may cause weight loss	
Fluvoxamine (Luvox)	50 mg/300 mg in divided doses	$t_{1/2}$ = 16 h adults, 26 h elderly; potent CYP3A4, 2C19, 1A2 inhibitor = most drug interactions; primarily used to treat OCD and panic disorders	
Paroxetine (Paxil)	20 mg/60 mg daily (50 mg max effective)	$t_{1/2}$ = 26 h; potent CYP2D6 inhibitor; mild affinity for muscarinic receptors = more anticholinergic side effects than other SSRIs; sedating	
Sertraline (Zoloft)	50 mg/200 mg daily	$t_{1/2}$ = 26 h; absorption increases when taken with food; weak CYP2D6 inhibitor = less potential drug interactions; more likely than other SSRIs to cause nausea; most cited reason for d/c	

d/c: discontinuation; max: maximum; OCD: obsessive compulsive disorder; SSRI: selective serotonin reuptake inhibitor; $t_{1/2}$: half-life.

Pharmacodynamics: citalopram and escitalopram are the most selective inhibitor of 5HT reuptake, having little inhibition of DA, NE, histamine, or GABA. Fluoxetine weakly inhibits NE reuptake and binds to 5HT 2C. Sertraline weakly inhibits NE and DA reuptake. Paroxetine has significant anticholinergic activity at higher doses.

Drug Interactions: 2D6 inhibitors will slow the metabolism of carbamazepine, diazepam, phenytoin, and antineoplastic agents. Sertraline may displace warfarin from proteins, leading to increased PTT. Fluvoxamine increases concentrations of multiple BZD, warfarin, clozapine, carbamazepine, methadone, propranolol, and diltiazem. It has little interaction with lorazepam.

Side Effects

- Sexual side effects: the most common side effect with long-term use of the SSRIs, with incidence of 50-80%. Treatment includes decreasing the dose, adding bupropion (increases DA) or buspirone (antagonism of 5HT via autoreceptor), or use of sildenafil
- GI: nausea, diarrhea, vomiting are most common with sertraline and fluvoxamine. Medicated through 5HT3. Paroxetine is associated with constipation (anticholinergic). Up to 30% of patients on SSRI will gain weight, especially with paroxetine
- CNS: increased anxiety (fluoxetine), insomnia (fluoxetine) and sedation (varied with many of the SSRIs), emotional blunting (feelings of apathy, in ability to cry, "zombie" effect), seizures (0.2%), and EPS
- Hematologic: can inhibit platelet binding, leading to bruising (Seen commonly with sertraline)
- Serotonin syndrome: a potentially fatal condition involving diarrhea, restlessness, agitation, autonomic instability, hyperthermia, myoclonus, rigidity, delirium, and coma. *On examinations, clinically distinguishing between NMS and Serotonin Syndrome generally comes down to myoclonus in Serotonin Syndrome*. Treatment is removal of the offending agents, nitroglycerine, dantrolene, BZD, cooling, and possibly ventilation

Pereau Basics on SSRIs: due to the majority of the SSRIs existing in generic formulation (exception: escitalopram), the medications we commonly prescribe today do not have the same side effects and profiles of the original brand medications. A generic medication is required by the FDA to have 70% bioavailability of the original brand medication. Thus, when a patient swallows citalopram, the amount of drug in the serum has to be 70% of what would be present had they swallowed Celexa. That's it. A generic medication does not have to be made with the same materials, is not required to have a similar side effect profile, and may not have the same efficacy due to the possibility of 30% less bioavailable. Imagine a patient stable on Wellbutrin XL 300 mg (max dose). A few years later the medication becomes generic and the patient's insurance changes to the generic budeprion XL due to lower cost. The insurance company is not required to continue to provide the patient with Wellbutrin XL because the FDA has approved the generic budeprion XL as equivalent to the brand medication. As a result, the patient now notes that he feels more depressed (loss of 30% of his medication) despite max dose of the medication. He has terrible headaches and irritability that were never present on the original medication. He calls his psychiatrist and says that he wants to go back on the brand Wellbutrin XL. He is informed that his insurance company will not pay for the medication as it now has a generic formulation and that he can instead pay $140 a month out of pocket to get Wellbutrin XL. Generics suck. But it's hard to argue with $4 a prescription.

Some Observations on the Generic Medications We Now Prescribe

Fluoxetine (originally Prozac): have noted that some patients get tired on the medication and benefit from pm dosing. While considered activating, the generic may not be. Another note is that each brand of generics is different; the side effects of generic fluoxetine capsules made by one company differ from another company. Is likely the safest medication used in pregnancy with a significant amount of clinical data present. For breastfeeding mothers, sertraline may be a better choice than fluoxetine.

Citalopram (originally Celexa): sexual side effects are severe. They appear to be dose dependent and may be equal to paroxetine. A number of patients get tired on it so I generally now start it at night. In addition to hyponatremia, SIADH has been seen a number of times with citalopram. Headaches similar to generic Wellbutrin are also seen with citalopram. Additionally, according to a report from the FDA (8/24/11)
"Citalopram causes dose-dependent QT interval prolongation. Citalopram should no longer be prescribed at doses greater than 40 mg per day." This likely will impact prescription of this common medication.

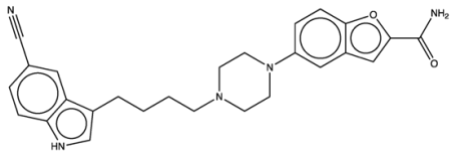
Sertraline (originally Zoloft): commonly has bruising and hair loss. The original medication was often sedating, leading to pm dosing. The generic often has the opposite effect, with patients initially experiencing feelings of restlessness, anxiety, and hypervigilance (which are problematic considering sertraline is used for anxiety). Have seen a couple cases of bruxism which improves with buspirone. Seen Torsades and neutropenia x1 recently with sertraline. Sertraline is probably the best medication to use when breastfeeding as a minimal amount is expressed in breast milk.

Paroxetine (originally Paxil): I avoided this medication for a long time due to fear of weight gain and sexual side effects. Now that the side effects of citalopram are more apparent, I am less hesitant to use paroxetine (a medication that may have better efficacy that citalopram). As associated with pulmonary hypertension in newborns when used during pregnancy.

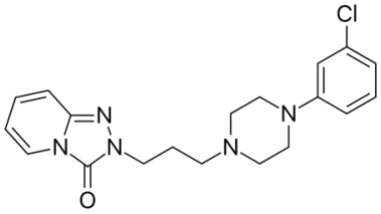
Take home point: when your patient complains of a SSRI side effect, believe them. Unless they endorse the side effect of "My right index finger is numb every other Thursday," go with it. Side effects often resolve 10-14 days after initiation of the medication. If they do not, consider managing the side effects or discontinuing the medication. Putting generic SSRIs at night seems to have a few less noted side effects.

Novel Mechanisms

Vilazodone HCL (Viibryd)



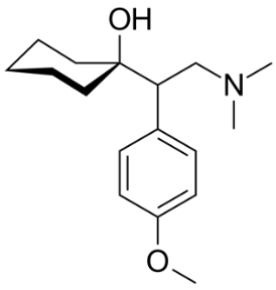
Vilazodone



Trazodone

Structurally similar to Trazodone, this is a selective serotonin reuptake inhibitor in addition to 5HT1A agonist (like buspirone). Thus, it is similar to combining citalopram+buspirone. This medication has less sexual side effects and weight gain than other SSRIs. Half-life is 25 hours and dosing starts at 10 mg to increase by 10 mg per week to a goal of 40 mg. Discontinuation symptoms may occur if stopping quickly. Is metabolized by CYP3A4. GI side effects are most common. There may be QTc prolongation a well in doses at or above 80 mg. This may be a “me too” medication; more studies to follow.

Venlafaxine (Effexor) and Desvenlafaxine (Pristiq)

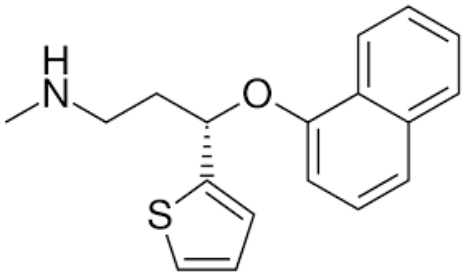


Indications: MDD, GAD, Panic Disorder. Has been used for diminishing symptoms of menopause, treating chronic pain, and dual diagnosis of MDD and cocaine dependence.

Profile: inhibits reuptake of 5HT and NE without much interaction at other sites. Exists as immediate release IR (BID dosing) and extended release XR (once daily). Due to short half-life, a discontinuation syndrome may exist if abruptly stopped. Metabolized by 2D6 to active metabolite desvenlafaxine (now marketed as Pristiq). Patients with poor 2D6 activity may have higher side effect profile, leading to the isolation and marketing of the metabolite as treatment (or so they say). The IR is most associated with nausea and often is started in low doses of 37.5 mg twice daily (use in the am and at 1pm due to risk of insomnia if taken at bedtime). As dose increases, affinity for NE transporter increases. As a result, HTN and anxiety are more associated with higher doses of the medication. When taken as the XR, the maximum dose is 375 mg. Desvenlafaxine has a therapeutic dose of 50 mg (which happens to be the starting dose) with no significant data to support improved efficacy of 100 mg.

Side Effects: nausea and sexual dysfunction in up to 30% are serotonergic side effects. While appearing anticholinergic, side effects of headache, insomnia, dizziness, constipation, sweating, and nervousness are due to NE effects. HTN occurs with higher doses. Discontinuation syndrome appears as dizziness, insomnia, nausea, and diarrhea.

Duloxetine (Cymbalta)



Indications: MDD and Neuropathic pain associated with diabetes (first drug FDA approved). For the treatment of stress incontinence, duloxetine increases the tone of the urethral sphincter and will be marketed as Yantreve (important to know if your patient is taking Yantreve aka duloxetine, especially before you start them on SSRI or SNRI).

Profile: similar to venlafaxine, but has equal affinity for 5HT and NE transporters at all doses. There is little data to show greater clinical efficacy in doses above 60 mg for the treatment of depression. BID dosing may reduce side effects seen with once-daily dosing. Starting dose is 20 or 30 mg.

Side Effects: similar to venlafaxine, including nausea, dizziness, constipation, insomnia, and sexual dysfunction. Less likely to cause HTN. May increase Hgb A1c in long term treatment. Potentially increases LFTs (especially in hepatically compromised patients). Discontinuation syndrome can occur.

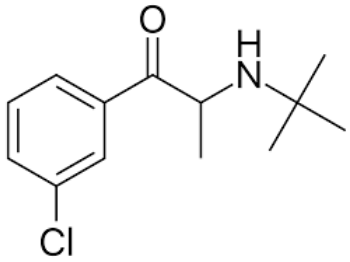
Serotonin-Norepinephrine Reuptake Inhibitors

Medications	Initial/Max Dose	Comments	Adverse Effects
Desvenlafaxine (Pristiq)	50 mg/100 mg daily (50 mg max effective dose)	Active metabolite of venlafaxine; BP elevation reported to be less common than with venlafaxine	Similar adverse effects to SSRIs, except more incidence of BP elevation with SNRIs
Duloxetine (Cymbalta)	40 mg/ 60 mg daily	$t_{1/2}$ = 12 h; moderate inhibitor of CYP2D6; GI adverse effects (nausea, dry mouth, constipation) are common; unique beneficial treatment for physical pain associated with depression	
Venlafaxine (Effexor)	25 mg tid/ 225 mg daily	5HT > NE at lower doses; NE > 5HT at higher doses; $t_{1/2}$ = 11 h; inhibitor of CYP2D6	

BP: blood pressure; 5HT: serotonin; GI: gastrointestinal; max: maximum; NE: norepinephrine; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; $t_{1/2}$: half-life.

Bupropion (Wellbutrin, Zyban)

Approved by the FDA and marketed in 1985 (a year before fluoxetine). The original recommended dose was 400-600 mg. This dosing was associated with a risk of seizures and resulted in the drug being pulled for 3 years before being reintroduced with a recommended max dosage of 450 mg. In 2007, in response to multiple patient reports about the generic Bupoprion XL having more side effects and being less efficacious than Wellbutrin XL, the FDA concluded that the discrepancy was due to "natural mood variation."



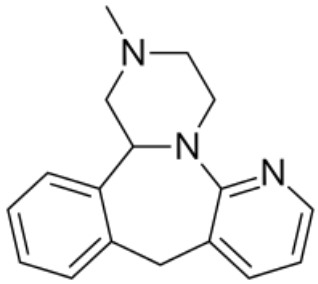
Indications: MDD and seasonal affective disorder, smoking cessation (under Zyban brand name, generally used in combination with nicotine substitutes), BMD (less likely to precipitate mania in BMD I than TCAs and in BMD II than most other antidepressants), ADHD, cocaine detoxification (reducing cravings), hypoactive sexual desire disorder due to SSRIs.

Profile: available in immediate release IR (BID or TID), sustained release SR (used BID), and extended release ER (once daily). The active ingredient is the same in each. The IR reaches peak concentration in 2 hours, SR in 3 hours and ER in 5 hours. The half-life is 12 hours. Mechanistically, bupropion inhibits the reuptake of DA and NE. Is metabolized to active metabolite hydroxybupropion by CYP2B6 (inhibited by fluoxetine). Hydroxybupropion itself inhibits 2D6. Bupropion has affinity for DA transporters while hydroxybupropion has more selective affinity for NE transporters. Bupropion may have a false positive UDS for amphetamines.

Side Effects: seizure risk is 2% with 600 mg and 0.1% with 300-450 mg (the SR and ER at same doses has risk of 0.05%, equivalent to the other antidepressants). Side effects most common include headache, insomnia, dry mouth, tremor, and nausea. Severe anxiety and panic disorder can be worsened by bupropion. Can worsen psychosis and delirium due to dopaminergic activity. Have seen severe psychosis with use of bupropion in pregnancy.

Mirtazapine (Remeron)

A tetracyclic antidepressant that is both serotonergic and noradrenergic through a mechanism different from serotonin reuptake blockade or monoamine oxidase inhibition.

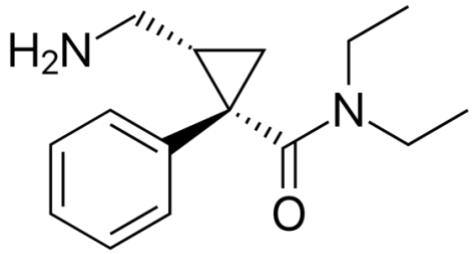


Indications: MDD (especially with insomnia or weight loss), reduction of side effects associated with chemotherapy, augmentation of antidepressant therapy.

Profile: half-life of 30 hours. Clearance is impaired in hepatic impaired patients by 30%, in renal impaired patients by 50%, and is impaired in the elderly (by 40% in males and 10% in females). Mechanistically, mirtazapine works to increase 5HT at the 1A receptor (the main site for the antidepressant actions of most antidepressants). It does this by blocking the 5HT2A, 5HT2C and 5HT3 receptors, resulting in all serotonin being directed to the 5HT1A receptor. As a result, there are less sexual and GI side effects than other antidepressants. Additionally, it increases NE and DA transmission (recall 5HT2C normally inhibits DA—think atypical antipsychotic mechanism of action). Strong histamine affinity causes sedation and weight gain. There is minimal anticholinergic effect. Starting dose ranges from 7.5 to 15 mg. Increasing dose above 30 mg leads to higher NE effects and less sedation. Metabolized by 2D6 and 3A4.

Side Effects: somnolence occurs in >50% (worsened by alcohol or other sedatives), increases appetite and cholesterol, reduction of ANC (monitor for fever, chills, sore throat), and agranulocytosis.

Fetzima (levomilnacipran)



Indication: MDD

Dosing: extended release capsules, 40-120 mg once daily, initiate at 20 mg.

Profile: milnacipran (Savella) is one of only 3 medications approved by the FDA for the treatment of fibromyalgia. As a racemic mixture of d and l-enantiomers, it inhibits 5HT and NE reuptake equally. It is considered less potent than other SNRIs and has less affinity for cortical sites (and possibly more peripheral affinity, thus management of pain) than do venlafaxine and duloxetine. The L-enantiomer, levomilnacipran, is also dual serotonin and norepinephrine reuptake inhibitor. However, it has much higher selectivity for reuptake blockade of NE than 5HT reuptake blockade. Unlike Savella, Fetzima is approved for the treatment of MDD in the United States. Additionally, Fetzima may inhibit a beta-site amyloid precursor protein cleaving enzyme (BACE-1). This enzyme is thought to be responsible for β-amyloid plaque formation. This medication may ultimately be considered in the treatment of Alzheimer's disease.

Side effects: HTN, tachycardia, GI symptoms (N/V, constipation), hyperhidrosis, urinary hesitancy/retention, erectile dysfunction

Other Antidepressants			
Medications	**Initial/Max Dose**	**Comments**	**Adverse Effects**
NDRIs			
Bupropion IR (Wellbutrin)	100 mg bid/ 150 mg tid	Contraindicated in patients with anorexia, bulimia, or seizure disorders	Similar to SSRIs but with less 5HT adverse effects such as nausea, somnolence, and weight gain; no sexual dysfunction
Bupropion SR (Budeprion SR, Wellbutrin SR, Buproban)	150 mg/ 200 mg bid		
Bupropion XL (Wellbutrin XL, Budeprion XL)	150 mg/ 450 mg daily		
Mixed-Action Antidepressants			
Mirtazapine (Remeron)	15 mg/ 45 mg daily	Blocks alpha$_2$, 5HT$_{2a,c}$, 5HT$_3$, and H$_1$ receptors	More weight gain, less sexual dysfunction, insomnia
Nefazodone (Serzone)	100 mg bid/ 300 mg bid	Blocks 5HT$_{2a}$ and 5HT reuptake; 3A4 inhibitor = many drug interactions will limit use	Black box warning = hepatotoxicity
Trazodone (Desyrel)	150 mg/ 600 mg daily	Blocks 5HT$_2$ and alpha$_1$ receptors	Too much sedation limits use

5HT: serotonin; IR: immediate release; max: maximum; NDRI: norepinephrine-dopamine reuptake inhibitor; SR: sustained release; SSRI: selective serotonin reuptake inhibitor; XL: extended release. Source: References 4, 10.

Anxiolytics

Buspirone (Buspar)

Indications: GAD (not panic, OCD, or social phobia). May reduce aggression and hostility in anxiety better than BZD. Less effective in managing somatic symptoms of anxiety than BZD. Can be used to treat sexual side effects and bruxism caused by SSRIs (through inhibition of 5HT2 and via DA agonism).

Profile: half-life 2-11 hours so is dosed TID. Has an active metabolite that is 20% less potent but 30% more concentrated in the brain than the parent compound. Primary mechanism is 5HT1A agonist, helping with anxiety (think: 5HT2 is activating, 5HT1 is calming). Dosing begins at 5mg TID and maximum dose is 60 mg. Metabolized by 3A4. Grapefruit juice increases buspirone concentrations.

Side Effects: does not cause weight gain, sedation, or sexual side effects (no 5HT2 or H1). Main side effects are headache, nausea, and dizziness. Safe in overdose (no deaths have been reported) and the estimated lethal dose is >300x the recommended daily dose.

Benzodiazepines

Indications: GAD, Panic, acute mania, agitation, short term management of insomnia, anticonvulsant, akathisia. They can be used for the short-term management of anxiety and panic (1-2 weeks) while a long-term agent is initializing (SSRI). Chronic use must be monitored closely and generally BZD with long half-life and gradual onset of action are less likely to be abused.

Profile: anxiolytic properties are due to modulation of GABA. All are lipid-soluble, allowing them to cross the blood brain barrier. The most addictive BZD are highly lipophilic with a short onset of action (patient notices the effects quickly). Tolerance with alprazolam, for example, can occur within 1-2 weeks. See chart on next page.

Side Effects: sedation, ataxia, dizziness, respiratory depression in COPD or sleep apnea, dependence to BZD (especially with rapid onset) and risk of withdrawal, which can be fatal if not managed. Most recent studies do not show fetal cleft/palate abnormalities or cardiac malformations. Use of BZD in the 3rd trimester can result in withdrawal symptoms, decreased APGARS and poor feeding in the newborn.

Generic **TRADE** **Class**	**Equivalent Dose/**	**Peak Level (hours)/ Absorption Rate**	**Average*** **Half- life (hr)**	**Active Metabolites**	**Comments**	**Initial Dose** **Max Dose**	**Usual Dose Range**
SHORT ACTING: more rebound anxiety effect & withdrawal reactions, better sedative/hypnotic; preferred over long acting in elderly (less accumulation) & patients with liver disorders (easier metabolized). MORE ADDICTIVE							
Alprazolam XANAX	0.5mg	1-2 Medium	12 (9-20)	Minor Oxidation	Anxiety, Panic attacks	0.25mg 4-10mg	0.25-0.5mg po tid
Lorazepam ATIVAN	1mg 3-Hydroxy	1-4 Medium	15 (8-24)	None Conjugation	Anxiety, Preanesthetic;	0.5mg 10mg	0.5-2mg po tid
Oxazepam SERAX	15mg 3-Hydroxy	1-4 Medium	8 (3-25)	None Conjugation	Anxiety, alcohol withdrawal	10mg 120mg	15-30mg po qhs
Temazepam RESTORIL	10mg 3-Hydroxy	2-3 Medium	11 (3-25)	None Conjugation	Sedative/hypnotic; no REM suppression	15mg 60mg	15-30mg po qhs
Triazolam HALCION	0.25mg Triazolo	1-2 Rapid	2 (1.5-5)	None Conjugation	Sedative/hypnotic	0.125mg 0.5mg	0.125-0.25mg po qhs
LONG ACTING: less rebound symptoms; better choice when tapering off of BZDs, LESS ADDICTIVE							
Chlordiazepoxide LIBRIUM	25mg 2-Keto	1-4 Medium	100	Yes Oxidation	Anxiety, preanesthetic, alcohol withdrawal	5mg 200-400mg	25-50mg po tid
Clonazepam KLONOPIN	0.25mg Nitro	1-4 Medium	34 (19-60)	None Oxidation & Nitro reduction	Anticonvulsant, panic attack; RLS, neuralgia	0.25mg 10-20mg	0.5-2mg po tid

Diazepam VALIUM	5mg 2-Keto	1-2 Rapid	100	Yes Oxidation	Anxiety, muscle relaxant, seizures, alcohol withdrawal	2mg 40mg	2-5mg po tid
Lorazepam DALMANE	15mg 2-Keto	0.5-1 Rapid	100 (40-250)	Yes Oxidation	Sedative/hypnotic; can accumulate	15mg 60mg	15-30mg po qhs

Flumazenil: reverses the effects of BZD and can be used in cases of OD. Use with caution as it may cause rapid symptoms of BZD withdrawal.

Cognitive Enhancers

In 1993, tacrine (Cognex) became the first medication approved by the FDA for the treatment of Alzheimer's Dementia. Initially created in Melbourne, Australia during WW2, its initial function was as an *analeptic* (stimulates respiratory muscles to aid recovery from anesthesia. Yeah, I had to look that one up). Ultimately, it was found to assist in cognition in Alzheimer's patients. It has since been removed from the market due to liver toxicity, but its mechanism of inhibition of the breakdown of acetylcholine (Ach) led to creation of other cognitive enhancers.

Long before tacrine, ancient Greek texts refer to the common snowdrop flower (*Galanthus nivalis*) being used to reverse poisons that were neurotoxic. Additionally, practitioners in Easter Europe and Southwest Asia have documented use of the flower for treatment of myopathy and sensory dysfunction. From the Galanthus flower and other botanical products (like daffodils), Bulgarian pharmacologists in the 1950s synthesized galantamine. Currently, galantamine continues to be produced from a combination of organic synthesis techniques and combination with natural resources (daffodils from Wales, UK).

Indications: treatment of mild to moderate cognitive impairment in Alzheimer's Dementia. They slow the progression of memory loss and diminish apathy, depression, hallucinations, and mood reactivity. They may also help to delay the need for nursing home placement. Donepezil and rivastigmine are also used in Parkinson's and Lewy Body Dementia in addition to being used for cognitive effects related to traumatic brain injury. Use in vascular dementia may produce improvement but not in all cases.

Profile: Alzheimer's is due to destruction and impaired production of acetylcholine. The cholinesterase inhibitors reversibly inhibit the enzymes that break down Ach, increasing synaptic concentrations of Ach especially in the hippocampus and cerebral cortex. Blocking the breakdown of Ach in the periphery leads to nausea, diarrhea, vomiting, and cardiac abnormalities including bradycardia. Side effects include nausea, diarrhea, vomiting, bradycardia, and syncope. Avoid with bethanechol and also avoid with other anticholinergic medications (like paroxetine).

Donepezil: has a half-life of 70 hours in the elderly and is taken once daily. Cirrhosis reduces the clearance by 20%. Donepezil works selectively in the CNS with less activity in the periphery on cholinesterases (less GI symptoms etc). Donepezil starts at 5 mg qhs with a maximum dose of 10 mg. Metabolized by 2D6 and 3A4. Highly protein bound but does not displace other medications. Benefit: least GI side effects and may be more effective than galantamine in treatment of cognitive disorders.

Rivastigmine: has a 1-hour half-life, but it remains bound to cholinesterases, leading to effective dose for 10 hours. Rivastigmine has more peripheral activity and inhibits *both* acetylcholinesterase and butyrylcholinesterase. As a result, it has more GI and cardiac effects. Rivastigmine starts at 1.5 mg BID and gradually increases to 3 mg BID gradually over the course of a month. The creation of a rivastigmine patch has led to more effective treatment with less peripheral effects. Unbound to proteins and has minimal drug-drug interactions as it is not metabolized in the liver. Benefit: patch good in patients with difficulty swallowing or with questionable compliance.

Galantamine: is extracted from daffodils and has a half-life of 6 hours. Side effects are minimal and transient. It is dosed at 4 mg BID per day for 4 weeks and any subsequent dose increases should occur at 4-week intervals. Maximum dose is 16 mg BID. Metabolized by 2D6 and 3A4 like donepezil. Is an allosteric agonist at the nicotinic receptor, similar to the way that BZD work on GABA receptors, in addition to stopping the breakdown of Ach? Benefit: least expensive of the cognitive enhancers with minimal side effects.

Miscellaneous Topics

Treatment of Medication Side Effects

- Tardive Dyskinesia: discontinue the medication, some indication for Vitamin E
- Akathisia: propranolol or BZD
- NMS: dantrolene, bromocriptine, cooling measures
- Sexual side effects: change SSRI, add bupropion, buspirone, sildenafil
- Anticholinergic side effects: take with food (GI), sugarless gum and pilocarpine mouthwash (dry mouth), pilocarpine eye drops (blurred vision), bethanechol (urinary retention)
- Orthostatic hypotension: increase fluid intake, decrease caffeine, increase sodium if approved by PMD, ted hose, consider changing HTN meds

Treatment of Overdose

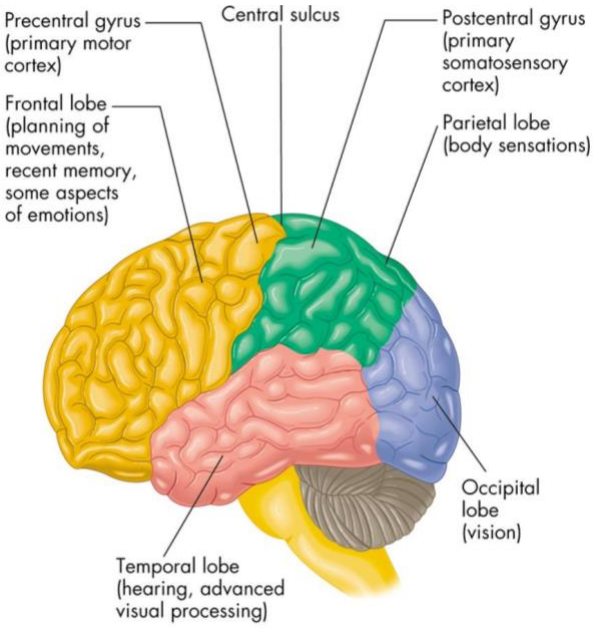
- BZD: emesis, lavage, charcoal, flumazenil
- Bupropion: lavage, charcoal, prophylactic BZD to prevent seizures
- Clozaril: charcoal and sorbitol
- Antipsychotics: lavage, charcoal, norepinephrine for hypotension, monitor EKG
- SSRI: lavage, charcoal, monitor EKG
- Lithium: emesis, lavage, dialysis (no charcoal), 0.9% NaCl if Na depletion caused toxicity
- MAOI: emesis, lavage, charcoal, pressors, BZD to prevent seizures, phentolamine for hyperthermia, avoid Demerol
- TCAs: lavage, charcoal, telemetry, EKG, anti-arrhythmia medications, BZD to prevent seizures
- Thyroid hormones: emesis, lavage, charcoal, cholestyramine, propranolol
- Opiates: naltrexone, monitor for respiratory depression and maintain airway

- ETOH: banana bag for volume and nutrient depletion, BZD to prevent seizure, maintain airway

A NINJA'S GUIDE TO NEUROLOGY

Cortex

Anatomy Overview



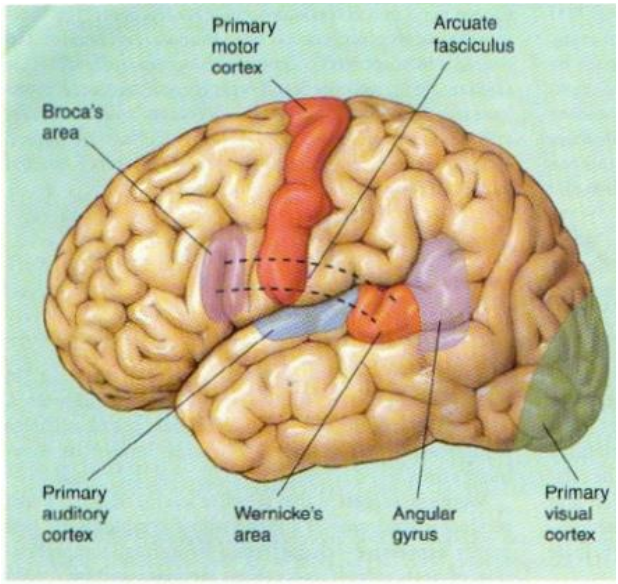


Figure 16.10 The seven components of the Wernicke-Geschwind model.

Frontal Lobes: primary motor cortex (precentral gyrus), impulse control/judgment (orbitofrontal cortex) socialization, executive functioning, working memory, language production (Broca's Area).
Parietal Lobes: primary sensory cortex (postcentral gyrus), knowledge of numbers, visuospatial processing, R-L orientation.
Temporal Lobes: primary auditory cortex, contains the hippocampus (memory), Wernicke's area (understanding language), comprehension/naming, recognition of faces, visual processing.
Occipital: primary visual cortex, lesions lead to visual field abnormalities.
Cerebellum: sensory perception, motor coordination/learning, proprioception, equilibrium, posture.
Basal Ganglia: composed of striatum (putamen/caudate/nuc accumbens), globus pallidus, subthalamic nucleus, and substantia nigra. Is associated with coordination of movement. Motor tracts go through the striatum. Abnormalities of BG include PD, Tourette's, CP, dystonia, OCD, and TD.

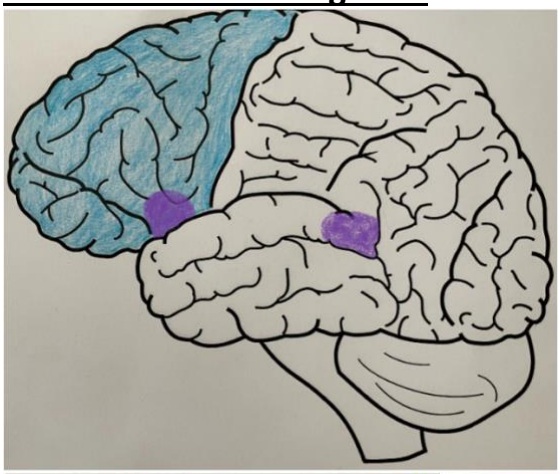
Learn the Brain Using the MoCA

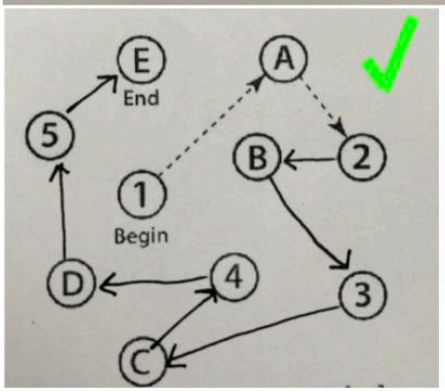
In previous versions of The Ninja's Guide to PRITE, the MMSE was used as a tool to teach neurobiology. The premise was for learners to use an already known clinical tool to identify the neuroanatomical region being tested in each MMSE task. As the MoCA becomes more widely used, this NEW 2022 section of The Ninja's Guide to PRITE utilizes this well-known tool to teach neurobiology, thanks to special contributors Drs. Gretchen Ascher and Carolina Osorio.

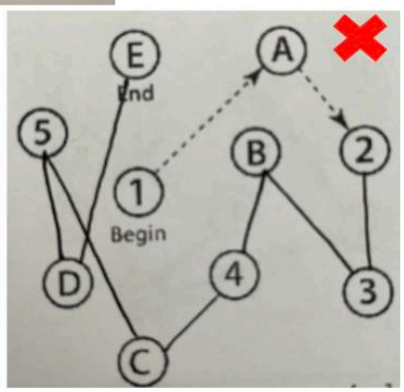
The Montreal Cognitive Assessment (MoCA) was created to screen and detect Mild Cognitive Impairment. It is scored out of 30 points and takes about 10 minutes to administer by paper and pencil. It is used around the world and has been translated into over 30 different languages. The test assesses many cognitive domains including attention, concentration, executive functioning, memory, language, visuospatial, abstraction, orientation, and calculation. The following information will review how the MoCA is used to assess neuro/anatomical areas, what is being tested with each question and common patterns seen with various pathologies.

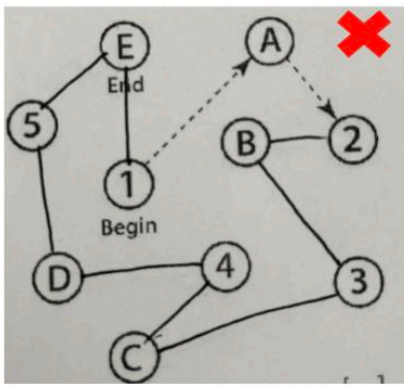
Tests of Overall Brain Integration

Modified Trail Making Test









What it tests: aside from the **visuomotor and visuo-perceptual skills** (see note below) required to complete the task, **language skills** are required to comprehend instructions. **Success** involves

understanding the instructions, knowing what the **letters and numbers mean**, and being able to **concentrate and plan** well enough to **switch back and forth** between a sequence of letters and numbers

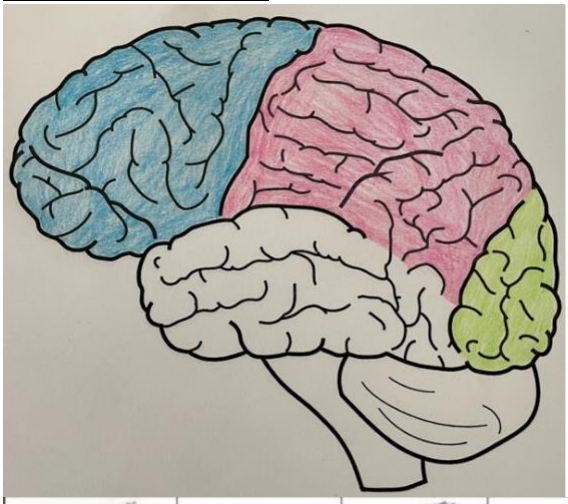
- **Language function** is controlled by **Broca's and Wernicke's Area** and is necessary to understand instructions and recognize letters/characters for task completion
- **Executive functioning** is controlled by the **Frontal Lobe** and **cortical subcortical circuits.** These regions allow switching between letters and numbers. An inability to perform the task indicates poor flexibility and concrete thinking

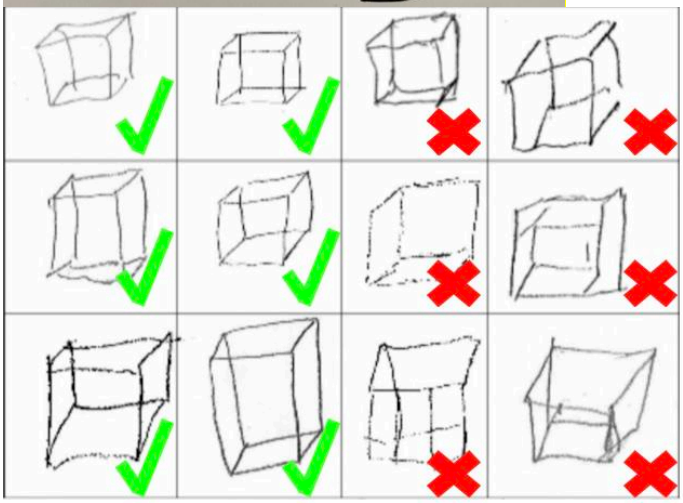
***Note*:** *visuomotor and visuo-perceptual areas are not shown in the drawing above for simplicity. These skills are required for the entire top row of tests on the MOCA (Trail Making, Cube Copy, and Clock Drawing) but are not the primary area being evaluated in the Trail Making Test. While many brain regions must be functioning together to properly complete most tasks on the MOCA, this guide will focus attention on the **brain region primarily being evaluated** by each MOCA subcategory.*

Clinical Correlation

Impairment in trail making often indicates Alzheimer's Disease, Frontal Subcortical Vascular Disease, Frontotemporal Dementia, or Lewy Body Dementia

Copy of the Cube





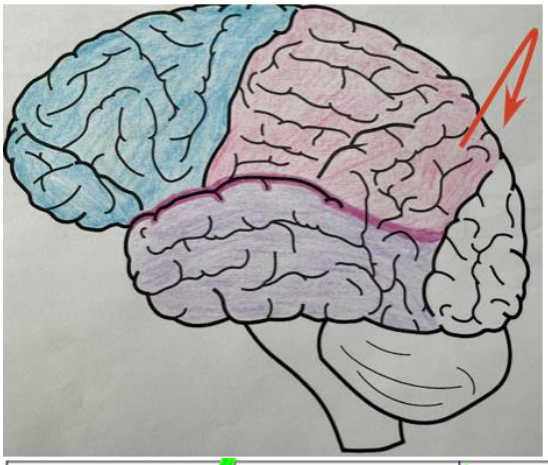
What it tests: **visuomotor and visuo-perceptual skills** in addition to **planning** and **fine motor ability.** **Success** involves being able to **see the design**, **perceive** this is a 3D object, **plan** on how to replicate it, and having the **motor ability** to draw it.

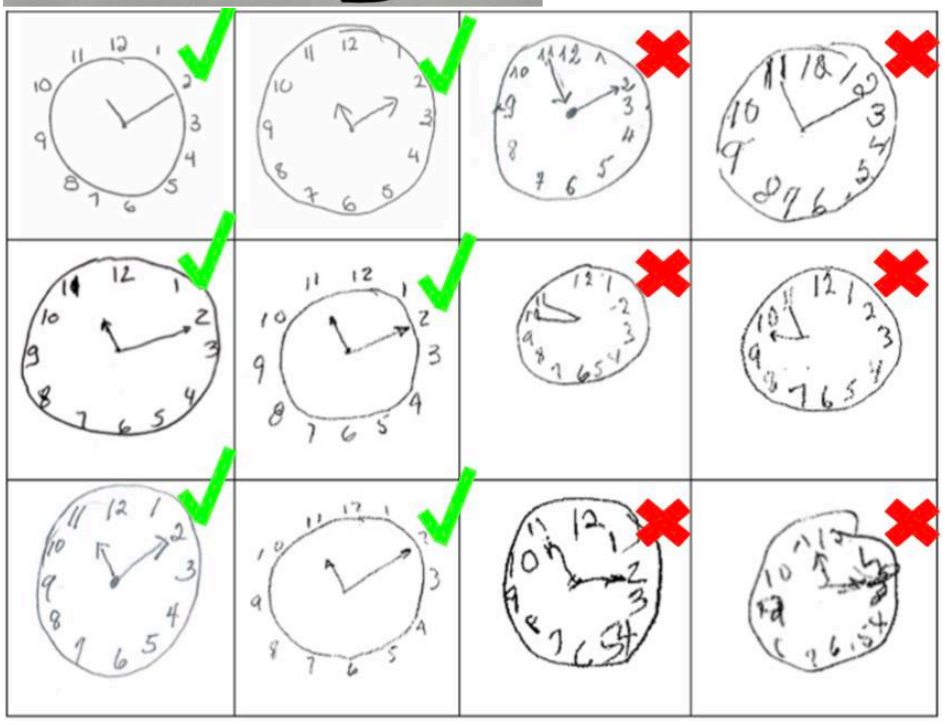
- Requires patients to convert a two-dimensional contour to a three-dimensional cube
- **Visual Perception** is controlled by the **parieto-occipital lobe**
- **Planning and executive functioning** are controlled by the **frontal lobe and frontal cortical subcortical circuits**
- **Visual and fine motor sequences** are controlled by the **fronto-parieto-occipital-cortices**

Clinical Correlation

Correlation between neuroimaging and cube copying specifically has not been reported.

The Clock Drawing Test





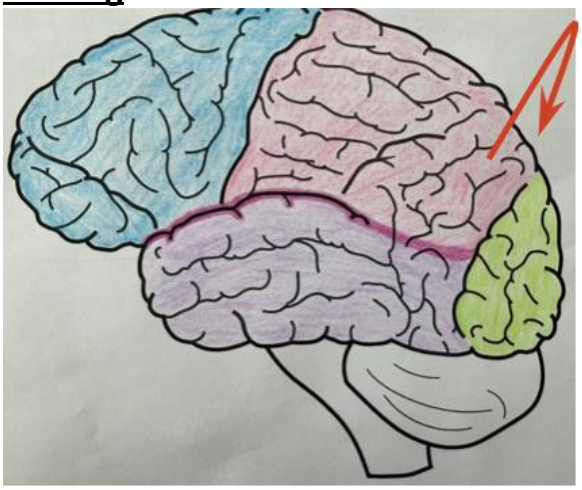
What it tests: visual-spatial functions, executive function for planning and language skills. **Success** involves **understanding the instructions**, recalling what a **clock looks like**, knowing what **numbers** are, being able to **plan** out the drawing, capturing the **spacing and design** of the clock face, and having the **motor ability** to draw the clock.

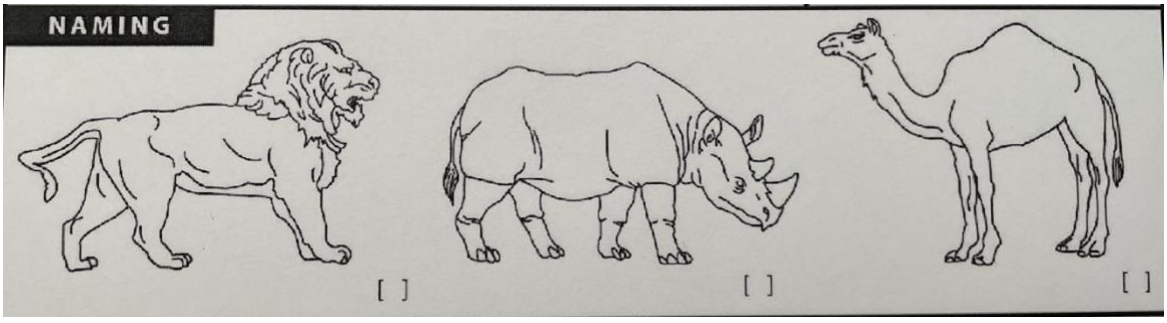
- **Language functions** are controlled by the **left parietal temporal lobe** (particularly the **Left Sylvian Valley**) in right-handed individuals
- **Visual-spatial functions** are controlled by **the right parietal lobe (** ↗ **)**
- **Executive functions** are controlled by the **Frontal Lobe, and Frontal subcortical circuits**
- **Visual and fine motor functions** are controlled by the **fronto-parieto-occipital-cortices**

Clinical Correlation

In **Alzheimer's Disease**, clock drawing **errors are mainly conceptual and due to semantic memory impairment**. Patients both with **White Matter Hyperintensities** and **Parkinson's Disease** also have poor performance on clock drawing due to disruptions in **subcortical dopaminergic pathways projecting to the prefrontal cortex**

Naming





What it tests: language abilities and perceptual-visual capacities. **Success** involves **seeing** the animal, **identifying the name** of the animal and **saying the name** of the animal.

- **Perceptual visual function** is controlled by the **Right Parietal (** ↗ **) and bilateral occipital lobes**
- **Semantic memory** stored in the **medial temporal lobes** must be retrieved to identify and name the animal

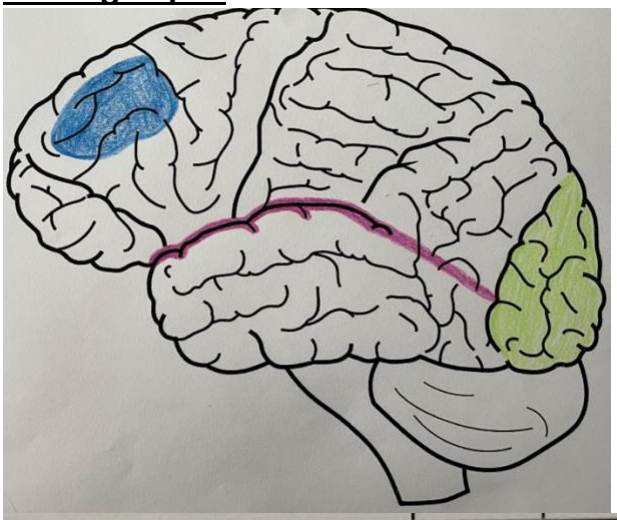
- **Language production** is controlled by the **left** **temporal-parietal** **lobe** and **left frontal lobe** **(Broca's Region)** in right-handed individuals

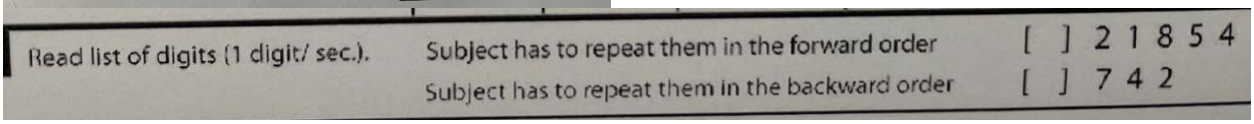
Clinical Correlation

Retrieval of names from semantic memory is impaired in Alzheimer's Disease, as is conceptual knowledge of animals. Interestingly, naming of animals is more associated with activation of the primary visual cortex whereas naming of tools is associated with activation of the frontal and parietal lobe

Tests of Attention

The Digit Span





What it tests: measures patient's retention of **auditory** stimuli and **articulatory rehearsal**, it also evaluates **attention** and **immediate memory**. This is required prior to evaluating recent memory. **Success** involves being able to **hear and understand the numbers**, be able to **recall** the numbers, **repeat** numbers, and then **concentrating** while **visualizing** the numbers in reverse order.

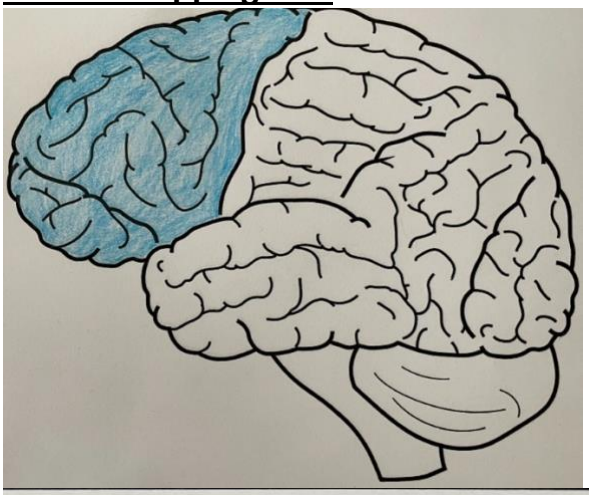
- **Language function** including understanding and speaking is controlled by the **Left Sylvian Valley**
- **Executive functioning** and **working memory** are controlled by the **Dorsolateral Prefrontal Cortex** as the backward Digit Span (DSB) must transform digits into a reversed order before articulating them
- The backwards digit span also activates the **visual cortex** which supports the hypothesis that visuospatial processing is involved during mental reversal imaging of digit sequences

Clinical Correlation

At the cutoff of **<3 digits for DSB**, sensitivity of detecting Major Cognitive Impairment including dementia, delirium, and cognitive impairment not otherwise specified is 77%. Specificity is 78%

Tests of Concentration and Calculation

Letter A Tapping Test



Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] FBACMNAAJKLBAFAKDEAAAJAMOFAAB

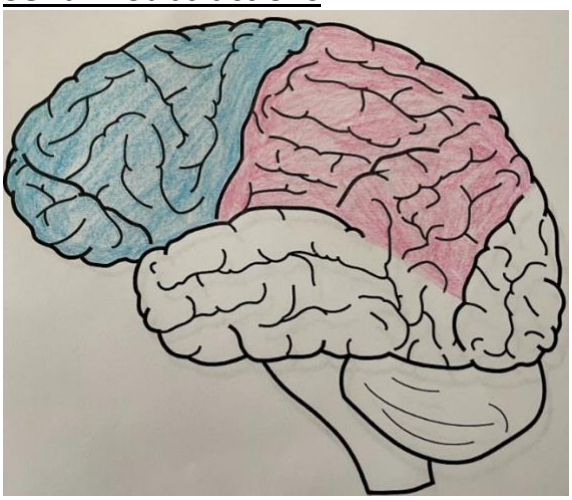
What it tests: concentration for sustained and focused **attention** to properly identify letter A and **inhibit** inappropriate non-letter A tapping. **Success** primarily involves **sustaining focus** on a single letter and not tapping on any other stimulus (letters).

- **Concentration** is controlled by the **Frontal Lobe and Frontal Subcortical Circuits**
- **Inhibition of tapping** when the wrong letter is called is controlled by the **Orbitofrontal cortex**

Clinical Correlation

Compared with normal controls, MCI patients had similar performance. Patients with Alzheimer's Dementia showed significant impairment. The test has good sensitivity to detect cognitive impairment in mild traumatic brain injury and persistent post-concussive syndrome, with patients being unable to inhibit tapping on unwanted letters (stimulus bound).

Serial 7 Subtractions



Serial 7 subtraction starting at 100	[ ] 93	[ ] 86	[ ] 79	[ ] 72	[ ] 65
	4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**				

What it tests: **concentration** and **calculation** abilities. **Success** involves being able know what numbers are, **subtract** 7 numbers **correctly**, and **sustain concentration** in order to repeatedly subtract another 7 numbers.

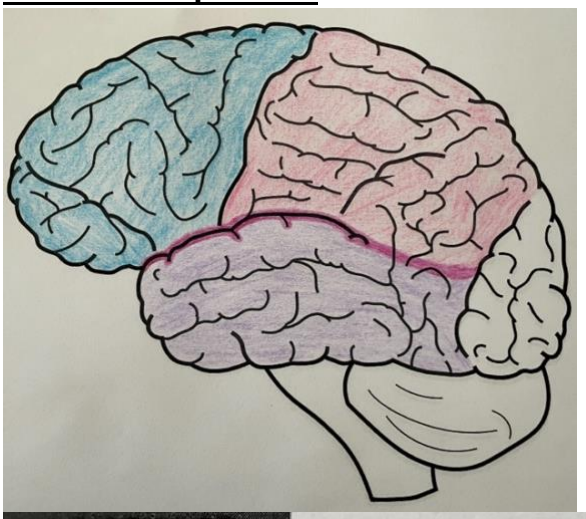
- **Concentration** controlled by the **frontal lobe and frontal-subcortical circuits**
- **Working memory** is controlled by the **Dorsolateral Prefrontal Cortex** to recall the previous answer in a loop for further subtractions
- **Calculation** requires function of the **left parietal lobe**

Clinical Correlation

In patients with Alzheimer's Dementia, mental calculation abilities in the inferior parietal cortex are impaired

Tests of Language Ability

Sentence Repetition

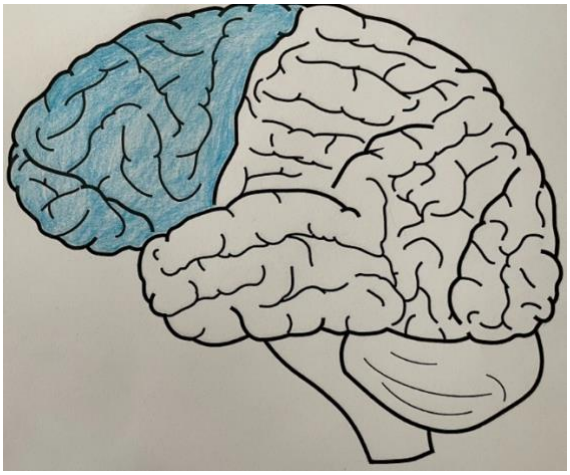


LANGUAGE	Repeat : I only know that John is the one to help today. [ ]
	The cat always hid under the couch when dogs were in the room. [ ]

What it tests: measures patient's retention of **auditory** stimuli and **articulatory rehearsal**, understanding of language, **attention** and memory (working and immediate recall). **Success** involves **hearing and understanding** the words, paying **attention** to the sentence, **memorize** the words, and **repeating** the words back.

- **Language skills** are supported by the **left temporo-parietal-frontal circuit, specifically the Left Sylvian Valley.** This circuit is involved in understanding and reproducing language
- **Working memory and attention** are supported by the **Dorsolateral Prefrontal Cortex**
- **Concentration** controlled by the **frontal lobe and frontal-subcortical circuits**

Letter F Fluency



Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

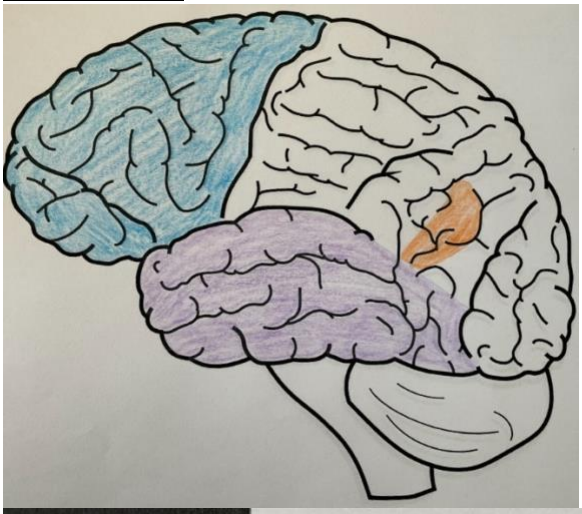
What it tests: working memory, **searching** strategy, and **inhibition** of irrelevant words while conjuring an abstract concept. Does not require semantic (categorical) memory. **Success** involves understanding and producing **language**, and the ability to search word inventory to **select appropriate** words while **ignoring wrong** words.

- **Set shifting and concentration** requires the **left frontal lobe and frontal subcortical circuits** to shift from word to word using searching strategy
- **Working memory** involves the **Dorsolateral Prefrontal Cortex** to recall words already used and remember what letter was assigned

Clinical Correlation

Patients with frontal lesions produced fewer words than healthy controls. Left frontal lesions play a greater role in letter fluency impairments compared to right frontal lesions

Abstraction



ABSTRACTION Similarity between e.g. banana - orange – fruit [ ] train – bicycle [ ] watch - ruler

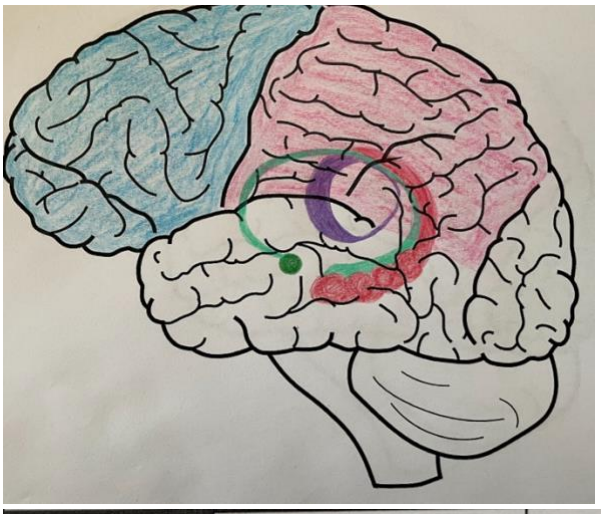
What it tests: semantic memory, **abstract** thought, and correctly identifies **associations**. **Success** involves understanding **language**, **semantic** knowledge of **categories** and meanings of words, and the **abstract** ability to link related concepts.

- **Semantic memory** is stored in the **medial temporal lobes**
- **Knowledge of categories and concepts** involves the **left temporal lobe** and **left angular gyrus**
- **Abstract thinking** is controlled by the **frontal subcortical circuits**

Clinical Correlation

Alzheimer's Disease patients who have impairments in identifying similarities for more difficult words have been found to have abnormalities in the **left temporal lobe** and **left angular gyrus**

Delayed Recall



MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	
	1st trial						No points
	2nd trial						

After about 5 minutes must recite words given above

Has to recall words WITH NO CUE	FACE [✓]	VELVET [X]	CHURCH [✓]	DAISY [X]	RED [✓]	Points for UNCUED recall only	3/5
Category cue	✓	✓	✓	X	✓		
Multiple choice cue	✓	✓	✓	✓	✓		

What it tests: recent **verbal memory abilities**. **Success** involves **hearing** the words, understanding and producing **language**, **encoding memory**, and then **retrieving the memory** at a later time.

- **Retrieval memory** (**cues are helpful for recall**) is a function of the **frontal lobe or frontal subcortical structures** and the **hippocampal-parieto-frontal networks**
- **Encoding memory** is a function of **Left Papez Circuit** which **includes the hippocampus, fornix, mammillary bodies, and Thalamus**.

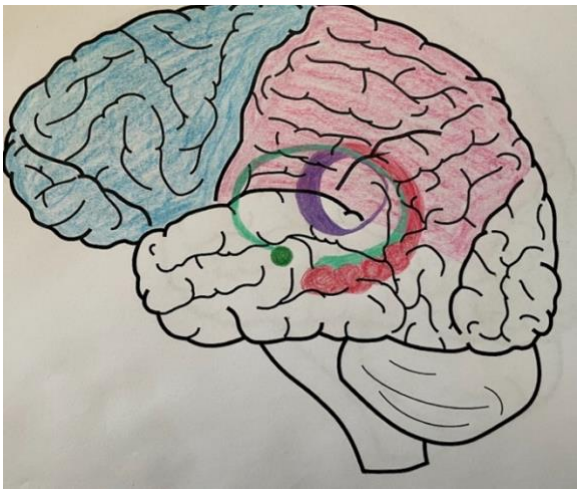
- Giving category and multiple-choice cues allows one to distinguish between encoding and retrieval memory impairment. **Encoding memory impairment does not improve with cuing** but retrieval memory impairment does.

Clinical Correlation

Retrieval memory impairment is seen with Vascular Cognitive Impairment, PD, HD, Depression, Frontotemporal Dementia, NPH, and HIV cognitive impairment. It is usually the result of poorly functioning **frontal lobe or frontal subcortical structures**. This can be associated with medial parietal and frontal white matter loss, posterior cingulate hypometabolism, pathologies of subcortical structures, and the **hippocampal-parieto-frontal networks**

Encoding memory impairment is seen with Alzheimer's Dementia, Wernicke's and Korsakoff Syndrome, ischemic or hemorrhagic strokes or tumors that affect the Papez Circuit, and surgical excision of the medial temporal lobe for epilepsy. It is correlated with hippocampal atrophy and hypometabolism. **Recent verbal encoding memory** requires function of the **Left Papez Circuit** which **includes the hippocampus, fornix, mammillary bodies, and thalamus**.

Orientation



ORIENTATION	[ ] Date	[ ] Month	[ ] Year	[ ] Day	[ ] Place	[ ] City	/6

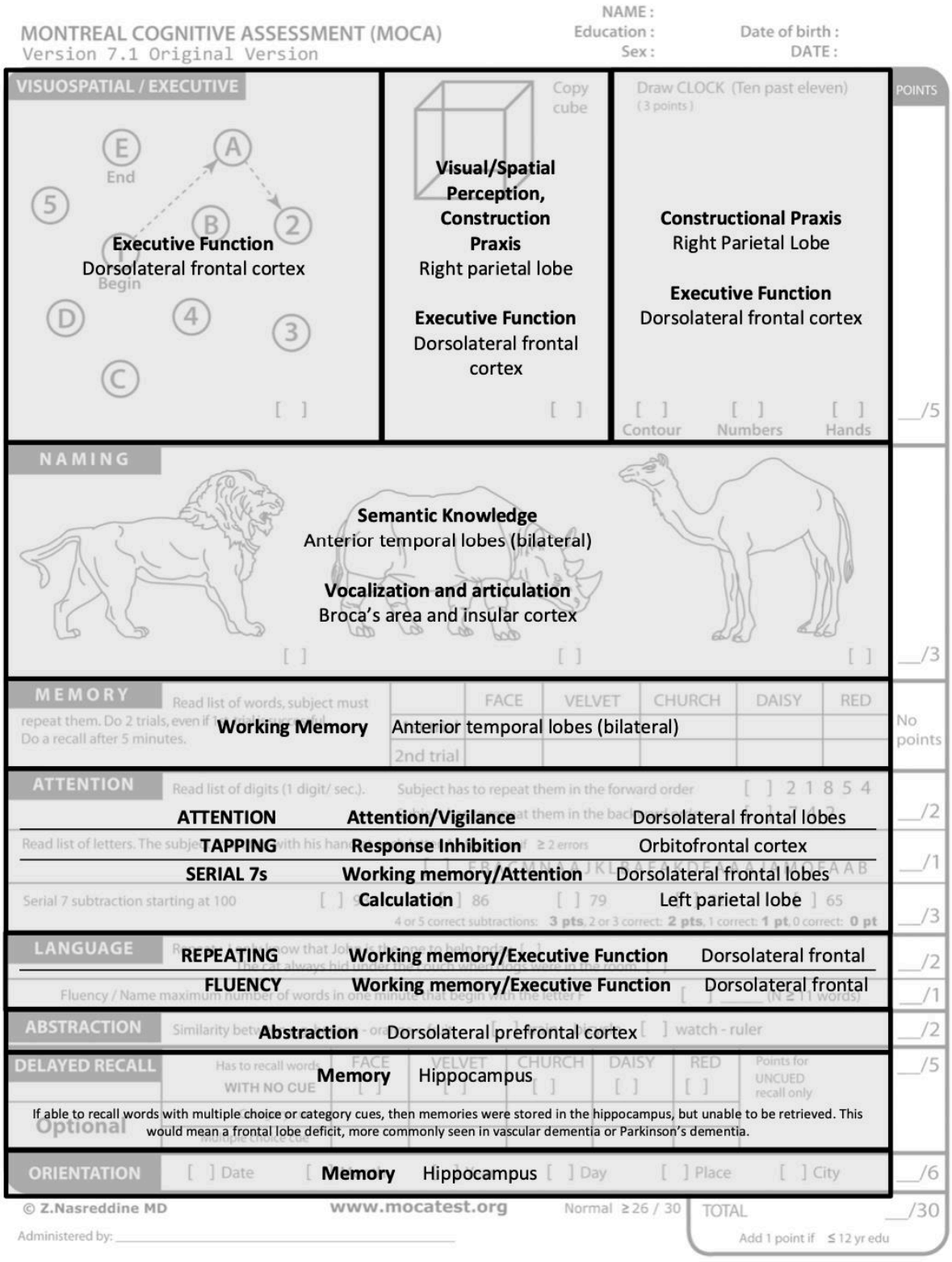
What it tests: recent memory. **Success** involves **recall** of the events of the day and retaining information about **location**

- **Orientation** is controlled by the **Papez Circuit** which **includes the hippocampus, fornix, mammillary bodies, and Thalamus**

Clinical Correlation

Orientation has a high sensitivity (95%) for detecting dementia and delirium, however it has a low specificity (38%). Abnormal orientation to month and year has strong validity for detecting those with cognitive impairment. Deficits in orientation have been found to be the single best predictor of poor daily function and caregiver burden in patients with dementia.

Lesion Localization Based on MoCA



https://www.psychdb.com/_media/cognitive-testing/moca_localization.pdf

MoCA Clinical Correlates

Mild Cognitive Impairment

- Compared to normal controls, MCI has deficits on word repetition, backward digit span repetition, serial 7 subtractions, sentence repetition, letter F fluency, abstraction and delayed word recall prior to being cued
- The average MoCA score seen in MCI ranges from **22-23** compared to an **average score of 16-17 seen in Alzheimer's Disease**
- MCI often has less impairments seen with clock drawing, naming, delayed recall after being cued, and orientation

Alzheimer's Dementia (AD)

- **Sensitivity to detect AD** using the MOCA has been shown to be about **97% on average**
- Depending on the severity of disease progression, deficits can be seen on all sections of the MOCA
- Alzheimer's disease patients often perform worse on initial MOCA's than would be seen with Frontal Temporal or Lewy Body Dementia
- Poor performance on cube drawing due to **right parietal cortex and inferior temporal atrophy** which creates deficits in **spatial perception and attention**
    - *Note this is a different mechanism than causes poor performance on cube drawing in FTD (see below)*
- **Semantic memory impairment** is seen early in the course of disease
- **Encoding memory** is impaired in Alzheimer's Disease, meaning patients **can't learn new information**. This is reflected in poor performance on delayed recall even when multiple choice or categorical clues are provided.

Lewy Body Dementia

- Lewy Body Dementia primarily affects **executive functioning** and **visuospatial** sections of the MoCA early on in disease course
- LBD can be differentiated from AD via MoCA testing as LBD patients tend to perform much **worse on the clock drawing section** and **better on delayed recall compared to AD patients**
- Patients with LBD also tend to score poorly on **serial 7 subtraction**

Fronto-Temporal Dementia (FTD)

- Tend to score higher on the MoCA compared to patients with Alzheimer's Disease
- Often perform worse than Alzheimer's Disease patients on the **Letter A tapping test** due to perseveration which impairs attention
- Perform poorly on **Letter F Fluency** due to impaired frontal lobe function

- Impairment in cube drawing is due to a different mechanism than is seen in Alzheimer's Disease. FTD patient's have impaired cube drawing due to right **dorsolateral prefrontal cortex atrophy** causing **deficits in spatial planning and working memory**
- Outperform Alzheimer's disease patients on serial 7 subtractions, delayed recall, and orientation sections reflecting the short term and working memory demands of these tasks
    - Despite performing better on these tasks, these MOCA subcategories are often still affected in FTD

Vascular Cognitive Impairment

- **Vascular Dementia** has been detected using MoCA with a sensitivity of 86.8% and specificity 92.9%
- **Hallmark of vascular dementia** is **executive dysfunction** which the MOCA tests with the trail making test, cube copy, clock drawing, animal naming, sentence repetition, and letter F fluency
- Deficits on serial 7 subtraction is one non-specific tool that may raise concerns of **frontal-subcortical vascular disease**
- MoCA detects cognitive impairment in patients with **white matter disease** and history of stroke with a sensitivity of 73% and specificity of 75%
- 54% to 70% of non-demented community dwelling adults with heart failure had scores on the **MoCA $\leq$ 26** thought to be due to chronic reduction of cerebral blood flow
- MCI diagnosed via MoCA in patients with cardiovascular disease has been shown to be a predictor of need for assistance of 1 or more activities of daily living

Parkinson's Disease

- Prevalence of dementia in this population is 20-40%
- Earliest cognitive changes are due to **frontal striatal disconnection** which creates **deficits in executive function and attention**
- As Parkinson's disease progresses, **memory** becomes affected
- Sensitivity for detecting Parkinson's Disease Dementia using MoCA is 81-82% and specificity is 75-95%
- Sensitivity for Parkinson's Disease Mild Cognitive Impairment is 83-90% and specificity is 53-75%
- Baseline MoCA scores in PD patients can predict the rate of cognitive deterioration. **Rapid decliners** have been shown to have **lower overall MoCA scores** and performed worse on **clock drawing, attention, verbal fluency,** and **abstraction**
- Of note, the MoCA requires fine motor movement on clock drawing, trail making, and cube drawing which can impact results

Major Depressive Disorder

- One study comparing the MoCA scores of patients with depression to the MoCA scores of those with Alzheimer's Disease, Frontal Temporal Dementia, and normal controls found that **half the patients with depression alone scored below the normal cut off of 26 points**

    - Depressed patients overall scored lower than normal controls but not as low as patients with Alzheimer's Disease and Frontal Temporal Dementia patients
- Common deficits seen in patients with depression when compared to normal controls include significantly worse scores on visuospatial/executive function tasks, repetition, Letter F Fluency, serial 7 subtraction, and delayed recall prior to being cued
- Much of the deficits are due to **global cognitive slowing** seen in depression

Delirium

- A core diagnostic feature of delirium is **impaired attention**. Because the MoCA has various categories that assess attention, it can be a tempting option to use for delirium diagnosis
- **Letter A Tapping, Serial 7 Subtraction, and Digit Span Backward** require intact attention and are often impaired in delirium
    - These have **good negative predictive value for delirium**, ie they are good at excluding delirium yet are not diagnostic
- Digit Span Backward can detect 81% of delirium patients however there is a false positive rate of 37%
- Orientation has 95% sensitivity for detecting delirium but low specificity of 38%
- The gold standard to assess for delirium is the Confusion Assessment Method (CAM) which assesses 4 criteria of delirium: 1. Acute onset and fluctuating course, 2. Inattention, 3. Disorganized thinking, 4. Altered Level of Consciousness
- Additional tools to assess for delirium include Global Clinical Subjective Rating of Attention and listing the months of the year backward

Obstructive Sleep Apnea (OSA)

- In patients with OSA, MoCA scores progressively decreased as OSA severity increases
- In severe OSA, domains often affected are delayed recall, visuospatial/executive function, and attention/concentration
- Mild OSA participants perform similar to those without OSA but who snore, however the mild OSA group still had more prominent impairments in visuospatial executive dysfunction and delayed recall

Huntington's Disease

- In asymptomatic Carriers, Global Cognitive Function is relatively preserved but there is often an early impairment in these individuals seen in **attention, psychomotor speed, working memory, verbal memory, and executive functioning**
- Deficits are due to abnormal **frontal-striatal circuitry**
- Deficits in **naming** on the MoCA are due to **visuo-perceptual deficits from subcortical dementia**
- Deficits in **letter F fluency** are often seen
- Delayed recall prior to providing a cue may be affected
- MoCA has better detection of impaired cognitive domains in early HD compared to MMSE due to the MOCA having more emphasis on executive and visuo-spatial dysfunction (Clock Drawing,

Trail Making, Cube Copy, abstraction, Letter F Fluency) and Memory and attention (Five word delayed recall, digit span, letter tapping)

Brain Metastases

- MoCA detected cognitive impairment in 70% of those who scored in the normal range on the MMSE
- Deficits were most significant in **delayed recall (90%) or Language (90%)** and **visuospatial/executive dysfunction (60%)**
- MoCA score <22 is predictive of worse overall median survival compared to those with scores ≥ 22
- Cognitive impairment alone does not directly cause decreased survival but may represent other confounders such as extent of disease, tumor location, etc.

Systemic Lupus Erythematous (SLE)

- In SLE, cognitive dysfunction can occur with or without clinical overt neuropsychiatric SLE
- There has been shown to be metabolic change in white matter of **non-neuropsychiatric SLE (non-NSLE) patients** with cognitive impairment
    - These patients have early impairments in **verbal fluency, digit symbol substitution, and attention**
- Those who develop **NSLE** have impairment in the domains of **memory, psychomotor speed, reasoning, and complex attention**

Idiopathic Rapid Eye Movement Sleep Behavior Disorder (Idiopathic RBD)

- Mild Cognitive Impairment is found in 50% of Idiopathic RBD. The most common affected domains are **executive function and attention**
- Possible impairment in visuospatial construction and visuospatial learning
- Association between idiopathic RBD and developing Parkinson's Disease, Lewy Body Dementia, and Multiple System Atrophy. MoCA findings may reflect the early stages of an early neurodegenerative disease

Summary of MoCA Clinical Correlates

	Overall MOCA Score	Subcategory Impairments that hint at diagnosis	Often Normal Performing Sections
Mild Cognitive Impairment (MCI)	18 - 25	- Sentence repetition - Serial 7 subtraction - Backward Digit Span - Letter F Fluency - Abstraction - Delayed recall prior to being cued	- Clock drawing - Naming - Delayed Recall when cued (still able to encode) - Orientation
Alzheimer's Disease (AD)	Less than 18	- Delayed recall even when cued (impairment in memory encoding)	- With disease progression, all areas eventually become affected
Lewy Body Dementia (LBD	Less than 18	- Significant impairment on clock drawing (worse than seen with AD) - Overall deficits in executive function/visuospatial sections	- Delayed recall often intact, helping to differentiate from AD
Frontal Temporal Dementia (FTD)	Less than 18 although often score higher than AD patients overall	- Poor performance on "letter A tapping" likely due to perseveration (tapping multiple times) seen in FTD - May also see perseveration on clock draw by writing numbers multiple times, drawing multiple clock hands etc. - Letter F Fluency	Compared to AD, overall better performance due to intact short term and working memory as seen with: - serial 7 subtraction - Delayed recall - Orientation
Vascular Cognitive Impairment	Less than 26 for MCI and less than 18 for Vascular Dementia	Executive dysfunction deficits: - Trail making - Cube copy - Clock drawing - Animal naming - Sentence repetition - Letter F Fluency Serial 7 subtraction (due to frontal subcortical vascular disease)	- Delayed recall with categorical/multiple choice cues often intact unless ischemic stroke of the Left Papez circuit has occurred
Parkinson's Disease MCI and Dementia (PD)	Varies depending if MCI or Dementia	- Executive/visuospatial domains - Backward digit span - Delayed Recall (without cue) - Abstraction - Letter F Fluency (Depends on Frontal lobe function for phonemic memory)	- Animal Naming - Digit Span Forward - Letter A Tapping - Serial 7 Subtraction - Delayed Recall with cue - Orientation
Depression	Often score lower than 26 but better than AD and FTD patients	- Executive Function/Visuospatial sections - Sentence Repetition - Letter F Fluency - Serial 7 subtraction - Delayed Recall (without cue)	- More or less tend to score similar to normal controls in other sections
Delirium	Varies depending on delirium severity and given waxing/waning quality	- Letter A tapping - Serial 7 Subtraction - Digit Span Forward and Backward - Orientation *Above not diagnostic, high negative predictive value but low positive predictive value	- Often significant impairments in most sections
Obstructive Sleep Apnea (OSA)	Scores decrease as OSA severity increase	Even with mild OSA, deficits often seen in: - Trail Making - Cube Copy - Clock Drawing - Delayed Recall	Unless severe OSA the following are often normal: - Sentence repetition - Letter A tapping - Serial 7 subtraction

High Yield PRITE Review

Q: A previously pleasant mother becomes profane and irresponsible over 6 months. Where is the lesion?
A: **Frontal Lobe**. The frontal lobe is associated with impulse control, judgment, sexual behavior, socialization, and memory/language production. This patient has evidence of frontal lobe dysfunction as evidenced by new onset of socially unacceptable behaviors.

Q: A 62-year-old male with DM speaks in nonsense, saying "thar szing is phrumper zu stalking." Normal intonation but nobody in the family can understand him. He cannot follow instructions. Diagnosis?
A: **Wernicke's Aphasia**. The patient has fluent aphasia (also known as receptive aphasia) due to damage to Wernicke's area in the superior temporal gyrus. The patient can produce nonsensical words with proper intonation, but comprehension is impaired. Temporal lobe is associated with hearing and language comprehension. This is different from Broca's aphasia, which is also known as expressive/non-fluent aphasia due to damage to the inferior frontal region of the brain (usually the L side). The frontal lobe is associated with motor ability and forming words. These patients cannot produce language but have normal comprehension. Conduction aphasia is produced by disruption of the pathways connecting Broca's and Wernicke's areas, leading to a patient being able to repeat phrases despite intact comprehension and language ability.
Q: 60-year-old male (R handed) who frequently gets lost, and only writes on the right half of paper. Where is the brain lesion?
A: **Right Parietal Lobe.** This is an example of Left-sided hemi-neglect. The parietal lobes are associated with "deployment of attention" of the contralateral space. This is a sensory deficit that has lack of attention to items in the left visual field. Damage of right parietal lobe is more commonly associated with hemineglect than left parietal lobes.

Q: A 55-year-old female presents with inability to write, calculate or do arithmetic, and inability to distinguish the different fingers on her hands. Where is the lesion?
A: **Left Parietal Lobe**. This is an example of "Gerstmann syndrome" and the collection of symptoms indicate abnormalities in left parietal lobe (dysgraphia, dyscalculia, finger agnosia).

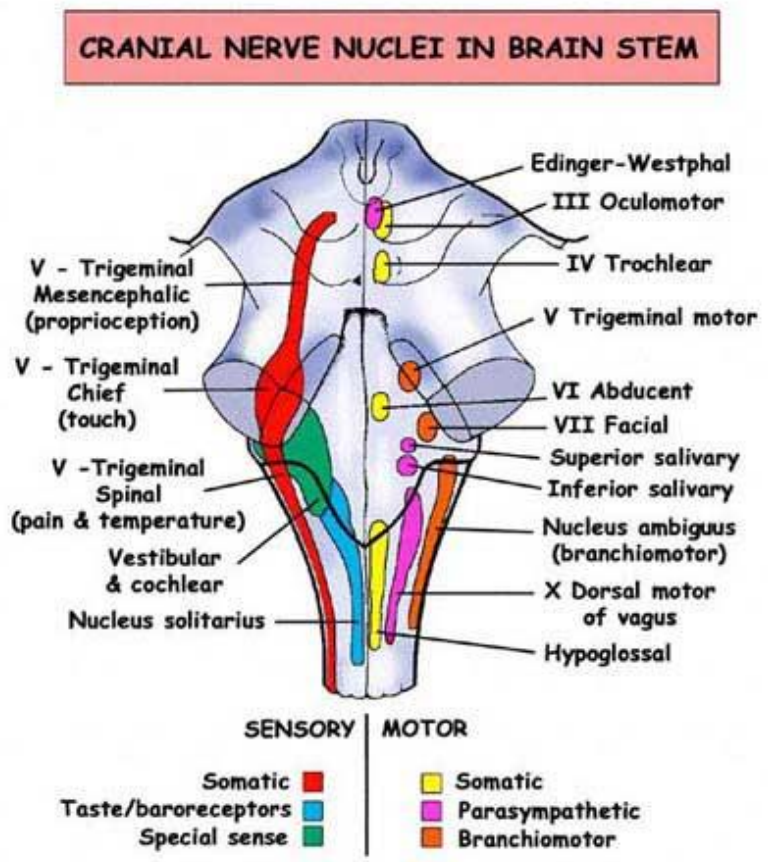
Q: A 28-year-old patient presents with a loss of vision in the bilateral temporal visual fields and abnormalities in prolactin. Where is the lesion?
A: **Pituitary adenoma**. This lesion compresses the optic chiasm leading to bitemporal hemianopsia. In addition, it leads to abnormal prolactin levels.

Q: A 22-year-old with fever, headache, seizures, confusion, stupor, and coma evolving over a few days. EEG has lateralized high-voltage sharp waves arising in the L temporal region, with slow wave complexes repeating at 2-3 second intervals. CT shows low-density lesion in L temporal lobe. Diagnosis?

A: **Herpes Simplex Encephalitis**. Retrograde transmission of Herpes virus from a peripheral site into the CNS along a nerve axon. Can lie dormant in the trigeminal (CN V) ganglion. Targets the temporal lobes of the brain, leading to seizures with high-voltage sharp waves and slow wave complexes. Diagnosis is made through EEG, CT, and CSF PCR for herpes simplex DNA or CSF viral culture (CSF has lymphocytic pleocytosis). Treatment includes acyclovir and supportive treatment.
Brainstem and Spinal Cord

Cranial Nerves

Anatomy Overview



Midbrain (CN III-V): upper part of brainstem, contains nuclei for

- CN III: oculomotor—eye movement except SO and LR muscles; Edinger-Westphal—autonomic functions like pupillary dilation
- CN IV: trochlear—supeior oblique muscle which turns eye down/in

- CN V: trigeminal sensory—facial sensation

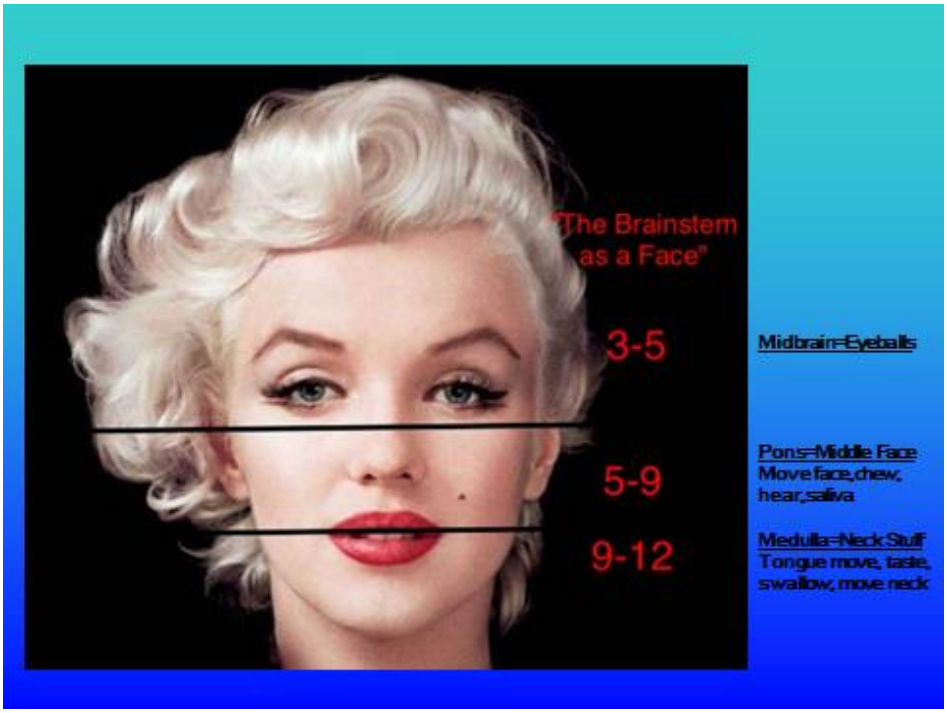
Pons (CN V-IX): middle brainstem, contains nuclei for

- CN V: trigeminal motor—motor branches of mandibular nerve for biting, chewing, swallowing has bilateral innervation, thus deficit in central lesion is rare
- CN V: spinal sensory
- CN VI: abducens—lateral rectus muscle laterally moves eye
- CN VII: facial—facial motor
- CN VIII: vestibular—balance/equilibrium (dysfunction leads to vertigo and nystagmus); Cochlear—hearing
- Salivary nuclei: Inferior nucleus—IX for parasympathetic parotid; Superior nucleus—VII for submandibular/sublingual salivation

Medulla (CN IX-XII): lowest portion of brainstem, is the location for decussation of motor tracts and dorsolateral column (proprioception/fine touch). Contains nuclei for

- Spinal CN V: sensory
- Solitary Nucleus: VII—taste to anterior $^{2}/_{3}$ of tongue; IX—taste to posterior $^{1}/_{3}$ tongue and info from carotid baroreceptors/carotid body chemoreceptors; X—sensation from outer ear
- Nucleus Ambiguous: motor nucleus for IX, X, XI; IX—lower motor neuron for stylopharyngeus; X—larynx/pharynx; XI—accessory nerve for movement of neck muscles
- Hypoglossal Nucleus: XII—moves tongue

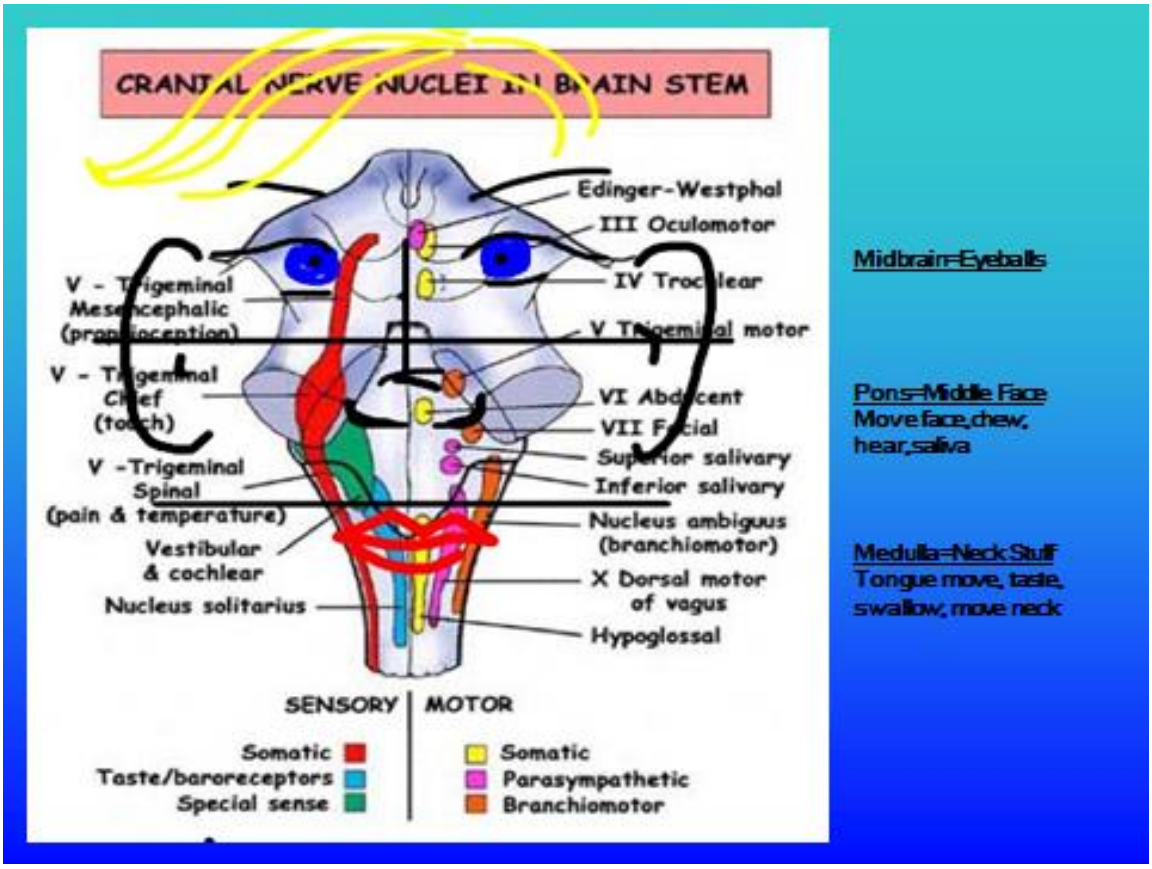
Pereau's "The Brainstem as a Face" Review Tool



Quick PRITE review: simplify the cranial nerves & nuclei to match 3 facial zones

- Zone 1: "Eyeballs." CN III-V. Midbrain lesions cause abnormality in eye movement (CN III) and face sensation (V)
- Zone 2: "Middle Face." CN V-IX. Pons lesions cause abnormalities in facial movement (VII), chewing (V), saliva production (IX), hearing/balance (VIII)
- Zone 3: "Neck Stuff." CN IX-XII. Medulla lesions affect tongue movement (XII), taste (VII, IX) swallowing (IX, X) and neck movement (XI)

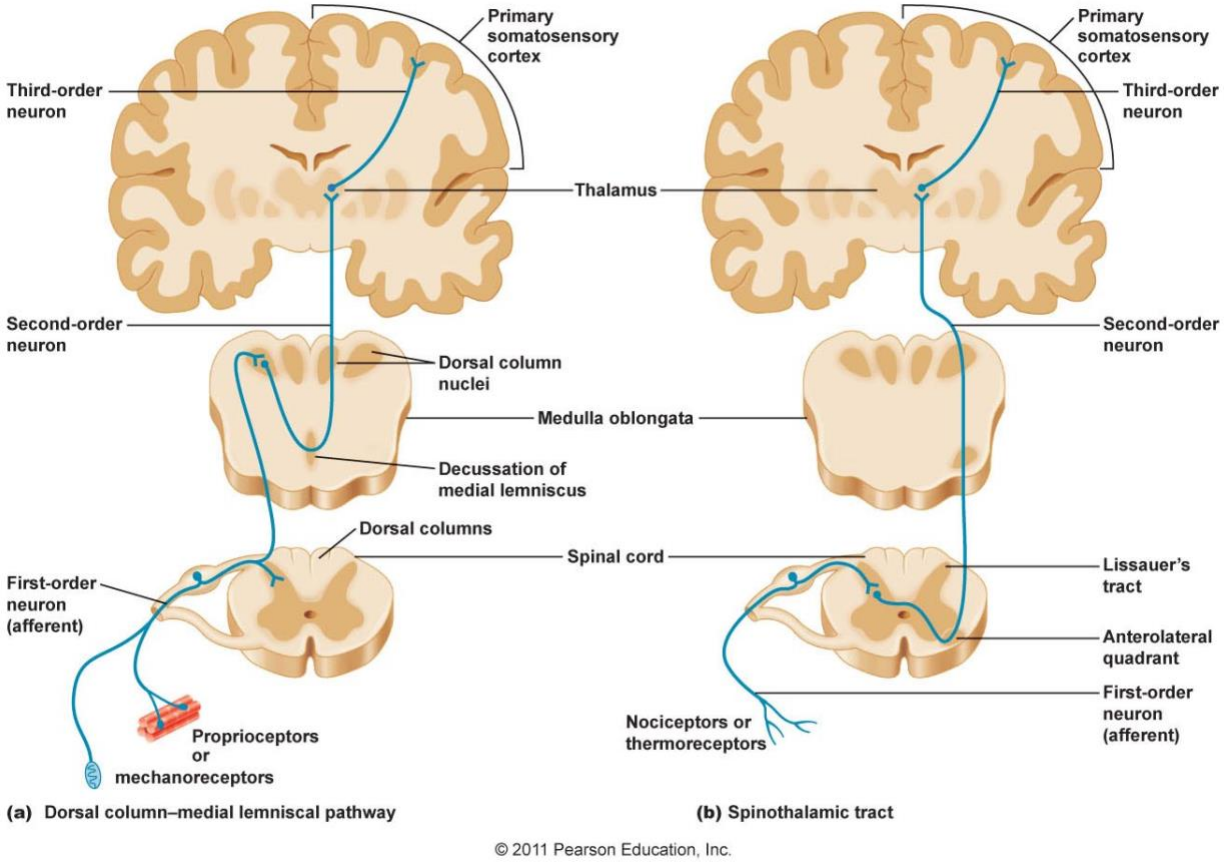
While not a perfect model (VI out of place, V facial sensation is higher than expected), this is a quick way to isolate brain stem lesions in PRITE vignettes. Remember that the cerebellum has connections at all levels of the brainstem. Thus, ataxia/nystagmus can occur in any zone


Edinger-Westphal
III Oculomotor
IV Trochlear
V Trigeminal motor
VI Abducent
VII Facial
Superior salivary
Inferior salivary
Nucleus ambiguus (branchiomotor)
X Dorsal motor of vagus
Hypoglossal
Nucleus solitarius
Vestibular & cochlear
V -Trigeminal Spinal (pain & temperature)
V - Trigeminal Chief (touch)
V - Trigeminal Mesencephalic (proprioception)
SENSORY
MOTOR
Somatic
Taste/baroreceptors
Special sense
Somatic
Parasympathetic
Branchiomotor
Midbrain=Eyeballs
Pons=Middle Face
Move face, chew, hear, saliva
Medulla=Neck Stuff
Tongue move, taste, swallow, move neck

Sensory Tracts

Dorsal Column: proprioception and fine touch. Ascends in the posterior portion of the spinal cord and crosses in the medulla, synapses in the thalamus and then goes to the sensory cortex. Spinal cord lesions lead to ipsilateral deficits. Medullary lesions or higher lead to contralateral deficits.

Spinothalamic tract: pain and temperature. Immediately cross upon entering the spinal cord, ascends through the brainstem, synapses in the thalamus, and goes to the sensory cortex. All lesions above the initial entrance to the spinal cord leads to contralateral deficits.



High Yield PRITE Review

Q: A 35-year-old female presents with unilateral hearing loss, unsteadiness, falls, headaches, mild facial weakness, and ipsilateral limb ataxia. Where is the lesion?
A: **Cerebellopontine angle**. The patient has clear symptoms of cerebellar dysfunction (ipsilateral ataxia is specific for cerebellum). The Pons has multiple CN nuclei, including the facial nerve (facial weakness) and vestibular nerve (unilateral hearing and balance). Zone 2: Middle Face=Pons

Q: A 48-year-old with history of hypertension develops vertigo, nausea, vomiting, hiccups, left-sided face numbness, nystagmus, hoarseness, deficits in pain/temperature on the right side of the body, ataxia of the limbs, staggering gait, and falls to the left. Diagnosis?
A: **Lateral Medullary Stroke**. Also, called Wallenberg's Syndrome and Posterior Inferior Cerebellar Artery Syndrome. Occlusion of the PICA leads to lateral medullary infarct. The symptoms include: contralateral deficits in pain/temperature (lateral spin thalamic tract, which crossed early in spinal cord), ipsilateral loss pain/temperature to face (trigeminal nucleus), dysphagia/hoarseness and diminished gag reflex (Nucleus Ambiguous: vagus and glossopharyngeal), vertigo/nystagmus (vestibular), ipsilateral Horner's (descending sympathetics), ipsilateral ataxia, and hiccups. Zone 3: Neck Stuff=Medulla. While VIII symptoms are present, the Zone 3 symptoms indicate medulla and would not be seen in pons lesions.

Q: A patient presents with pain behind the left ear progressing to numbness of the L face, tearing of the L eye, discomfort with low frequency sounds, and L facial weakness on exam. Diagnosis?
A: **Bell's Palsy**. Abnormality of CN VII with LMN paralysis, is related to Lyme disease and Herpes Zoster. This is isolated VII lesion. A Zone 2 lesion would have issues with chewing, saliva, hearing, etc. Inflammation of the facial nerve as it exits the skull leads to symptoms of facial paralysis. Often the trigeminal nerve may be involved, leading to numbness. Tinnitus is the result of involvement with CN VIII. CN VII has bilateral innervation of the forehead (2 nerve innervation for each side of the forehead). In UMN lesions, the forehead may be spared due to this BL innervation. However, in LMN conditions (Bell's) the forehead is affected due to the BL innervation gets inflamed going through the canal. Treatment is steroids or treatment of underlying Herpes.

Q: A 38-year-old with severely sensitive, lancinating pain on the cheek, lasting a few seconds, and is triggered by light touch on the face. Diagnosis?
A: **Trigeminal Neuralgia**. Also, called Tic doloureux. Neuropathic disorder of the trigeminal nerve (CN V) that causes intense pain in the eyes, lips, nose, scalp, forehead, and jaws. Associated with high rates of suicide due to significant pain. Suspected cause is superior cerebellar artery compressing CN V near its connection with the pons. Per PRITE, treatment is cited to be carbamazepine or gabapentin.

Q: A 48-year-old presents with unsteady, lurching, broad-based gait, appendicular ataxia in LE only, and normal eye movement. He noted progressive leg weakness and clumsiness over the past year. Diagnosis?
A: **Alcoholic Cerebellar Degeneration**. Irreversible alcohol toxicity in Purkinje cells, related to glutamate abnormalities and possibly nutritional deficiency. Presents with tremor, unsteady gait, and truncal ataxia. Predominant in the LE. Irreversible, even after ETOH is stopped. Symptoms evolve from weeks to months. On MRI there is cerebellar shrinkage. Thalamus and periaqueductal gray matter are intact, and cognition is normal (vs. Wernicke's Encephalopathy). Treatment include improved nutrition, thiamine, and cessation of alcohol.

Q: A 62-year-old presents with paralysis of eye movement, ataxia, and global confusion. He also has short term memory impairment. Diagnosis?
A: **Wernicke's Encephalopathy**. Severe syndrome due to chronic alcoholism, precipitated by thiamine deficiency. Damage is caused to the mammillary bodies, medial thalamic nuclei, and periaqueductal areas. Clinical triad include confusion, truncal ataxia/gait imbalance, and opthalmoplegia (extraocular paralysis of CN, especially CN VI). MRI shows abnormal hyperdensity of mammillary bodies and periaqueductal grey matter. Can progress to Korsakoff's Syndrome (anterograde/retrograde amnesia, confabulation, and apathy) and coma/death. Treatment is thiamine replacement. DO NOT administer glucose before thiamine, leads to cell death by providing substrates for biologic pathways without sufficient coenzymes (thiamine). IV thiamine/nutritional replacement is needed as well as supportive care. Mainstay of treatment is cessation of ETOH use.

Q: A 65-year-old male with 6-months of episodic confusion, disorientation, VH of children playing in his room, no AH, and is normal between episodes. Exam: normal language/memory, difficulty with trails test and serial subtractions, and symmetric rigidity/bradykinesia. MRI, labs, UDS, and CSF are normal. Diagnosis?
A: **Lewy Body Dementia**: overlaps Alzheimer's Dementia and PD. Triad of abnormal proteinaceous cytoplasmic inclusions (Lewy bodies), abnormal DA neurons in substantia nigra (like PD), and loss of Ach-producing neurons in Basal Nucleus of Meynart (like Alz Dementia) lead to the classic symptoms of VH, Parkinson's features, and cognitive deficits. Treatment includes use of cholinesterase inhibitors.

Q: A 36-year-old male progressive involuntary, irregular movements of all four extremities, bradykinesia, unsteady gait, masked facies, gradual inability to chew/talk, cognitive difficulties, and significant change in personality, including depression, agitation, and impulsivity. The patient has relatives who had presented with similar symptoms. Diagnosis?

A: **Huntington's Disease**. Autosomal dominant disorder with trinucleotide (CAG) repeat leading to neuronal cell death. On PRITE, this vignette often shows a significantly atrophied cross section of the brain. The more CAG repeats, the earlier the onset of the disorder, thus each successive generation develops the disease earlier (called anticipation). Hallmarks of the disease include symptoms due to degeneration of the basal ganglia/striatum/caudate (chorea, unsteady gait, bradykinesia, inability to chew/swallow) and symptoms due to frontal lobe degeneration (deficits in cognition, executive functioning, abstract thinking, memory and psychological symptoms like agitation, depression, impulsivity, hypersexuality, compulsion). Suicide is common in these patients. Genetic testing can detect the trinucleotide repeat, helping family planning. Mainstay of treatment includes haloperidol and other high potency antipsychotics (per PRITE), and other symptomatic treatment.

Q; A 54-year-old patient presents with shuffling gait and involuntary acceleration, postural instability, festination, and truncal rigidity. He has tremor at rest that decreases with voluntary movement, cogwheeling rigidity, drooling/dysphagia, and masked facies. Diagnosis?

A: **Parkinson's Disease**. Increased activity in the subthalamic nucleus and GP leads to DA inhibition and movement disorder. Symptoms include bradykinesia, tremor that decreases with voluntary movement, rigidity/cogwheeling, shuffling gait, dystonia, festinating speech (rapid, soft, poorly-intelligible), drooling (due to infrequent swallowing), dysphagia, fatigue, masked face, and mood symptoms like depression. Treatment is Levodopa, a dopamine agonist. In the event of the development of VH on Levodopa, decrease the dose. Another treatment is deep brain electrode stimulation in subthalamic nucleus.

Q: A 35-year-old male awakens frequently in middle of night with severe headaches lasting 1-2 hours. Headaches are so painful that the patient is afraid to go to sleep. Located around L eye and associated with lacrimation, ptosis, and mitosis. Diagnosis?

A: **Cluster Headaches**. Vascular headaches with intense pain caused by dilation of blood vessels leading to pressure on Trigeminal nerve. May be associated with Horner's syndrome (sympathetic chain lesion, leading to deficiency of sympathetic tone: ptosis, lacrimation, miosis, rhinorrhea, and sweating on affected side of face). Treatment with NSAIDs is rarely helpful. Mainstay of treatment are triptans (abortive) or cooling measures (cold shower, breathing cold air). There is some support for the use of Topamax or Lithium for treatment, in addition to Ca channel blockers or steroids.

Q: A 22-year-old female has gained 70 lbs. in the past year and now presents with daily severe headaches sometimes associated with graying out of vision. Papilledema is present on exam. Diagnosis?
A: **Pseudotumor Cerebri**. Associated with increased intracranial pressure, and increased opening pressure on LP. This leads to significant headaches and papilledema/visual problems that can eventually cause blindness. The CSF composition and neuroimaging are normal. Treatment is weight loss, therapeutic LP, and Topamax (inhibits carbonic anhydrase leading to decreased CSF production and lowering of intracranial pressure. It is also helpful in weight loss).

Q: A 23-year-olds after recovering from a flu-like illness, develops tingling paresthesia in the lower extremities, followed several days later by progressive weakness R>L. Exam shows decreased sensation at T10 to pinprick, 3/5 weakness of LE (weaker on R), knee and ankle jerks are hyperactive and there is +BL Babinski. Patient has difficulty walking and has a broad based stiff-legged gait. Has urinary incontinence. Diagnosis?
A: **Transverse Myelitis**. Inflammatory process of the gray/white matter of spinal cord leading to axonal demyelination. May be a forerunner of MS or immune-mediated reaction to a virus. Long tracts are affected first (LE). Sensation is affected. Cervical involvement can lead to respiratory paralysis; Thoracic lesions can produce spastic paraplegia; and Lumbar lesions lead to combination UMN/LMN symptoms. Symptoms generally present rapidly, first with sensory symptoms and progress to spasticity. Hyperactive reflex/+ Babinski is UMN. CSF has elevated protein due to demyelination and mononuclear cells. Diagnosis is made with MRI detecting lesions. Treatment is steroids to decrease swelling and compression.

Q: A 28-year-old with diplopia, isolated L eye nystagmus when looking L, inability to adduct the R eye. She has symptoms of depression and history of episodic dysarthria/dysphagia. Has recent decreased sensation in the arms, unsteady gait, and problems with balance. CSF shows elevated protein, oligoclonal bands, and nucleated cells. Diagnosis?
A: **Multiple Sclerosis**. Chronic, demyelinating disease affecting the CNS. Can lead to a change in sensation, visual problems, muscle weakness, depression and problems with gait/balance. Transverse myelitis is a forerunner. Internuclear opthalmoplegia is a problem with the communication between CN III (moves eyes medially) and CN VI (moves eye laterally). In INO, there is inability for both eyes to track together (when looking to the L, the L eye abducts properly with LR muscle [CN VI], but R eye does not adduct due to abnormal MR muscle innervation [CN III]). This leads to nystagmus. Diagnosis is obtained through MRI detection of demyelinating lesions. Treatment is steroids (acute exacerbation) and interferons, in addition to newer medications that stimulate T cells to fight inflammation (Copaxone). Course is relapsing/remitting, with exacerbations caused by infections (common cold, URI), heat, pregnancy, and emotional stress.

Q: Patient presents with spasms of LE while sleeping. Has stiff-legged gait, adducts legs while walking, increased LE tone/spastic catch, hyperactive knee jerks and ankle jerk clonus. Increased Romberg sway. Diagnosis?
A: **Cervical Spondylosis**. Spinal deformity when two vertebrae compress a nerve root, resulting in sensory and motor deficit. This leads to cervical pathology and radicular signs (LMN). Over time, the spinal cord may be compressed, leading to hyperreflexia, and other UMN symptoms. May feel "electric shocks" going down arms/legs. Diagnosis is through MRI. Treatment is symptomatic or surgical. Distinguished from transverse myelitis by course (TM is rapid onset), CSF (TM has elevated protein) and MRI (spondylosis has compression).

Q: A 32-year-old patient recovers from a GI viral infection, and now presents with new onset lower limb weakness, areflexia in lower limbs, gradually leading to flaccid paralysis, and decreased sensation. All symptoms have started in a "stocking-glove" pattern, ascending up the body. Nerve conduction studies show slowed conduction velocity and conduction block. Diagnosis?
A: **Guillain-Barre Syndrome**. Also called Acute Inflammatory Polyneuropathy. Often preceded by an infection that triggers and autoimmune response against peripheral nerve myelin. The symptoms are purely LMN, with paresthesias in the LE that ascend to arms and even diaphragm. LMN signs also include areflexia and sensory loss. The autonomic system can be effected by orthostatic hypotension, and rarely are CN involved, leading to BL facial weakness. CSF has elevated proteins, without an increased cell count. EMG and NCS show slowed conduction due to loss of myelin. Treatment includes plasmapheresis, and treatment with immunoglobulins.

Q: A 43-year-old male has gradual progressive weakness over 3-4 months, atrophy of extremity muscles, brisk reflexes, plantar reflexes are extensor, spasticity, fasciculations, fibrillations, positive sharp waves on EMG, and dysarthria. Diagnosis?
A: **Amyotrophic Lateral Sclerosis**. A progressive, fatal neurodegenerative disease involving the anterior horn cells, leading to both UMN (increased reflexes, Babinski, clonus) and LMN symptoms (atrophy, fasciculations). Sensation is normal. Affect LMN in the brainstem (particularly medulla—nuc ambiguous, and hypoglossal nucleus) leading to dysarthria and dysphagia. EMG is most helpful diagnostic test, with active fibrillations and changes affecting only the motor nerve fibers. Sensory nerves NOT affected (vs. TM and spondylosis). Most patients die within 4 years and treatment is purely symptomatic

Disorder	Onset	Mechanism	Symptoms	Diagnosis
Guillain–Barré	Rapid	Post-viral autoimmune against myelin	Pure LMN, motor and sensory affected, "stocking glove"	CSF↑ proteins, slow NCS
Transverse Myelitis	Rapid	Post-viral autoimmune against spinal cord grey/white matter leading to demyelination	UMN (↑reflexes)/LMN, sensory first affected, then spastic gait/ weakness, can affect bowel/bladder	CSF↑proteins, MRI with spinal cord lesions
Multiple Sclerosis	Slow	Autoimmune demyelinating disease against CNS	CN: INO, optic neuritis, dysphagia, dyarthria. Sensory and motor deficits. Mood sx.	CSF↑proteins and oligoclonal bands, MRI with brain and spinal lesions
Amyotrophic Lateral Sclerosis	Slow	Neurodegenerative disease of anterior horn cells	UMN/LMN, fasciculations, fibriliations, weakness. Sensation is normal. CN: dysarthria, dysphagia	EMG with fibrilations most helpful test
Spondylitis	Slow (vs TM)	Impingement of nerves with cord compression	UMN/LMN, motor and sensory, spastic broad based gait. Sx similar to TM	MRI with cord compression, CSF normal

Q: A 85-year-old with gait abnormality, slow movement, asymmetric UE rigidity, and difficulty in voluntary vertical upward/downward gaze. Improved slightly with levodopa. Later the patient has involuntary visual saccades, and difficulty with horizontal/vertical gaze. Occulocephalic reflex is normal. Diagnosis?
A: **Progressive Supranuclear Palsy**. Atypical Parkinsonian movement disorder. It affects gait and balance generally first, with progressive degeneration. The most obvious sign is paralysis of vertical gaze. There are associated mood and behavioral symptoms in addition to progressive dementia. Treatment is currently symptomatic.

Q: A 52-year-old with insidious onset of blurred vision, diplopia x1 day, ptosis, 6th nerve palsy, unreactive pupils, hoarse voice, dysarthria, weak neck muscles, and increased amplitude with repetitive nerve stimulation on EMG. Diagnosis?
A: **Botulism**. A paralytic illness caused by the nerve toxin, botulin. It prevents the presynaptic release of Ach and disables both muscarinic and nicotinic receptors. Presents with motor paralysis (nicotinic) and autonomic symptoms (muscarinic) of constipation, blurred vision (dilated pupils—MG has normal pupils), dry mouth, nausea, and vomiting. Respiratory failure can be lethal. Diagnosis is by testing blood or stool for toxin. Treatment is mainly supportive.

Q: A 23-year-old with persistent numbness of the L hand, decreased sensation in the 4th/5th digits (palmar dorsal), weak finger adduction/abduction especially in the 5th digit. Cause?
A: **Ulnar Nerve Entrapment at the Elbow**. Cubital Tunnel Syndrome occurs when the ulnar nerve is entrapped along the outer edge of the elbow. Compression leads to ulnar nerve symptoms, including weakness of abduction/adduction of fingers and sensory deficit in 4th/5th digits, which is the normal distribution of the ulnar nerve. Generally, altering sleeping positions will relieve symptoms.

Q: A 43-year-old presents with progressive weakness of extremities, mild ptosis, dry mouth, impotence, and reduced reflexes. NCS shows incremental response to repetitive nerve stimulation. Diagnosis?
A: **Lambert Eaton Syndrome**. Progressive weakness as the result of antibodies directed against presynaptic Ca channels, preventing the release of Ach. Has both motor weakness and autonomic symptoms, like Botulism. However, facial muscles and diaphragm are rarely affected. Reduced reflexes (not seen in MG). May be associated with small cell lung cancer, and approximately 50% of LE has identifiable malignancy. Diagnosis through chest X-ray (lung malignancy), serum antibodies to Ca channels, and incremental response of muscle fibers to repeated stimulation (MG=decremental). Treatment is focused on underlying malignancy and steroids.

Q: A 20-year-old with occasional double vision when looking to the R and normal acuity in each eye alone. L ptosis and difficulty keeping the L eye adducted. Pupils are round and reactive, speech is nasal and neck flexors are weak. No paresis or reflex abnormalities. Diagnosis?
A: **Myasthenia Gravis**. Autoimmune disorder caused by IgG antibodies to the postsynaptic Ach receptor, inhibiting stimulation of Ach. Adequate Ach is released, (vs. botulism and LE), but the post-synaptic gates are blocked. The first symptoms to develop are ocular (3rd nerve palsy symptoms of ptosis and inability to adduct) or bulbar (dysarthria, dysphagia). Later, extremities develop weakness, proximal>distal. Does not affect muscarinic (autonomics) so the pupil is NOT affected (vs. LE and Botulism). Fatigability is a hallmark, and symptoms are worse later in the day and after exertion. Diagnosis can be made by tension test (Ach-esterase inhibitor increases the available Ach, showing temporary improvement), EMG (repetitive stimulation causes decremental response), and Ach receptor antibodies in serum. Treatment includes anticholinesterase medications, thymectomy (associated with thymus abnormality, 85% of patients have improvement after this procedure), and steroids. Acute management of Myasthenic Crisis includes plasmapheresis and airway protection.

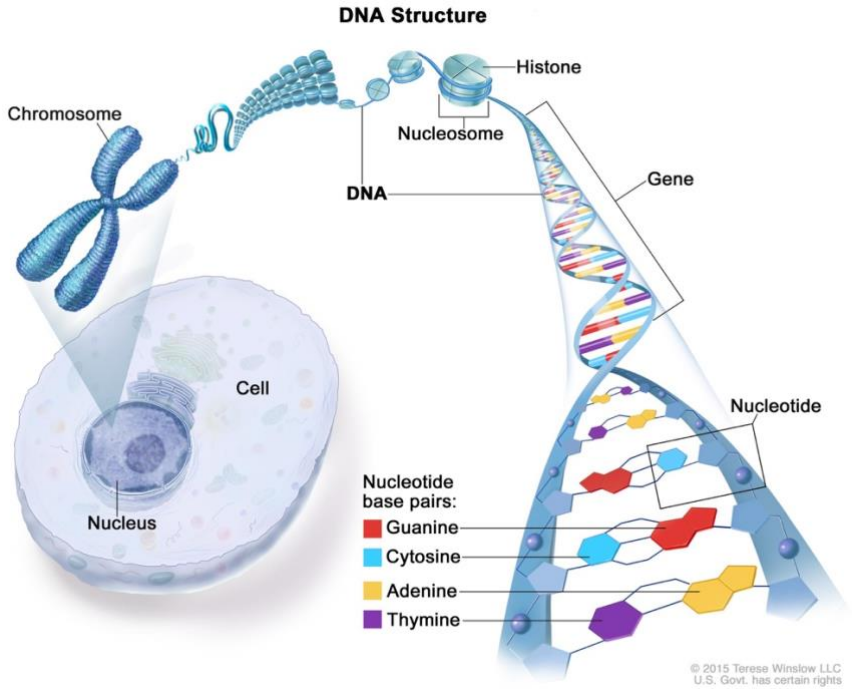
Disorder	Mechanism	Symptoms	Diagnosis
Botulism	Prevents presynaptic Ach release in Muscarinc and Nicotinic nerve terminals	Nicotinic: motor paralysis. Muscarinic: autonomic, blurred vision, unreactive pupils, constipation	EMG: incremental response with repeated stimulation. Test blood/stool for botulinum toxin
Lamberton-Eaton	Abs against presynaptic Ca^{2+} channels preventing release of Ach	Motor and autonomic like botulism, but face/diaphragm rarely affected. Decreased reflexes	Incremental response to repeated stimulation, serum Abs to Ca^{2+} channels, XR for lung mass

Myssthenia Gravis	IgG Abs to postsynaptic-Ach receptors	No autonomic (pupils normal), motor sx primary. First sx are ocular/bulbar (ptosis/dysarthria), then extremity weakness prox>distal, fatiguability	Tensilon test inhibits Ach-esterase, producing temporary reduction of sx. Decremental response to repeated stimulus. Ach IgG Abs in serum.

A NINJA'S GUIDE TO GENETICS

The Genetic Code

DNA: Deoxyribonucleic acid, a macromolecule with two strands of nucleotides twisted into a double helix and joined by hydrogen bonds between complementary bases, A/T and C/G. This molecule carries the genetic information of the cell. The negatively charged DNA wraps around positively charged histone proteins forming tight coils, resulting in condensed chromatin that form chromosomes found in the nucleus.



Heterochromatin: condensed, transcriptionally inactive, inaccessible chromatin (eg. Barr bodies on inactive X chromosomes).

Euchromatin: less condensed, transcriptionally active, sterically accessible chromatin

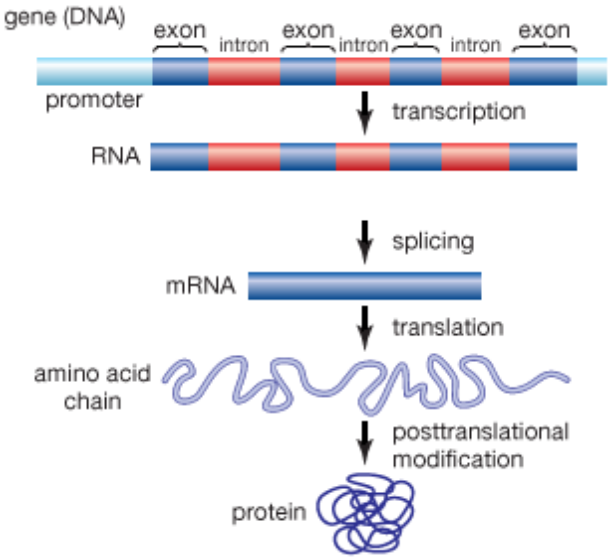
RNA: Ribonucleic acid, a single stranded molecule composed of four bases A, U, C, G which acts as messenger molecules, carrying genetic information from the nucleus to the ribosome where protein synthesis takes place.

microRNA: small, noncoding RNA that regulates protein expression post-transcriptionally. miRNA blocks mRNA to decrease protein translation.

Transcription: the process by which the genetic information stored in a strand of DNA is copied onto a strand of messenger RNA (mRNA). Requires RNA polymerases.

Introns: Portions of the DNA that do not code for proteins or interrupts the sequence of genes. Introns are present in the initial mRNA transcript (pre-RNA), but are spliced out before the mRNA leaves the nucleus to go to a ribosome.

Exons: Portions of the DNA that directly code for proteins. *Ex*ons are *ex*pressed



Regulation of Gene Expression

Promoter: DNA site where RNA polymerase and transcription factors bind upstream of the gene locus.

Enhancer: DNA sites that alter gene expression by binding transcription factors. May be close to, far from or within the intron of the genes they regulate.

Silencer: Site where repressor proteins bind to reduce transcription. May be close to, far from or within the intron of the genes they regulate

Epigenetics

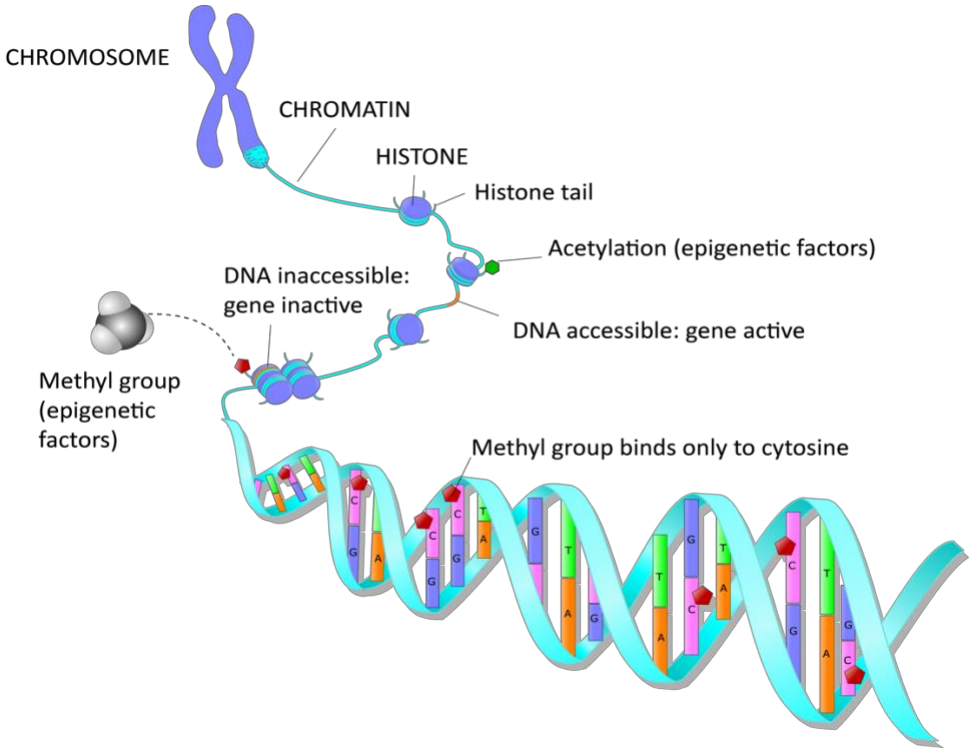
DNA methylation: Methyl groups on some template cytosine and adenine nucleotides represses transcription. DNA *m*ethylation *m*asks. Example: CpG islands are areas of C followed by G, which are usually found near promoter regions and often methylated to silences gene expression.

Chromatin Remodeling: Addition or deletion of molecules to histones affects chromatin structure.

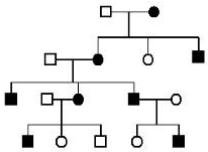
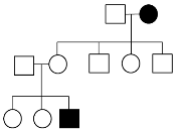
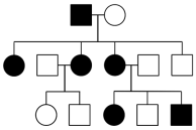
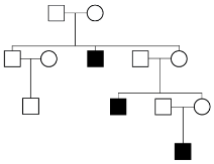
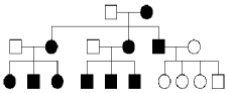
Histone methylation: Reversibly represses DNA transcription. Rarely can activatate transcription. Histone *m*ethylation *m*ostly *m*utes.

Histone acetylation: Relaxes tight coils of condensed chromatin to make DNA sterically accessible and transcriptionally active. Histone *a*cetylation *a*ctivates.

Environmental Stimuli: Toxins, radiations, trauma alter gene expression through epigenetic mechanisms



Patterns of Inheritance

Autosomal		X-linked		Mitochondrial
Dominant	**Recessie**	**Domninant**	**Recessive**	
				
• Disease present in every generation • Either sex equally affected • Commonly involves mutation of structural proteins • Huntington's, NF, von Hippel-Lindau	• Disease skips generations • Either sex equally affected • Commonly involves mutations of catalytic proteins • Sickle cell anemia, PKU, CF	• Disease present in every generation • Either sex equally affected • No father to son transmission • Affected females tend to have milder and more variable disease phenotype • Fragile X	• Disease skips generations • Male preponderance • No father to son transmission • Affected females may sometimes have mild symptoms • Lesch-Nyhan, Duchenne muscular dystrophy	• Maternal transmission only • Either sex equally affected • Commonly involves neuropathies or myopathies • myoclonic epilepsy, MELAS

Genetic Terms

Term	Definition	Clinical Examples
Codominance	• Alleles of a heterozygous gene pair are equally expressed	• ABO blood types • sickle cell anemia • alpha-1-antitrypsin deficiency
Penetrance	• Complete- disease/clinical symptoms are present in all individuals with a given allele • In incomplete or reduced, the disease/clinical symptoms are present in only some of the individuals with the allele	• Complete-Huntington's • NF-1 • FAP • MEN • Incomplete-Familial breast/ovarian cancer due to mutations in BRCA-1

Variable expressivity	• Same genotype yielding varying phenotypes/ clinical features (most notably difference in disease severity)	• NF-1 • multiple sclerosis
Pleiotropy	• Single gene affecting multiple phenotypes	• PKU—a single gene mutation results in multiple phenotypes including intellectual disability, growth retardation, seizures, fair skin, musty body odor
Anticipation	• Increased severity or earlier onset of disease with subsequent generations	• Trinucleotide diseases e.g. Huntington's
Imprinting	• Epigenetic phenomenon whereby gene expression is dependent on which parent passed down the mutant gene.	• Angelman syndrome—Paternal imprinting; dad's gene is normally silent and lack of function in mom's chromosome 15 • Prader-Willi—Maternal imprinting; mom's gene is normally silent and father's chromosome 15 is deleted
Uniparental disomy	• Offspring inherits 2 copies of chromosome from 1 parent and none from the other	• Angelman—5% due to paternal uniparental disomy Prader-WIlli—25% due to maternal uniparental disomy
Locus heterogeneity	• Mutations in different loci result in the same disease phenotype. Mutation in only one loci required to result in disease.	• Retinitis pigmentosa
Mosaicism	• Presence of genetically distinct cell lines in the same individual	• 1% of Downs • McCune-Albright Syndrome
Robertsonian Translocation	• Chromosomal translocation occurring on pairs of acrocentric chromosomes (have centromeres near the end leading to long q arms and short p arms) • Usually pairs 3, 14, 15, 21 and 22. • The long arms fuse at centromere and the 2 short arms are lost.	• Downs • Patau • Miscarriage • Stillbirth
Meiotic Nondisjunction	• Failure of one or more pairs of homologous chromosomes (Meiosis I) or sister chromatids (Meiosis II, mitosis) to separate normally • Results in abnormal distribution of chromosomes in daughter nuclei	• Klinefelter (male; 47,XXY) • Turner (female; 45,XO) • 95% of Downs

Types of Mutations

Defined as an allele variant with frequency of 1% of less.

Gene mutations

- Point mutations: mutation affecting only one or a few nucleotides in a single gene
- Substitution: exchange in one base for another
- Silent: change in base but due to redundant code, does not lead to a change in amino acid
- Missense: base change leads to change in AA. Example: sickle cell anemia, cystic fibrosis
- Nonsense: base change leads to introduction of premature stop codon and shortened protein

Frameshift mutations

- Insertion: extra nucleotides inserted into DNA. Results in misreading of all codons downstream of mutation. Example: Huntington's disease, Fragile X syndrome
- Deletion: loss of nucleotides from DNA sequence. Also results in misreading of all codons downstream of mutation
- Splice site: Mutation at a splice site leads to intron retained in the mRNA. Causes impaired or altered protein function

Chromosomal mutations

- Inverse: portion of a single chromosome breaks off and reattaches to itself in reverse order
- Translocation: rearrangement of portions of non-homologous chromosomes. Detected with cytogenetics e.g. FISH

Research in Genetics

Genetic Epidemiology

Family Studies: Similar to case-control studies where people with the illness are questioned about family members with similar illness vs. people with the illness. A higher prevalence of the illness within families suggests the disorder has a familial component. Measured using the "recurrence risk ratio" for 1st-degree relatives (λ_1), defined as the ratio of the risk of the disorder in a 1st-degree relative of an affected individual to the prevalence in the general population. Example: siblings of family members with schizophrenia have a roughly 10-fold increased risk of the disorder compared to an individual randomly drawn from the general population ($\lambda_1 \approx 10$). However, because the population prevalence is approximately 1%, the absolute risk of the disorder for the sibling is only about 10%. Family studies can also provide information traits or similar diagnoses. Example: relatives of probands with Tourette syndrome have an elevated risk of obsessive-compulsive disorder (OCD), suggesting that these conditions have overlapping familial determinants.

Twin Studies: Traits and disorders may run in families for non-genetic reasons (i.e., environment). Twin studies compare *concordance* rates between monozygotic (MZ) twins (who are genetically identical) and dizygotic (DZ) twins (who share on average 50% of their alleles). A twin pair is concordant if both co-twins have the phenotype. Because environments are assumed simiarl, significantly higher concordance rates in MZ twins means a genetic basis is more likely. Twin studies can provide an estimate of the *heritability* of the disorder, which refers to the proportion of the phenotypic differences among individuals in a population that can be attributed to genetic factors.

Adoption Studies: comparison of rates of a disorder in biological family members with those in adoptive family members. If rates are higher with adoptive family, more likely environmental. If rates are higher with separated siblings, more likely genetic.

Genome Studies

Single Nucleotide Polymorphisms (SNPs): Disorders may arise not from one single problematic gene, but the cumulative effect of many small one-letter variations, or SNPs. Identified with genome-wide studies. Low predictive value thus far.

Copy Number Variations (CNVs): Term for small insertions, deletions or duplications within DNA larger than SNPs (hundreds to millions of base pairs). Identified with microarray technology. (Ex: 22q11 in DiGeorge, and 15q11-13 in autism, also some associations with increased *de novo* CNVs in schizophrenia, autism, ADHD.)

Microsatellites: repeats of 2 to 4 nucleotides (CA repeats, TATA, CGG, GAA, CAG)

Linkage Analysis: studies where in the genome (i.e., in which chromosomal region) a disease mutation or susceptibility locus may reside. The likelihood that two loci on a chromosome will co-segregate is inversely proportional to the distance between them (genes physically close to each other shouldn't spereate during random crossover in meiosis). Measured using *Logarithm of the odds (LOD)* with score of 3 (1,000:1 odds) as the threshold for declaring linkage.

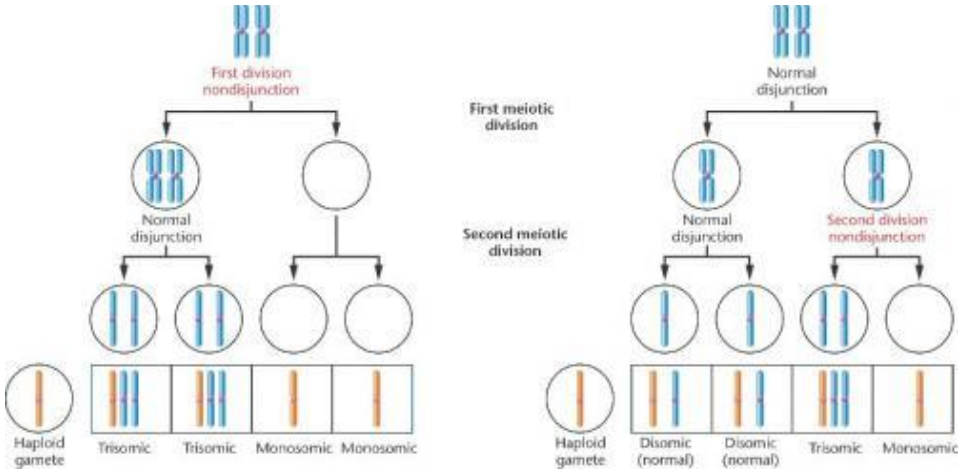
Genome-Wide Association Studies: looks for common SNPs and variants to identify genes influencing complex disorders in an "unbiased" way because they look at the whole genome and don't need prespecified hypothesis about which genes are important. High risk of false-positives. Has iidentified genetic loci associated with autism, bipolar disorder, and schizophrenia.

Genetic Diseases with Psychiatric Manifestations

Autosomal Trisomies:

A type of chromosomal mutation that results from nondisjunction during meiosis

Nondisjunction: failure of homologous chromosomes or sister chromatids to separate during metaphase. Results in gain or loss of chromosomes.



Disease (Incidence)	Genetics	Clinical Manifestations
Downs 1:700	Trisomy 21 • 95% meiotic nondisjunction • 4% Robertsonian translocation • 1% mosaicism	• Most common cause of genetic intellectual disability • Intellectual disability, flat facies, epicanthal folds, single palmar crease, gap between 1st and 2nd toes • Duodenal atresia, Hirschsprung disease, congenital heart disease (AV septal defect), Brushfield spots • Associated with early onset Alzheimer Disease, ALL, and AML
Edwards 1:8000	Trisomy 18	• Severe intellectual disability • Rocker-bottom feet, micrognathia, low set ears, clenched hands with overlapping fingers, prominent occiput, congenital heart disease • Death within 1 year of birth

Patau 1:15,000	Trisomy 13	• Severe intellectual disability • Rocker-bottom feet, microphthalmia, microcephaly, cleft lip/palate, holoprosencephaly, polydactyly, congenital heart disease, cutis aplasia • Death within 1 year of birth

(Micro)Deletions

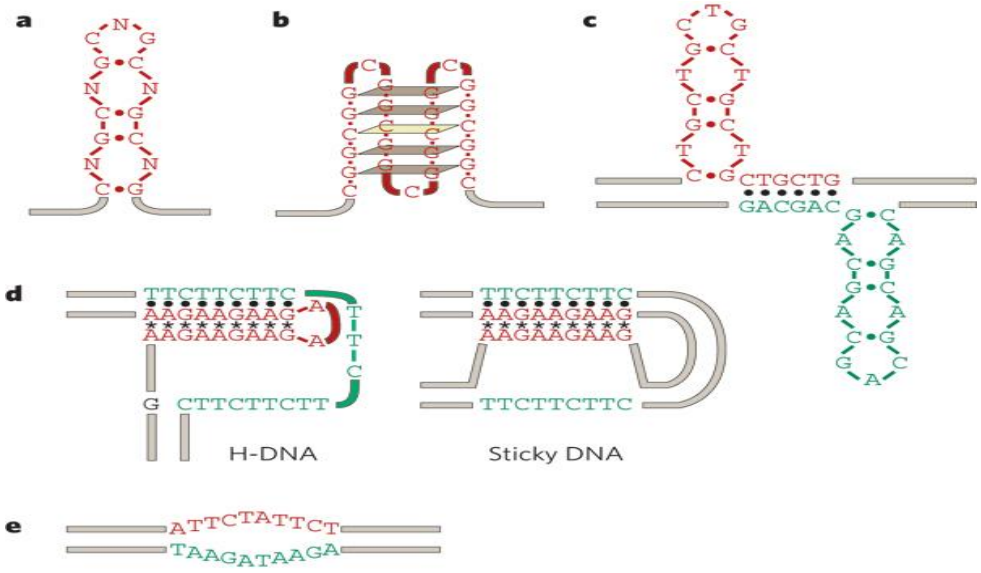
Disease	Genetic	Clinical Manifestations
Angelman	• Deletion of **15q11-q13** in mother • Paternal imprinting	• "Happy Puppet" • Always smiling but lacks speech • Hyperactive, hypotonic • Mental retardation, seizures • Dysmorphic facial features • Ataxic, puppet-like gait
Prader Willi	• Deletion of **15q11-q13** in father • Maternal imprinting	• Short stature and obese with small hands and feet • Hyperphagia • Dysmorphic facial features • Mental retardation
Cri-du-chat	• Microdeletion of **5p**	• Mental retardation • "Cat-like" cry • Microcephaly, low set ears, micrognathia • Epicanthal folds • Cardiac abnormalities (VSD)
Williams	• Microdeletion of **7q** • Loss of elastin gene	• "Elfin" facies • Intellectual disability • Hypercalcemia (increased Vitamin D sensitivity) • Well-developed verbal skills • Extreme friendliness with strangers • Cardiovascular problems
Smith-Magenis Syndrome	• Microdeletion of **17p11.2**	• Sleep disturbance • Tantrums, impulsivity, stereotypies, aggression, self-injurious behavior • Self-hug when excited • Broad square face, prominent forehead, deep-set eyes, short nose • Skeletal abnormality, short stature, hearing loss, intellectual disability

DiGeorge Syndrome Or Velocardiofacial Syndrome	• Microdeletion of **22q11** • Aberrant development of 3rd and 4th branchial pouches	CATCH 22 • **C**-cleft palate • **A**-abnormal facies • **T**-thymic aplasia → T cell deficiency • **C**-cardiac defects • **H**-hypocalcemia 2/2 parathyroid aplasia DiGeorge Syndrome • Thymic, parathyroid, and cardiac defects • Velocardiofacial Syndrome • Associated with Schizophrenia • Palate, cardiac, and facial defects

* p = short arm, q = long arm

Trinucleotide Repeat Expansion

Caused by *slippage* in DNA replication or "copy choice" DNA replication. "Loop out" structures form due to the repetitive DNA sequence at these regions, while complementary base pairing is maintained between the parent strand and the newly synthesized daughter strand. Loop out structures formed on the daughter strand will result in increased number of repeats.



Disease	Genetic	Clinical Manifestations
Fragile X	• **CGG** repeats • X-linked defect affecting increased methylation and decreased expression of the **FMR1** gene	• Second most common cause of genetic intellectual disability (after Down's Syndrome) • Post-pubertal macroorchidism • Long face with large jaw • Large everted ears • Autism • Mitral valve prolapse
Friedreich's Ataxia	• **GAA** repeats • Chromosome 9 (encodes Frataxin, an iron binding protein) • Autosomal Recessive inheritance	• Childhood kyphoscoliosis • Impaired mitochondrial function leads to spinal cord degeneration → muscle weakness, decreased DTRs, loss of vibratory sense, proprioception • Staggering gait, frequent falls, dysarthria, pes cavus, hammer toes, DM, HOCM
Huntington's	• **CAG** repeats • Chromosome **4** (Huntingtin gene) • Autosomal Dominant inheritance	• Onset at age 20-50 (anticipation) • Choreiform movement, aggression, depression, dementia • MRI: Atrophy of caudate with ex vacuo dilatation of frontal horns

Metabolic Disorders

Disease	Genetic	Clinical Manifestations
Phenylketonuria	• Deficiency of phenylalanine hydroxylase or tetrahydrobiopterin cofactor • Build up of phenylalanine • Autosomal Recessive inheritance	• Intellectual disability • Growth retardation • Seizures • Fair skin • Eczema • Musty "mousy" body odor
Tay-Sachs	• Deficiency of hexosaminidase A • Build up of GM2 gangliosides • Autosomal Recessive inheritance	• Age of onset: 3-8 months • Psychomotor arrest • Exaggerated startle reflex • Seizures • Retinal cherry-red spot
Neimann-Pick type A	• Deficiency of sphingomyelinase • Build up of sphingomyelin • Autosomal Recessive inheritance	• Age of onset: 1 to 6 months • Psychomotor arrest • Splenic enlargement • Retinal cherry-red spot (sometimes)

Metachromatic Leukodystrophy	• Deficiency of cerebroside sulfatase / arylsulfatase A • Build up of sulfatides • Autosomal Recessive inheritance	• Age of onset: early childhood • Central and peripheral demyelination • Progressive mental and motor deterioration
Krabbe Disease	• Deficiency of galactocerebrosidase • Build up of galactocerebroside and psychosine destroys myelin sheath • Autosomal Recessive inheritance	• Age of onset: 3-6 months • Irritability, crying, mental and motor deterioration, seizures • Peripheral neuropathy • Optic atrophy • Globoid cells
Galactokinase Deficiency	• Deficiency of galactokinase • Build up of galactitol • Chromosome 17 • Mutation of GALK1 gene • Autosomal Recessive inheritance	• Failure to track objects or to develop social smile • Infantile cataracts
Classic galactosemia	• Deficiency of galactose-1-phosphate uridyltransferase • Build up of galactose-1-P • Autosomal Recessive inheritance	• Intellectual disability • Failure to thrive, jaundice, hepatomegaly • Infantile cataracts
Hurler Syndrome	• Deficiency of alpha-L-iduronidase • Build up of heparan sulfate, dermatan sulfate • Autosomal Recessive inheritance	• Developmental delay • Gargoylism • Corneal clouding • Airway obstruction • Hepatosplenomegaly
Hunter Syndrome	• Deficiency of iduronate sulfatase • Build up of heparan sulfate, dermatan sulfate • X-linked Recessive inheritance	• "Milder Hurler Syndrome" + aggressive behavior • No corneal clouding
Lesch-Nyhan syndrome	• Deficiency of hypoxanthine-guanine phosphoribosyltransferase (**HGPRT**) → defective purine salvage • Excess uric acid production and de novo purine synthesis • X-linked Recessive inheritance	• **H**-hyperuricemia • **G**-gout • **P**-pissed off (aggressive, self-mutilation) • **R**-retardation (intellectual disability) • **T**-dys**T**onia • Intellectual disability
Acute Intermittent Porphyria	• Defect Porphobilinogen deaminase / hydroxymethylblane synthase →accumulated porphobilinogen, and urine coporphobilinogen	**5 P's**: • **P**ainful abdomen • **P**ort wine-colored urine • **P**olyneuropathy • **P**sychological disturbance (delirium, agitation, psychosis, anxiety, somnolence) • **P**recipitated by drugs, alcohol, starvation

Homocystinuria	• Mutation on **21q22.3** → cystathionine-B synthase gene → elevated homocystine, homocysteine, methionine	• Skeletal abnormalities (tall, long extremity, pectus excavatum, scoliosis) • Ectopia lentis • Risk of thrombus formation • Increased rates of schizophrenia, depression, OCD, learning disorder, ID
Adrenoleukodystrophy	• Mutation of ***ABCD1*** → loss of peroxisomal lignoceroyl-CoA ligase → build up of very long-chain fatty acids (VLCFA) in peroxisome, in myelin of CNS, adrenal cortex, and Leydig cells • X-Linked	3 presentations: • Childhood cerebral form: ADHD-like symptoms, cognitive impairment, vision and hearing loss, gait abnormality, dysarthria/dysphagia • Adrenomyeloneuropathy: later onset, slowly progressive; mood and psychotic symptoms • Addison's disease: adrenal findings only

Other Neurological Conditions

Disease	Genetic	Clinical Manifestations
Wilsons	• Chromosome **13** • Mutation in **ATP7B** gene → copper accumulation Autosomal Recessive inheritance	Liver disease **Kayser Fleischer** rings Parkinsonism, wing-beating tremor, seizures, migraines, dementia Depression, anxiety, psychosis
Neurofibromatosis type I (von Recklinghausen disease)	Chromosome **17** Mutation of **NF1** tumor suppressor gene (Ras GTPase activating protein neurofibromin) Autosomal Dominant inheritance	**Cafe-au-lait spots** **Lisch nodules** (pigmented iris hamartomas) Cutaneous neurofibromas Optic gliomas Pheochromocytomas
Neurofibromatosis type II	• Chromosome **22** • Mutation of **NF2** gene (Merlin or schwannomin protein) • Autosomal Dominant inheritance	• Bilateral acoustic schwannomas • Juvenile cataracts • Meningiomas • ependymomas
Tuberous Sclerosis	• Mutation of ***TSC1*** (hamartin) or ***TSC 2*** (tuberin)	• Ash leaf spots, shagreen patches, angiofibromas • Tumors (CNS tubers, retinal hamartomas, cardiac rhabdomyomas, renal angiomyolipoma) • ADHD and PDD-spectrum symptoms
Sturge-Weber syndrome	• Non-inherited (somatic) developmental anomaly of neural crest derivatives • Activating mutation of **GNAQ** gene	• Seizures/epilepsy • Intellectual disability • Episcleral hemangioma
Klinefelter (male; 47,XXY)	• Meiotic nondisjunction	• Testicular atrophy • Tall • long extremities • eunuchoid body • gynecomastia • Developmental delay • increased rates of ADHD • schizophrenia-spectrum

Turner (female; 45, XO)	• Meiotic nondisjunction	• Short stature • ovarian dysgenesis • shield chest • bicuspid aortic valve • coarctation • web neck • horseshoe kidney • Visual-spatial learning deficits • increased rates of ADHD

Diseases by Chromosome

Chromosome	Associated Disease
4	Huntington
5	Cri-du-chat
7	William's syndrome
9	Freidrich Ataxia
13	Patau Syndrome Wilson disease
15	Prader-Willi Syndrome Angelman Syndrome
17	Neurofibromatosis type I
18	Edwards Syndrome
21	Down Syndrome
22	Neurofibromatosis type II Velocardiofacial Syndrome
X	Fragile X

A NINJA'S GUIDE TO PSYCHOTHERAPY

Disclaimer: This therapy guide is not designed to be a comprehensive review of psychotherapy. The purpose of this guide is to introduce you to terms associated with various therapies to help with PRITE multiple-choice questions. Not all of this is high-yield, but it may help fill in any gaps in your therapy education to date. If nothing else, you may learn common terms that go together in PRITE (CBT: automatic negative thoughts, Psychodynamic: transference, Melanie Klein: object relations) to pick up points. This material is a summary from Kaplan and Sadok texts and the Mass General Psychiatry Review.

First, an overview of the spectrum of techniques used in therapy, from more psychoanalytic to more supportive: Interpretation → Confrontation → Clarification → Encourage to elaborate → Empathic validation → Advice/Praise → Affirmation

More Psychoanalytic

- Interpretation: bringing the unconscious thoughts to the surface (conscious)
- Confrontation: openly addressing suppression through confronting the patient
- Clarification: reformulation, "So do you mean to say…."

More Supportive

- Encourage to elaborate: request more information
- Empathic validation: "That must be really hard for you"
- Advice/Praise: therapist gives concrete advice or direct praise to the patient
- Affirmation: "uh-huh," "I see"

The spectrum goes from most psychoanalytic ("couch therapy") to most supportive, with *interpretation* being more psychoanalytic and *affirmation* being primarily supportive. Psychoanalytic therapy tends to have more neutral interactions between the therapist and patient (praise, advice, and validation are not generally psychoanalytic techniques), while more supportive forms of therapy use more praise and encouragement in therapy.

Psychoanalytical Psychotherapy

Overview: Based on Freudian tradition of uncovering unconscious aspects of a patient's mental life. Focuses on unconscious conflicts, repressed feelings, family issues from early in a patient's life, and difficulty with current relationships. Occur 5-6x per week x1 hour for 3-5 years.

Therapist: may not be visible to the patient, sometimes a couch is used, and the therapist remains neutral.

Patient: must be very motivated, good frustration tolerance, and have minimal pathology.

Goals/Techniques: resolve internal conflict and symptom relief through examination of transference as a means of unlocking unconscious.

- Transference: the patient's unconscious redirection of feelings from the past toward therapist. Unconsciously, "Hey this therapist reminds me of my overbearing mother"
- Countertransference: the therapist's unconscious association of feelings from the past directed at the patient. Unconsciously, "Hey, this patient reminds me of my jerk ex-husband"
- Resistance: unconscious and conscious forces within a patient that resist treatment. Example: patient repeatedly comes to sessions late due to unconsciously resisting treatment
- Free Association: undirected expression of conscious thoughts and feelings as an attempt to "tap into" the unconscious. Basically, say the first thing that comes to your mind, as it may be related to unconscious stuff

Four Subtypes of psychoanalytic therapy (High Yield PRITE Famous People associations)

1. Classical Psychotherapy: *Freud*
2. Ego psychology: *Anna Freud*
3. Objects relations psychotherapy: *Melanie Klein* (Object relations are related to drives; "ego splitting;" infant-mother relationships; "depressive/paranoid/schizoid positions") and *Donald Winnicott* (transitional object; "good enough mother")
4. Self-psychology: *Heinz Kohut* ("mirroring;" stuff on narcissism)

Expressive Psychotherapy ("Insight-Oriented Therapy")

Overview: same goals and techniques used in Psychodynamic therapy with a few differences. Occur 3x/week for 30-50 minutes.

Therapist: face-to-face interaction, modified neutrality.

Patient: can tolerate frustration, has intact reality testing, good impulse control, and ongoing significant emotional suffering.

Goals/Techniques: focuses on a current interpersonal transference in an attempt to reorganize personality, resolve conscious conflict, and increase insight into interpersonal events. Improve object relations. Uses "here and now" interpretation, confront/clarification. May use medications (as opposed to Psychodynamic psychotherapy, which generally doesn't use meds).

Brief Psychotherapy

Overview: Main focus is on brevity (limited # of sessions understood at the beginning), patient selection (rigid criteria), a specific treatment focus (one specific thing to be worked on/resolved), and high levels of therapist activity.

Famous PRITE People: *Franz Alexander* first started to alter traditional psychodynamic therapy by shortening sessions, decreasing frequency, and other measures to develop modern short-term therapy. Other people involved in conceptualizing this form of therapy were *Mann, Malan, Sifneos.*

Essential Features of Brief Therapy: Patients selected with specific inclusion criteria (moderate emotional distress, desire for relief, a *specific* problem to work on, functional, ability to commit to treatment) and exclusion criteria (no psychosis, substance abuse, or risk of self-harm). Limited to 12-20 hour long sessions, after which therapy is terminated.

Therapist: must keep treatment focused and moving forward as there are pre- established limited # of sessions. Sessions begin with summary of last session, and restating focus. Homework is given. Clarification is important. Transference must be quickly identified and worked through.

Patient: see above exclusion and inclusion criteria. Mainly, the patient must have a specific area to work on (loss, conflict) and understand that # of sessions is limited.

Goals/Techniques: four common foci are losses, being out of step with expected developmental stage, interpersonal conflicts, and symptom reduction. Brief therapy works on transference issues, explores specific past trauma, reestablishes defense mechanisms, and resolution of what initially brought the patient to therapy.

Three phases of therapy

1. Initial phase: (evaluation thru session 3) evaluates the patient, selects focus, and establishes working alliance
2. Middle phase: (session 4-9) where patient starts to worry there won't be enough time in treatment, issues of separation and aloneness, feels worse during this phase
3. Termination phase: (sessions 8-16) patient accepts treatment ending, discuss termination of therapy relationship

Interpersonal Therapy

Overview: developed by *Klerman*, utilized by *Harry Stack Sullivan*, it is a brief therapy that addresses relationships in the "here and now." Primarily used to treat depression. Occurs for 12-16 weeks with monthly maintenance thereafter.

Patient: most commonly treats MDD.

Goal/Techniques: Interpersonal therapy works to improve interpersonal communication, clarify feelings, and provide reassurance. May be combined with medication management. Improve interpersonal skills.

4 problem areas:

1. Unresolved grief: facilitate grieving process
2. Social role disputes: make plan of action to solve interpersonal role disputes (conflict with co-worker, spouse, etc)
3. Social role transitions: mourn and accept the loss of an old role (demotion in job, children move out of home) and earn self-esteem in mastering a new role
4. Interpersonal deficits: learn to establish healthy relationships and decrease social isolation

Supportive Psychotherapy

Overview: Usually brief, with an active focus on helping the patient deal with a life crisis. Especially effective for acute grief reactions. Occurs 1x/week for 30-50 minutes, can last months.

Therapist: face-to-face with patient, non-neutral, provides advice, sympathy, and support while reinforcing the patient's strengths.

Patient: may be undergoing a life crisis, poor reality testing, low level of frustration tolerance, impaired object relations, poor impulse control, may have ego deficits. These patients are generally less functional that patient participating in the other above types of therapy.

Goals/Techniques: form a therapeutic alliance, focus on conscious external events (no analysis of transference), reintegration of coping skills, and strengthen defenses. Uses reality testing, advice, empathy, and cognitive restructuring.

Behavioral Therapy

Overview: focuses on reducing overt behaviors that are symptoms of mental illness. Uses conditioning and modeling. Developed by *John Watson.*

Types of Behavioral Therapy

- Systematic Desensitization: *Wolpe.* Counterconditioning to decrease maladaptive anxiety. Works on decreasing response to anxiety-provoking stimuli. Treats phobias. Example: patient has fear of heights. Make a hierarchy of least feared to most feared. Think about less feared and use relaxation techniques (mental imagery, relaxing muscles and decreasing autonomic responses) to desensitize self to fear/anxiety. Now go up on the hierarchy (increased anxiety-provoking) and repeat the above to desensitize gradually up the hierarchy
- Flooding: similar to systematic desensitization in that a stimulus is presented and the goal is to desensitize oneself to fear/anxiety. However, no hierarchy, no relaxation techniques, and has in-vivo exposure (actually presented with real fear rather than imagining it). Example: patient fear of heights, go to top of highest building and sit there until fear subsides
- EMDR: saccadic eye movements used to treat PTSD
- Positive reinforcement: using a "token economy" to reward patients for desired behavior. Good use in Schizophrenics. Can also be used in addicts, similar to methadone maintenance, where abstinence from illicit drugs leads to positive reinforcement with methadone

- Dialectical Behavioral Therapy: treats BPD/personality disorders using combination of supportive/cognitive/behavioral techniques. Works to improve interpersonal skills, and decrease self-destructive behaviors. Addresses ambivalence, increases motivation, seeks to not reinforce maladaptive behaviors, learn new skills, and restructure the patient's environment. Uses homework, advice, and confrontation

Biofeedback

Overview: Designed by *Miller* to assume voluntary control of the autonomic nervous system and other biologic systems using operant conditioning.

Conditions treated: include Reynaud's, tension HA, migraines, TMJ, epilepsy, asthma, arrhythmias, fecal incontinence, HTN, and many others.

Methods: uses EMG, skin temperature, BP, and other measurements to monitor physiologic states. The patient uses relaxation techniques to self-modify autonomic functions to produce resolution of multiple symptoms.

Cognitive Behavioral Therapy

Overview: focuses on the interplay of maladaptive thoughts, feelings, and behaviors that cause mental disorders. Basically, maladaptive thoughts and feelings lead to unhealthy behaviors. CBT combines cognitive therapy (identifying and challenging underlying cognitive errors) with behavioral therapy (removing unwanted behaviors). Occurs over the course of 15-20 weeks.

Therapist: the goal is to teach the patient to become their own therapist through a series of assignments, homework, and close interaction between therapist and patient

Patient: CBT is proven to help with patients with MDD, BMD, Panic Disorder, Social Anxiety Disorder, GAD, OCD, Phobias, EDO, Psychotic Disorders, and Substance Abuse.

Goals: identify and alter "cognitive distortions" that maintain symptoms. CBT strives to identify negative "automatic thoughts" that are generated by "cognitive distortions." Example: patient believes he is too fat to have friends. This is an automatic negative thought that is the result of a maladaptive cognitive distortion/error.

The cognitive triad

1. Negative self -perception
2. Patient sees the world as a negative place
3. Patient expects failure and hardship.

Techniques: 3 main components

1. Didactics: teach the patient about their mental disorder, the cognitive triad, their faulty logic, and cognitive distortions
2. Cognitive techniques: elicit automatic thoughts, test logic of automatic thoughts, identify cognitive distortion, test validity of cognitive distortion. Example: after her boyfriend breaks up with her, a patient believes nobody will ever love her (automatic negative thought). Therapist states this cognitive distortion is an "overgeneralization" and is untrue that NOBODY will ever love the patient. Then the patient works to disprove the distortion (test validity)
3. Behavioral techniques: various homework with activities to improve self-reliance and find new healthy ways to cope (replacing substances, suicidality, eating disorders with exercise, art, etc.)

Techniques for Specific Disorders

- MDD: provides education (informational intervention), activity scheduling (behavioral modification of anhedonia and PMR), cognitive restructuring (challenge negative views of self), and problem solving (assertiveness training)
- BMD: stress management, monitoring mood to detect early destabilization, improving regularity of circadian system through healthy behaviors (exercise, diets, etc), problem-solving skills to improve compliance with care
- Panic Disorder: education to stop the "fear-of-fear" cycle and stop catastrophic misinterpretations ("I am having a heart attack"), cognitive restructuring (decrease negativity and catastrophizing), interoceptive exposure (exposure to physiologic symptoms of anxiety through running in place or hyperventilating, similar to desensitization), desensitization, relaxation training
- Social Anxiety Disorder: education, cognitive restructuring, monitoring and "catching" thoughts that precipitate anxiety. Example: "All these people think I'm an idiot." Exposure intervention (desensitization exercises), social skills training, and some interoceptive exposures (as used in panic d/o)
- GAD: education, cognitive interventions (examine cognitive distortions and negativity), imaginal exposure to worries, relaxation techniques
- OCD: education, exposure and response prevention (desensitization and flooding), cognitive interventions to help break intrusive thoughts/ritualistic behaviors
- PTSD: education, cognitive interventions to challenge perpetual fear of danger, imaginal exposure (narrate trauma, extinguish extreme emotional response, learn to feel safe), desensitization in-vivo, relaxation techniques
- Phobias: exposure interventions, participant modeling (therapist exemplifies a behavior [touching a snake] and encourages patient to copy the behavior)

- Bulimia Nervosa: education (including health education), self-monitoring and reporting EDO behaviors, stimulus-control (decreasing triggers [Example: don't eat in mall with all skinny friends]), cognitive restructuring body image and challenging negative thoughts about body, problem-solving (find new ways to cope with stressors rather than binge/purge)
- Anorexia Nervosa: positive and negative reinforcement procedures initially to protect health and decrease hospitalization/decompensation. Also use the above techniques for Bulimia
- Substance abuse: motivational interviewing, functional analysis (examine function before vs. after substance abuse), self-monitoring, cognitive interventions to challenge "all or nothing" thoughts ("I had one drink, I blew it, I might as well continue") and other dysfunctional thinking, problem-solving (identify new means of coping with stressors), and contingency management (contracts, positive reinforcement)
- Psychotic Disorders: education, cognitive interventions to promote medication compliance, social skills training, stress management
- Personality disorders (need longer treatment CBT than Axis I d/o): emotional regulation (identify, tolerate and modify emotions), reduction of therapy-interfering behaviors (resistance), challenge cognitive distortions, stress management and problem-solving (new coping skills rather than unhealthy mechanisms)

Group Therapy

Overview: group therapy offers the opportunity for purposefully created, closely observed, and skillfully guided interpersonal interaction in a collection of patients brought together by a leader for a shared therapeutic goal.

Therapist: plans and organizes group after identifying specific goals of the group.

Patients: patients selected for a group based on needs/diagnosis/goals of group. Active SI, manic, psychotic, and emotionally sadomasochistic individuals are contraindicated. Groups need to be somewhat homogeneous in ego development for psychodynamic groups.

Goals: Re-establish pre-morbid levels of functioning in people with acute distress, support targeted populations (medical illness like cancer, or mental illness support groups), provide relief for target symptoms (ex: eating disorders), encourage and stimulate character change (helps identify malignant character deficits in a patient through group reflection, and to promote healthy change).

Therapeutic Factors in Group Therapy (PRITE questions in past)

- Abreaction: unearth repressed emotions, and relive them to increase insight
- Acceptance: feeling of being accepted by the group, absence of censure and difference of opinion is tolerated
- Altruism: one member helps another, helps to establish cohesion
- Cohesion: group is working together for a common goal
- Contagion: expression of an emotion in one member elicits the expression of emotion in another member
- Corrective Familial Experience: group re-creates family of origin for one member to help them work through original conflict
- Empathy: group member can put himself in the psychological framework of another member and understand the thinking, feeling, and behavior
- Imitation: emulation or modeling of one's behavior after another person
- Inspiration: imparting a sense of optimism to group members
- Reality Testing: person's ability to evaluate the world outside of themselves and perceive reality accurately
- Universalization: the idea that an individual is not alone with their problems
- Ventilation: expression of suppressed feelings, ideas, or events to group members to ameliorate a sense of shame or guilt (aka self disclosure)

Types of Group Therapy

- Supportive: weekly over months, shared universal dilemmas, helps adapt to environment. Universalization and Reality Testing
- Psychodynamic: 1-3x/week for years, for neurotic disorders, work on present/past life situations, focus on interpret unconscious conflict to challenge defenses and reduce shame. Catharsis, reality testing, examine transference
- CBT: weekly up to 6 months, phobias or compulsions treated, works on cognitive distortions to relieve specific psychiatric symptoms. Reinforcement, cohesion, conditioning
- Inpatient: daily groups with rapid turnover of patients, heterogeneous groups, emphasis on the "here and now," problem solving, education on treatment. Empathy and reality testing

Family Therapy

Overview: seeks to resolve family conflict, meets family members 'individual needs, establish healthy role relationships, cope with destructive forces inside and outside the family, and integrate the family into society. Occurs weekly for 1-2 hours. Family may present with a single-family member identified as the "problem" but the dynamic is likely much more complex than that.

Goals: alter interactions and improve functionality of the family as a unit of individuals. Bring to light hidden patterns and understand the purpose of these patterns.

Techniques: collect a thorough history, including a family life chronology in the first 2 sessions. Understand how the parents operate from models from their own parents/families. One technique used is "reframing" Example:" This child is impossible," can be changed to "This child is trying to distract you from an unhappy marriage.

Types of Family Therapy

- Behavioral/CBT: core concepts are functional analysis, social learning, and communication. Goals are to resolve problems by improving communication and problem-solving skills while balancing change vs. acceptance. This is the #1 empirically supported family/couples therapy
- Bowen Family Systems: core concepts are differentiation of self, triangulation, family emotional system, and sibling order. Goals are to increase family member differentiation, decrease triangulation, and manage anxiety. Uses genograms
- Experimental/Humanistic: core concepts are attachment theory and "psychotherapy of the absurd" (seriously). Goals are creativity, increasing self-esteem and fostering cohesion through wacky activities like family sculpture. May have 2 therapists
- Milan System: core concepts are neutrality, circular interaction between family and therapists, families get stuck in patterns of interaction, solutions reside with the family, not the therapist, "long-term brief therapy" (long session with a month between sessions). Goals are unmasking the "family game," changing maladaptive patterns. Techniques include therapist team behind a one-way mirror, "hypothesizing," "counter paradoxical interventions" (intentionally engage in unwanted behaviors to increase insight), and "circular questions" designed to improve empathy ("What do you think concerns your wife most about your illness"). This is super famous family therapy and sometimes gets tested
- Narrative: core concepts are narrative stories of the family system designed to make others understand the dynamic, understanding the family system in the context of a narrative story. Goals are creation of newer, more useful life stories, externalize problems rather than blaming single members for problems, enhance communication through therapeutic letters

- Psychodynamic: core concepts are projective identification (projecting your undesirable characteristics onto another person), splitting, scapegoating, and change occurs through conscious insight into unconscious processes. Goals include increasing insight/empathy, disentangle interlocking pathologies, identify transference within the family dynamic, and challenge resistance. Creation of a "holding environment"
- Psychoeducational: core concepts are expressed emotion, engagement with the family, education workshops, and rehabilitation. Goals include improving social skills and communications, problem-solving, relapse prevention. This is the #1 family based therapy for families with a member with schizophrenia or another major psychiatric disorder
- Structural: core concepts are boundaries, family hierarchy, coalition/alliance, and engagement/enmeshment. Goals are improving flexibility/adaptability, finding a balance between connectedness and differentiation, and homework based problem solving
- Strategic: core concepts are power/control, family life cycle transitions, role changes, adapting to change. Believe individual cannot change until the system that sustains them changes. Goals are problem-solving with identification of "exception to the rules," address double binds, disrupting sequences of behavior that perpetuate problems, "paradoxical directives"

Couples Therapy

Overview: focuses on the pattern of interactions between two people while taking into account the individual history of each member.

Basic Principles: monitor for projective identification and re-enactment of childhood attachment issues with spouse. A couple's relationship has a life cycle context, within the context of changes in the individual and changes in the family. Life cycle implies that transition from one life cycle to another has the highest risk for divorce and conflict (mid-life crisis, aging, etc). Communication skills are essential. Contraindicated in cases of domestic violence, psychosis, or when divorces is actively being sought out.

The Interview: components should include evaluation of each partner's motivation to participate in treatment, providing a safe environment in the first session, identifying each member's view of what the problem is, assessing for infidelity, and identifying the biggest sources of conflict.

Goals: alleviate distress, promote well-being as a unit, problem-solving, promote accountability and responsibility.

Treatment Interventions: interpretation of unconscious processes, communication skills training (including learning active listening skills and learning to fight constructively with specific rules), role playing (role reversal to increase empathy), and paradoxical interventions (reverse psychology stuff where a therapist tells member NOT to change, leading to change).

A NINJA'S GUIDE TO FREUD & OTHER STUFF

Sigmund Freud

Associated with the terms resistance, transference, countertransference, parapraxes ("Freudian slips"), abreaction (recovering repressed feelings to remove symptoms), catharsis, repression (hiding distressing material in the unconscious) and many more.

Interpretation of Dreams

Based on the premise that dreams are unconscious wishes (potentially childhood wishes) that are not accessible in waking life. The following terms are sometimes seen on PRITE, requesting a definition.

- Two layers in dreams: manifest layer is what is remembered/recalled of dream; latent layer is the unconscious wish that is not recalled
- Condensation: several unconscious impulses are attached to one manifest dream image. Example: a man with a face made of bread playing a trumpet may be the dreamer's fear of men consuming creative instincts…or something like that
- Displacement: intensity toward an object is redirected to a more neutral/acceptable object. Example: dreamer unconsciously wants to kill their mother; in the dream, they want to kill an unknown female stranger (more acceptable object)
- Projection: dreamer's unacceptable wishes are put onto another person in the dream. Example: dreamer wants to rob a bank; in dream they are concerned about their brother's desire to rob a bank
- Symbolic representation: innocent symbol represents a complex set of feelings. Example: dreamer sees a puppy, which actually represents their feelings of vulnerability and fear of being castrated/neutered…or something like that
- Primary process: the above incoherent esoteric characteristics of the manifest layer (nonsensical dream aspects that are recalled)
- Secondary revision: rational portions of dreams that resemble waking life (dreams acting out work/home scenarios, being on call, etc)

The Topographical Model of the Mind

Based on principle that the mind is divided into layers. Freud used this theory to identify the workings of the conscious and unconscious mind.

- Conscious: ideas/thoughts are in the conscious mind due to "psychic energy" (attention cathexis), which pushes these thoughts into the conscious forefront
- Preconscious: this is the area where thoughts are held before being pushed into the conscious mind. Unacceptable unconscious wishes held here may be pushed into consciousness by psychic energy
- Unconscious: the area of the primary process (see above definition) that is incoherent and represents wish fulfillment. Memories are separate from words, and psychotherapy helps to attach words to unconscious thoughts and bring them to the conscious mind

Instinct and Drive Theory

After developing the topographical model of the mind, Freud began to consider instinct theory. Instinct refers to a pattern of genetically derived behavior that is independent of learning. The instinct has 4 basic characteristics: the source (part of body from which instinct arises), the impetus (intensity of instinct), the aim (generally an action toward decreasing tension), and the object/target of the instinct.

Specific types of instinct

- Libido: sexual/pleasure drives
- Ego: non-sexual instincts/drives
- Aggression: dual instinct theory refers to the balance between libido and aggression, where aggression aims to destroy

Pleasure vs. Reality Principles

The Pleasure principle is that humans avoid pain and seek pleasure. The Reality principle is that which delays/postpones the pleasure principle when it is not appropriate. The Reality principle is generally learned.

Narcissism

Basic principle is that the person's libido is invested in the ego rather than in other persons. There can be a loss of reality testing and grandiosity. Freud regarded homosexuality as a narcissistic form of object choice, when a person falls in love with an idealized version of themselves projected onto someone else.

- Primary narcissism: after birth, the neonate is completely narcissistic, with all libido invested in meeting their own needs. The addition of the mother figure leads to withdrawal of the libido from self and redirected onto the external object (mom). This is object attachment

- Secondary narcissism: if after object attachment occurs with the mother, there is a later trauma, the libido is withdrawn from the mother (object) and reinvested in the person's ego. It's a regression

The Structural Theory of the Mind

Freud moved from the topographical model of the mind to the structural theory of the mind, which focused on the ego, id, and superego.

- Id: unorganized instinctual drives that are part of the primary process (see above). Occurs unconsciously
- Ego: spans all three areas of the mind (conscious, preconscious, and unconscious). It is responsible for logic/abstraction (conscious), defense mechanisms (unconscious), perception, contact with reality, and delay/modification of drives (to make them socially acceptable). The ego helps to modify the id, which sometimes leads to conflict
- Superego: establishes and maintains the moral conscience, based on values internalized from parents. Proscribes what a person should not do

Functions of the Ego

- Controls instinctual drives: mediates between the id and the external world and delays socially unacceptable drives
- Judgment: anticipates the consequences of actions
- Relation to reality: mediates between internal world and external world. Develops a sense of reality (distinguish inside body vs. outside body), reality testing (distinguish between fantasy and reality), and adaptation to reality (adapt to change)
- Object relations: developing satisfying relationships stems from early interactions with parents and other early significant figures

Defense Mechanisms

These are very common on PRITE, and basically are grouped together from the most primitive (e.g., projection) to most mature (e.g., sublimation).

Narcissistic: most primitive

- Denial: abolishes external reality ("I don't have cancer")
- Distortion: reshapes reality to suit internal needs (delusions, hallucinations)
- Projection: endowing your feelings onto someone else ("Why is mom so angry today?" when really YOU are angry). Can include paranoid delusions and delusional disorders, which puts one's feelings onto others ("They want to harm me")

Immature

- Acting out: giving in to an impulse to relieve tension (burning down a house)
- Blocking: inhibiting or blocking thoughts, pushing them into the unconscious. Blocking thoughts can lead to increased tension
- Hypochondriasis: overemphasizing illness, is a regression to avoid guilt and responsibility
- Introjection: internalizing an object's quality. An example is identification with an aggressor (internalization) leading to belief that the aggression is under one's control. ("Poor thief, he probably really needs a car. Look how benevolent I am")
- Passive aggressive behavior: indirect aggression that is not overt (like procrastination that makes someone else suffer)
- Regression: return to a less developed phase ("I want my teddy bear")
- Schizoid fantasy: autistic retreat to avoid conflict. Repels others and avoid intimacy
- Somatization: transform conscious or unconscious conflict into body sensations/symptoms to avoid dealing with it. (Kid with stomach pain on test days)

Neurotic

- Controlling: obsessive management of external environment to decrease anxiety and resolve conflict
- Displacement: shift emotion from one object to another (bad day at work, go home and yell at your spouse)
- Externalization: generalized projection where the entire world/external environment is attributed with personal elements (feeling angry, "The whole world is an angry place!" "This job is so uncaring!")
- Inhibition: renounce ego functions to decrease anxiety
- Intellectualization: use intellect to avoid an emotional/affective experience (get cancer, spend all your time on internet learning about it to avoid emotionally experiencing having cancer)
- Isolation: separate an idea from an affect ("isolation of affect" PRITE question has a patient who blankly tells therapist that, as a child, his dad kicked a puppy to death. No affect in telling story)
- Rationalization: using rational explanations to justify an unacceptable behavior or belief ("I'm allowed to take stacks of napkins home from McDonald's because they'll just throw them away anyway")
- Disassociation: modify one's character/identity to avoid emotional distress. ("dissociative fugue" is when a person goes places/does things but retains no memory and appears confused afterwards. Disassociation is often used by patients with borderline personality disorder, and is a numbing of sensorium in response to trauma)
- Reaction formation: unacceptable impulse/emotion is converted to an acceptable impulse (you hate your neighbor because they are noisy at all hours of the night, but this hatred feels unacceptable/elicits guilt. As a result, you go give your neighbor a present even thought you hate them)

- Repression: put an undesirable thought/feeling into the unconscious to avoid dealing with it. This is different from suppression, which consciously avoids the thought. (Repression: unconsciously forgetting a rape at the age of 5. Suppression: choosing not to think about the rape that happened at age 5). Repression is similar to thought blocking, except no tension is observed with repression
- Equalization: making a neutral object sexual to decrease anxiety related to a prohibited impulse (No clue. Have fun with that one….)

Mature Defenses

- Altruism: providing a gratifying service to others for the vicarious experience (volunteering to raise money for cancer makes you feel all warm and fuzzy inside)
- Anticipation: anticipate future discomfort (coming up with a realistic back-up plan for problems in the future, like an earthquake safety kit in the garage)
- Asceticism: gratification through limitation and renunciation
- Humor: using humor to tolerate terrible experience. This defense mechanism actually focuses on the experience ("Well, now that I've lost both my legs, I'll save loads of money on shoes.")
- Sublimation: impulse gratification by converting socially unacceptable impulses to acceptable actions (gardening, painting). Feelings/impulses are acknowledged and modified
- Suppression: consciously postponing discomfort (one child in car accident, rather than first rushing to ER, suppresses fear and calls the other kids at home to make sure they are safe and cared for, then goes to ER)

Psychosexual Developmental Stages

Basically, these are Freudian Developmental stages that often are tested on PRITE. The goal is to progress through these stages linearly, confronting pathology specific to each stage, leading to resolution of conflict/pathology and moving onto the next stage in life. Failing to resolve pathology leads to incomplete passage through each stage, and the person will continue to struggle with unresolved issues from previous stages. Example: A person who does not resolve the issues of overcontrol vs. undercontrol in the anal stage (age 1-3 years) will forever struggle with autonomy issues and balance of control (making them "anal retentive" and overcontrolling). Therapy seeks to find these unresolved issues and bring resolution towards better mental health. While some theories seem a bit weird (penis envy, castration fears), the overall principle of working through unresolved early-life issues is reasonable. These stages correlate with Eriksonian Stages (discussed next).

Oral (0-18 months)

Concepts of thirst, hunger, and satiation. Libido (oral eroticism) vs. Aggression (oral sadism, biting, devouring, and destroying)

- Goal: develop trust and dependence and gratify libido without conflict with aggression
- Pathology: narcissism, pessimism, dependence on objects/people for self-esteem, envy, jealousy
- Resolution of this stage: learn to give and receive without excessive dependency/envy and build trust/self-reliance
- Common defense mechanisms: projection and denial in early oral, displacement and "turn against self" in later oral

Anal (1-3 years old)

Concepts of control (over anal sphincter), increasing aggressive drives, and the shift from a passive/dependent phase (oral) to an active phase

- Goal: separation, individualization, maintaining a balance between overcontrol/undercontrol. Related to autonomy/independence with a good balance of control vs. shame/self-doubt due to lack of control
- Pathology: overcontrol leads to being overly neat/orderly, stubborn, and willful. Loss of control leads to messiness, ambivalence, and defiance. Obsessive-compulsive neurosis pathology develops in this stage
- Resolution: autonomy, initiative without guilt, self-determining behaviors without shame and doubt
- Common defense mechanisms: undoing, reaction formation, regression, and isolation

Urethral Transition Stage (between anal and phallic stages)

Release vs. retention. There is the potential for regression in this transition from anal stage (balance of control, autonomy) moving onto phallic stage. Regressive enuresis can occur here.

- Pathology: competitiveness/ambition, feminine shame due to lack of strong urine stream (seriously…)
- Resolution: pride and self-competence, sets the stage for gender identity

Phallic (3-5 years old)

Sexual interest, stimulation, and excitement. Unconscious oedipal issues (boy's competition with father for the mother's love) and castration anxiety

- Goals: gender identity, overcome oedipal issues for organization of character
- Pathology: neurosis, castration anxiety in males, penis envy in females, abnormal development of human character
- Resolution: ability to maintain curiosity without embarrassment, initiation without guilt, sexual identity, regulation of drive impulses, generate superego based on identification with parent of the same sex
- Common defense mechanisms: Intellectualization vs. repression

Latency (5/6-11/13 years old)

Development of the superego in the phallic stage leads to instinct control. In latency, the libido gets sublimated (directed into socially acceptable behaviors). Start to play and learn while fighting overcontrol and obsessions

- Goals: finish the work started in the phallic stage by further integrating oedipal identification and consolidating sex roles. Develop Ego and begin to master skills
- Pathology: Issues of control (like in anal stage), with problems with overcontrol/undercontrol. Overcontrol leads to closure/stunting of personality development. Undercontrol leads to not focusing on learning in this stage
- Resolution: integrating psychosexual development, mastering tasks/objects, becoming autonomous, and learning to take initiative
- Common defense mechanisms: sublimation

Genital (11/13-Adulthood)

Physical maturity, hormonal development, increasing drives. There is a struggle against regression and this stage may reopen all conflicts in previous stages, leading to the need to re-resolve them

- Goals: separate from dependence on parents, develop mature object relations, develop adult roles, and accept cultural values
- Pathology: reopening/reworking previous development and potential for regression; previous unsuccessful resolution leads to pathology in adulthood
- Resolution: reintegration and resolution of previously unresolved conflicts leads to maturation of personality and capacity for self-realization

Erik Erikson

Adapted some of Freud's theories of development to formulate a theory of development that covers the entire span of the life cycle, from infancy and childhood through old age and senescence. Epigenetic principle: development occurs in sequential, clearly defined stages, and that each stage must be satisfactorily resolved for development to proceed smoothly. A virtue is associated with each stage. "If everything goes back to childhood, then everything is somebody else's fault and taking responsibility for oneself is undermined."

Trust vs. Mistrust (0-18 months, correlates with Oral)

Starting to take in the world and learn trust based on quality maternal relationship. "Taking and holding onto things."

- Defense mechanisms: projection and introjection
- Virtue: hope
- Pathology: schizophrenia (aggravated crisis due to failing to develop hope), depression (feeling empty, no good), addictions issues

Autonomy vs. Shame and Doubt (18 months-3 years, correlates with Anal)

Developing a sense of justice and maintaining a balance between good will/cooperativeness and willfulness. Self-certain vs. self-conscious. Regulate the will. Will to be oneself vs. self-doubt. "Holding on and letting go."

- Virtue: will
- Pathology: persecutory paranoia (stuck between trust/autonomous will and mistrust/doubt), OCPD (conflict with hold on/let go, leading to doubt > autonomy and a harsh conscience), impulsivity

Initiative vs. Guilt (3-5 years old, correlates with phallic)

Exploration, conquest, curiosity, competitive, aggressive, preoccupation with genitals. Compete with same sex parent, jealousy, and rivalry. Failure leads to guilt. Role anticipation vs. role inhibition. The superego is developed to regulate initiative. Oedipal impulse is overcome and the child can then compete in the outside world and learn to lead an active adult life. "Being on the make."

- Virtue: purpose
- Pathology: overcompensation for the conflict between initiative and guilt. This can cause conversion disorder, inhibition, paranoia, and psychosomatic illnesses

Industry vs. Inferiority (5-13 years old, correlates with latency)

Learning new skills, pride, work ethic, and diligence. Identify with teachers. Learn to find role in society. Task identification vs. sense of futility.

- Virtue: competence
- Pathology: failure to complete previous stages leads to mistrust/pessimism, imbalance between overcontrol/undercontrol, poor development of the superego and guilt. If there is no development of trust/balance of control/creation of superego, the child will not integrate well into society. In addition, they will not learn new skills or become competent. This all leads to creative inhibition and conformity

Identity vs. Role Confusion (13-21 years old, correlates with genital)

Puberty, compairing self with others and caring how others perceive them, cliques. Failure leads to identity diffusion and role confusion. Intolerance of individual differences is the way the youth wards off a sense of their own identity loss. Falling in love serves to clarify one's sense of identity projecting your identity onto another person.

- Virtue: fidelity, sustaining loyalties to others despite contradiction of value systems (accepting people for who they are)
- Pathology: role confusion ensues when the person cannot formulate a sense of identity. This results in delinquency, gender-related identity disorders, and borderline psychotic episodes

Intimacy vs. Isolation (21-40 years old)

Looks at the virtue of love within a balanced identity. Intimacy is tied to fidelity, to make compromise and to self-sacrifice. Ego loss occurs while becoming closer to others; the reaction may be to become detached and self-absorbed.

- Virtue: love
- Pathology: isolation and detached states, including schizoid personality disorder

Generativity vs. Stagnation (40-60 years old)

Establishing and guiding the next generation, not just specifically your own offspring. Person has already learned to form intimate relationships, and this stage serves to broaden social scope to include groups, organizations and society. Importance of feeling needed. Failure of generativity leads to stagnation, escapisms (alcohol and other sexual infidelity), and mid-life crisis.

- Virtue: care
- Pathology: alcoholism, divorce, withering of leadership roles/destruction of companies, premature invalidism

Integrity vs. Despair (60 years old until death)

Accepting responsibility for one's own life, holding onto integrity, and a "detached yet active concern with life."

- Virtue: wisdom
- Pathology: failing to attain integrity leads to becoming deeply disgusted with the external world and contemptuous of persons and institutions. Disgusts masks the fear of death and a sense of despair that "time is now too short for the attempt to start another life and try out alternate routes to integrity."

"Healthy children will not fear life if their elders have integrity enough not to fear death." Erik Erikson

Pathologic Development

In both Freud and Erikson's developmental theories one concept is central: failure to resolve conflict and mature through each stage leads to significant residual pathology. Plainly stated, if you don't resolve the bad stuff in each stage, you will go on to the next stage with unresolved baggage and continue through life with that baggage. A person who does not resolve oral/trust/mistrust stages will have a lifelong struggle with dependence, trust, hopelessness and mental pathology. This section is not high-yield for PRITE, but it is very useful for providing good care for your patients, understanding the roots of pathology, and making a kickass bio-psycho-social-spiritual formulation for oral examinations in residency.

Birth to 18 months

Freud: *Oral stage* (feeding, nutrition, needs, narcissism, object relations), trust/give/receive.

Erikson: *Trust vs. Mistrust* (taking and holding onto things), hope, projection.

Pathology: Impaired trust leads to mistrust.

- Separation in infancy leads to depression, hopelessness, dysthymia
- Projection (defense mechanism associated with this stage) leads to social mistrust, paranoia, delusional disorders, schizoid personality disorder, and paranoid schizophrenia
- Social mistrust leads to oral dependency and substance abuse due to the feelings of emptiness and hunger
- Feeling starved and empty also leads to thrill seeking behaviors

18 months to 3 years

Freud: *Anal stage* (control of sphincters), balance between over control/under control, individualization.

Erikson: *Autonomy vs. Shame and Doubt* (holding on vs. letting go), independence and the development of will.

Pathology: develops when shame and doubt dominate autonomy.

- Doubt > autonomy leads to obsessive personality
- Shame > autonomy leads to feeling dirty, delinquent behavior and paranoia about control
- Rigorous toilet training leads to excessive cleanliness and compulsions
- Overcontrol leads to obsessions/compulsions, willfulness and anal retention
- Undercontrol causes ambivalence, messiness, and sadomasochism
- Mistrust (in earlier stage) plus shame and doubt leads to persecutory delusions
- Refusal to be controlled causes impulsivity

3 to 5 years

Freud: *phallic stage* (issues of oedipal conflict, gender identity, penis envy/castration anxiety), identification with parents leading to the development of superego to regulate drives.

Erikson: *Initiative vs. Guilt* (expedition, competition with parent), conscience, purpose, child learns values and recognizes the external world, guilt secondary to drives vs. initiative.

Pathology: guilt related to impulses and desires leads to symptom formation.

- Guilt leads to anxiety disorders, phobias, sexual inhibition (due to fear of punishment)
- Punishment for impulses leads to conversion disorder due to oedipal wishes, and sexual inhibition/impotence
- Fear of not fulfilling one's purpose leads to psychosomatic disease

5 to 13 years

Freud: *Latency stage* (superego developed in phallic stage now controls/regulates desires and wishes), sexual identity, learning, mastery of skills.

Erikson: *Industry vs. Inferiority* (learn skills, begin to establish identity), competence, integration into society.

Pathology: development of inferiority due to problems completing goals.

- Work inhibition, feeling inadequate, compensatory drive for money/power/prestige later in adulthood at the expense of intimacy (later stages suffer due to incompletion of this stage)

13 years to 20s (Adolescence)

Freud: *Genital stage* (maturation, reworking conflict), separation/independence, emphasis is on reworking unresolved issues from the previous stages.

Erikson: *Identity vs. Role Confusion* (puberty, ego identity), roles, fidelity to oneself.

Pathology: identity confusion.

- Loss of identity through overidentification with others and formulation of cliques
- If unable to leave the home, there may be prolonged dependence
- Role confusion leads to conduct disorder, gender identity disorder, and disruptive behavior

20s to 40s

Freud's last sage was the genital stage, which focused on continuing to work through previous conflict throughout adulthood. The remaining discussion on development of psychopathology will focus on Erikson.

Erikson: *Intimacy vs. Isolation* (maintaining identity while establishing intimacy), sacrifice/compromise, love.

Pathology: the inability to take risks, capacity to love and isolation leads to schizoid personality disorder.

40s to 60s

Erikson: *Generativity vs. Stagnation* (guiding the next generation), tribal leaders, caring, newly achieved personal intimacy with social groups, knowledge and skills.

Pathology: develops when a person cannot generate of skills and share knowledge with the next generation

- Stagnation leads to "escapism" into alcohol/substances, infidelity and mid-life crisis
- Society suffers, the patient suffers, leading to depression and disappointment
- Contemplation of past failures, current problems, and losing hope for the future

60s to End of Life

Erikson: *Integrity vs. Despair* (accept the life cycle and the proximity of death), healthy detachment and wisdom.

Pathology: the knowledge that time has run out, no generativity, and inability to accept life

- Declining physical health leads to anxiety, psychosomatic illness, hypochondria and depression.

- Lacking generativity and acceptance often leads to suicide

Neuropsychologic Testing

This is a highly-tested area on PRITE. Examples are questions asking you to choose the "projective test" or will give you the name of the test and ask you its function. Reliability refers to the ability to reproduce the test results. Validity shows if a test can accurately test what it is supposed to.

Types of Tests

- Objective: typically pencil-and-paper tests with specific questions that can yield numeric scores to be analyzed. Example: MMPI
- Projective: ambiguous stimuli that the patient responds to and the response is then interpreted. Example: Rorschach test. *Projective tests detect the presence of subtle psychotic thought processes*

Intelligence Tests

The IQ test was introduced in 1905 by *Alfred Binet*. The intelligence quotient (IQ) is the ratio of mental age/chronological age, which is multiplied by 100. An IQ of 100 would imply that your mental age (thinking ability) matches your chronological age (how old you are). The average IQ is 100.

Wechsler Adult Intelligence Scales (WAIS) is the most widely used intelligence test. The latest revision is the WAIS-III. It uses verbal IQ (previously learned factual info) and performance IQ (visuospatial/visuomotor skills). An IQ of 90-100 is normal, 50-70 is mild MR, and below 20 is profound MR. *The WAIS has high reliability and the WAIS-II vocabulary test most strongly correlates with pre-morbid functioning in a patient with early dementia.*

Personality Assessment

Objective Tests

- MMPI: uses 10 scales in a configurational approach (see a nice little graph based on responses in 10 categories) to "identify major areas of psychopathologic functioning" and measures test-taking attitudes during the examination (can detect malingering, answering questions falsely, etc. It's super cool)
- Millon Clinical Multiaxial Inventory: test with brief administration time and correlates well with DSM-III. Per PRITE, it is the test that is "the most helpful in confirming a personality disorder"
- Structured Clinical Diagnostic Assessments: these are tests that give a numerical score to show severity of a particular illness. Includes Hamilton Rating Scale for Depression, Yale-Brown Obsessive-Compulsive Scale (YBOCS), and the SCID. The Beck Depression Inventory is the *most appropriate brief screening instrument that a patient can fill out alone at a physician's office to screen for depression*

Projective Tests

- Rorschach Test: set of 10 inkblots are a stimulus for associations, half are black and white, they are shown in a particular order, and reaction times are recorded. Interpretation of responses requires an experienced clinician. It is the most widely used projective test
- Thematic Apperception Test (TAT): A test in which a patient is shown pictures of situations and asked to describe what is going on in each picture. Example: a woman seated on a couch looking up at an older man. *Serves to "infer motivational aspects of behavior"*
- Sentence Completion Test (SCT): has sentence stems that the patient completes ("Sometimes I wish…" "My greatest fear is…")
- Word-Association Technique: created by Jung, patient is presented with a word and must give the first word that comes to mind. *This is similar to free association and brings unconscious to conscious.*
- Draw-a-Person Test: first used to test intelligence in children, the patient draws a person. *Shows a representation of the expression of the self*

Cognitive Testing

Executive Functioning

- Wisconsin Card Sorting Test (WCST): assesses "abstract reasoning and flexibility in problem solving" per PRITE. Cards are sorted into groups (color, suit) that the patient is not aware of, with the goal of learning the groups through trial and error
- Trail Making Test: patient connects letters and numbers together in sequential order to test concentration and executive functioning

Visuomotor Coordination

- Bender Gestalt Test: tests visuomotor coordination by copying designs on paper. Has two phases, first with the patient allowed to copy the design with the original design in front of them, and then a memory testing portion where the original design is removed and the patient must copy the design from visual memory. Helps screen for organic dysfunction. *Determines neuropsychologic impairment*

Receptive and Expressive Language

- Token Test: examines patient's ability to comprehend verbal instructions, grammatical complexity, and attention span
- Boston Naming Test: examines verbal confrontation and naming. *Discriminates cognitive difficulties in Alzheimer's disease from those in depression*

Test Batteries

- Halstead-Reitan Battery of Neuropsychological Tests: determines neuropsychologic impairment, is composed of 10 separate test that function to differentiate brain damaged patients from those who are neurologically intact. Schizophrenics function similar to chronic brain damaged patient

Child and Adolescent Psychological Assessment

Intelligence

- Wechsler Intelligence Scale for Children-III (WISC-III): WAIS-III can be modified for children ages 5-15 in the WISC-III. *It is closest to the original Stanford Binet*. For preschoolers, there is the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)

Achievement

- Woodcock-Johnson Psychoeducational Battery-Revised (W-J): scores reading and mathematics, written language, and other measures of academic achievement. *This test helps to more specifically identify learning disability with children that have otherwise normal IQ*
- Wide Range Achievement Test-3 (WRAT-3): screen for deficits in reading, spelling and math. *This is a useful test to screen academic performance*

Adaptive Behavior

- Vineland Adaptive Behavioral Scales: evaluates adaptive behavior, communication skills, living skills, socialization, and motor domains. Can be modified to test those with visual and hearing impairments

A NINJA S GUIDE TO SUBSTANCE USE DISORDERS

Overview

Substance use disorders are prevalent among patients in all clinical settings. Regardless of medical specialty, a clinician should be able to recognize the signs and symptoms of substance use disorders, while keeping in mind possible underlying emergent conditions (withdrawal, delirium, seizures, etc.). There is high co-morbidity between substance use disorders and other psychiatric disorders and medical conditions. Empathic and non-judgmental care for patients with substance use disorders leads to a significant decrease in morbidity and mortality. *Substance related disorders are broken down into two categories: Substance Use Disorders and Substance-Induced Disorders.*

Etiology of Substance Use

Multifactorial

- Psychodynamic (substance use to treat depression/escape reality)
- Behavioral (positive reinforcement)
- Genetic (twin studies, adoption studies)
- Neurochemical (abnormal receptor/neurotransmitters leading to substance modulation of neurochemistry; reward pathways involving dopamine (DA) in the *nucleus accumbens* and *ventral tegmental* area)

Comorbidity

- Antisocial Personality disorder
- Depression/Mood disorder, Anxiety disorders, Schizophrenia
- Suicide: people who abuse substances are 25x more likely to die by suicide than the general population. 15% of alcoholics have been reported to commit suicide

Screening for Addiction

When interviewing a patient, ask about each chemical from the standpoint of the least likely drug to cause denial to the most likely drug to cause denial. Example: prescription meds (BZDs), then tobacco, then EtOH, then illicit drugs.

CAGE Questions (EtOH Screening): Each "yes" answer is scored 1 point. One "yes" raises suspicion of an EtOH use problem; more than one "yes" is a strong indication that a problem exists.

1. Have you ever felt the need to **C**ut down on your use of EtOH?
2. Have people **A**nnoyed you by criticizing your use of EtOH?
3. Have you ever felt bad or **G**uilty about your use of EtOH?
4. Have you ever had a drink in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)?

Abbreviate CAGE: Yes to both is 80% sensitive and specific.

1. Have you ever used a substance more than you intended?
2. Have you ever felt the need to cut down?

Always obtain a history of consequences of substance use. These include medical, legal, occupational, family/relationships, and emotional consequences of use. This allows you to find objective markers of problematic use despite the patient's denial. *If a patient has a history of DUI, they're probably NOT just a social drinker.*

Motivational Interviewing

This is a form of interviewing to help maximize the patient's intrinsic desire to change. Example: "Currently, your motivation to quit smoking is at a 4/10. What would it take to get it to a 5/10? What are the advantages/disadvantages of smoking for you?"

The stages of change

- Prec-ontemplation: patient does not intend to change behavior in the foreseeable future. A patient at this stage may be unaware or only vaguely aware of his/her problem
- Contemplation: patient is aware of the problem and is seriously considering changing behavior but does not make a commitment to take action. Patients at this stage often feel ambivalent about the sense of loss they may feel despite the perceived gain of overcoming their problem
- Planning/Preparation: patient intends to take action within the next 30 days and has taken some steps toward treatment. This stage combines intention and behavioral criteria (such as making small modifications to behavior that signal a decision to change)
- Action: patient changes behavior and commits a considerable amount of time and energy to overcoming the problem. This stage lasts from the time of the initial action to 6 months
- Maintenance: the patient continues to meet the goals set up in the planning/action stage and uses coping skills to avoid relapse

Substance Use Disorders

An essential feature is a cluster of cognitive, behavioral, and physiological symptoms that occur due to a substance despite consequences. In general, the diagnosis of substance use disorder requires *the presence of at least 2 criteria over a 12-month period of time*. The severity of the disorder is determined by the number of diagnostic criteria present. For all substances, the DSM-5 criteria for substance use disorder can be grouped into *impaired control, social impairment, risky use, and pharmacological criteria.*

Impaired Control

- The individual takes the substance in larger amounts or over a longer period of time than intended
- The individual expresses a persistent desire to cut down or regulate the substance use or may have multiple unsuccessful attempts to decrease or discontinue use
- Individual spends a great deal of time obtaining, using, or recovering from the effects of a substance
- Craving is manifested by an intense desire or urge for the drug at any time but is more likely in an environment where the drug was previously obtained or used (*classical conditioning*)

Social Impairment

- Recurrent substance use leads to failure to fulfill major role obligations at work, school, or home
- Continued use of the substance despite social or interpersonal problems caused by use of the substance
- Important social, occupational, or recreational activities are given up or reduced due to substance use

Risky Use

- Recurrent substance use in situations that are physically hazardous
- Continued use despite knowledge of having a persistent or recurrent physical or psychological problem caused by or exacerbated by the substance

Pharmacological Criteria

- Tolerance: requires a markedly increased dose of the substance to get the desired effect or there is a markedly reduced effect when the usual dose is consumed
- Withdrawal: a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. The individual may consume the substance to remove withdrawal symptoms

Note: appropriate medical treatment with a prescribed medication (opiates, stimulants, etc.) often leads to requiring more medication to get effect or withdrawal upon discontinuation. This is *not* counted in diagnosing a substance use disorder. There is normal, expected pharmacological tolerance and withdrawal with many commonly prescribed medications, leading to erroneous diagnosis of "addiction" when these are the only symptoms present. If tolerance and withdrawal are the *only* symptoms present, a diagnosis of substance use disorder is not made

Severity: determined by the number of symptoms present

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe*:* substance use is diagnosed in the presence of 6 or more of the above symptoms

The diagnosis of a substance use disorder is coded by the specific substance. Thus, you would *not* diagnose a patient with "Benzodiazepine Use Disorder, Moderate." Instead, the diagnosis would be "Moderate Alprazolam Use Disorder." The word *addiction* is not used, with the focus on the more neutral term *substance use disorder* to eliminate negative connotation.

Substance-Induced Disorders

This category includes intoxication, withdrawal, and other substance or medication-induced mental disorders (such as a substance causing psychosis or depression).

Substance Intoxication

Criteria are specific to substance, as each substance has its own intoxication profile. The most common behavioral changes include disturbance in perception, wakefulness, thinking, attention, judgment, psychomotor behavior, and interpersonal behavior. Short-term intoxication can present very differently than long-term, chronic intoxication. Example: acute use of cocaine leads to outgoing, gregarious behavior. Daily use can actually cause irritability and social withdrawal. The presence of physiological symptoms alone may not meet criteria for *intoxication.* Example: if the person has methamphetamine-induced tachycardia, but that is the only symptom present, it would not be considered intoxication. Substance intoxication can be present in individuals who do not otherwise meet criteria for a substance use disorder (i.e., person gets drunk once but does not otherwise have criteria for Alcohol Use Disorder).

Basic criteria for intoxication

- A reversible, substance-specific syndrome due to the recent ingestion of a substance
- During or shortly after using a substance, there are physiological effects of the substance on the CNS, causing problematic behavior or psychological changes
- The symptoms are not due to another medical condition or mental disorder

Routes of administration that produce more rapid and efficient absorption into the blood (smoking, snorting, injecting) tend to have more intense intoxication and a higher likelihood of an escalating pattern of substance use leading to withdrawal. Rapidly-acting substances are more likely than slower-acting substances to produce immediate intoxication.

Drugs that are high potency, have rapid onset of action, are lipophilic, and have a short half-life have the greatest liability for abuse.

Substance Withdrawal

Like intoxication, the presence of physiologic withdrawal alone does not mean that a substance use disorder must be diagnosed. However, unlike intoxication, the presence of withdrawal is usually associated with a substance use disorder. Most individuals with withdrawal have an urge to re-administer the substance to reduce the symptoms.

Basic criteria for intoxication

- The development of a substance-specific behavioral change, with physiological and cognitive components, due to cessation or reduction of substance use that was previously heavy and prolonged
- Syndrome causes significant distress or impairment in social or occupational functioning
- The symptoms are not due to another medical condition or mental disorder

Short-acting substances tend to have higher potential for development of withdrawal than do long-acting substances. However, longer-acting substances tend to have a longer duration of withdrawal (days or weeks). The longer the duration of action, the longer the time between drug cessation and onset of withdrawal symptoms and the overall duration of withdrawal is longer. Example: discontinuing clonazepam (long half-life, long duration of action) may not have initiation of withdrawal symptoms for 1-2 days after stopping use, and the symptoms of withdrawal may remain present for a week or longer.

Intoxication and withdrawal diagnoses are coded by the name of the specific substance. Thus, a person intoxicated with methamphetamine would **not** be diagnosed "Stimulant Intoxication," but would be diagnosed "Methamphetamine Intoxication." A person withdrawing from diazepam would *not* be diagnosed "Benzodiazepine Withdrawal," but would be diagnosed "Diazepam Withdrawal." The ICD10 coding system in 2014 requires withdrawal diagnoses to be associated with a Substance Use Disorder, showing the association between withdrawal and likely substance use problems.

Drug	Intoxication	Withdrawal
Alcohol	**Clinical significant dysfunctional behavior:** • Disinhibition • Agitation/aggression • Mood lability • Impaired judgment **One or more of the following:** • Slurred speech • Incoordination • Unsteady gait • Nystagmus • Memory/attention impairment • ↓ Consciousness (stupor/coma) Severe: Hypotension, hypothermia, depressed gag reflex	**Two or more of the following:** • Autonomic hyperactivity (sweating, tachycardia, HTN) • Tremor of tongue, eyelids, or outstretched hands (asterixis) • Insomnia • Nausea/vomiting • Transient visual, tactile, or auditory hallucinations, or illusions • Psychomotor agitation • Anxiety • Generalized tonic-clonic seizures *Can be lethal*
Amphetamine, Cocaine, and other Stimulants	**Clinically significant dysfunctional behavior or perceptual abnormality:** • Euphoria & sensation of ↑ energy • Hypervigilance • Changed sociability • Abusive/aggressive • Mood lability • Repetitive stereotyped behaviors • Impaired judgment **Two or more of the following:** • Tachycardia • Pupillary dilatation • HTN • Sweating/chills • Nausea/vomiting • Weight loss (2/2 ↓ appetite) • Psychomotor agitation • Muscular weakness • Chest pain, arrhythmias • Respiratory depression • Seizures, dystonias, dyskinesia • Confusion, coma	**Dysphoric mood + two of the following:** • Lethargy and fatigue • Vivid, disturbing dreams • Insomnia/hypersomnia • Increased appetite • Psychomotor retardation/agitation

Caffeine	**Five or more of the following:** • Restlessness/anxiety • Excitement • Insomnia • Flushed face • Diuresis • GI disturbance • Muscle twitching • Rambling flow of thought and speech • Tachycardia or cardiac arrhythmias (PVCs) • Periods of inexhaustibility • Psychomotor agitation	**Three in 24 hours:** • Headache • Marked fatigue and drowsiness • Marked anxiety or depression • Nausea/vomiting or muscle aches
Tobacco	There is no recognized nicotine intoxication state	**Four or more within 24 hours of stopping:** • Dysphoric/depressed food • Insomnia • Irritability/frustration/anger • Anxiety • Difficulty concentrating • Restlessness • ↑ appetite/weight gain
Cannabinoids	**Clinically significant dysfunctional behavior or perceptual abnormality:** • Euphoria & disinhibition • Anxiety or agitation • Temporal slowing (i.e. feels like time passes slowly) • Impaired Judgment • Social withdrawal **Two or more of the following:** • Conjunctival injection • Increased appetite (“munchies”) • Dry mouth • Tachycardia	**After daily use for a few months, has three or more within the first week after stopping:** • Anger/irritability • Anxiety • Insomnia • Decreased appetite • Restlessness • Depressed mood • One: tremor, sweating, fever, chills, headache, abdominal pain

Hallucinogens	**Clinically significant dysfunctional behavior or perceptual abnormality:** • Anxiety • Ideas of reference • Fear of losing one's mind • Paranoid • Impaired judgment • Perceptual changes despite wakefulness and alertness **Two or more of the following:** • Pupils dilated • Tachycardia • Sweating/chills • Palpitations • Blurred vision • Tremors • Incoordination	There is no recognized hallucinogen withdrawal state

Inhalants & Volatile Solvents	**Clinically significant dysfunctional behavior:** • Apathy & lethargy • Argumentativeness/abusiveness/ aggression • Impaired judgment, attention, and memory **Two or more of the following:** • Dizziness • Nystagmus • Incoordination • Slurred speech • Unsteady gait • Lethargy • Depressed reflexes • Psychomotor retardation • Tremor • Generalized muscle weakness • Diplopia • Stupor or coma • Euphoria Severe: Hypotension, hypothermia, depressed gag reflex	There is no recognized solvent/inhalant withdrawal state

Opiates	**Clinically significant dysfunctional behavior:** • Initial euphoria followed by apathy & sedation • Psychomotor retardation or agitation • Impaired judgment **Pupillary Constriction & one of the following:** • Drowsiness or coma • Slurred speech • Impairment in attention or memory Severe: Respiratory depression, hypoxia, hypotension, hypothermia. In severe overdose, anoxia leads to dilated pupils.	Occurs after cessation in heavy opiate use or administration of opioid antagonist **Three or more of the following:** • Dysphoric mood • Nausea/vomiting • Muscle aches • Lacrimation or rhinorrhea ("the sniffles") • Pupillary dilation • Piloerection ("cold turkey") • Sweating • Diarrhea • Yawning • Fever • Insomnia May present with tachycardia and HTN.
Phencyclidine (PCP)	**Clinically significant dysfunctional behavior:** • Belligerence/assaultive • Impulsivity/unpredictability • Psychomotor agitation • Impaired judgment **Two or More of the Following:** • Vertical/horizontal nystagmus • HTN/tachycardia • Numbness or diminished responsiveness to pain • Ataxia • Dysarthria • Muscle rigidity • Hyperacusis • Seizures or coma	There is no recognized PCP withdrawal state.

Sedatives, Hypnotics and Anxiolytics (BZDs, Barbuturates)	**Clinically significant dysfunctional behavior:** • Abusiveness/aggression • Mood lability • Impaired judgment **One or more of the following:** • Slurred speech • Incoordination • Unsteady gait • Nystagmus • Impairment in attention or memory • ↓ level of consciousness (stupor/coma) Servere: hypotension, hypothermia, decreased gag reflex	**Two or more of the following:** • Autonomic hyperactivity (sweating, ↑ HR, HTN) • Tremor of tongue, eyelids, or outstretched hands (asterixis) • Insomnia • Nausea/vomiting • Transient visual, tactile, or auditory hallucinations/ illusions • Psychomotor agitation • Anxiety • Grand mal seizures Can Be lethal.

Substance/Medication-Induced Mental Disorders

To review, Substance-Induced Disorders include intoxication, withdrawal, and the development of specific mental disorders due to the presence of the substance or medication. The Substance-Induced Mental Disorders are potentially severe, usually temporary (but can persist) CNS syndromes that *develop due to the influence of substances, medications, or toxins*. As opposed to the Substance Use Disorders, which are attributed to 10 classes of drugs/medications, the Substance/Medication-Induced Disorders can be due to many different agents, including medicines and toxins. Example: psychosis due to the use of corticosteroids to treat Crohn's Disease. When due to drug use, Substance-induced mental disorders usually develop within the context of intoxication or withdrawal. The condition is usually temporary and likely to disappear within one month after cessation of acute drug intoxication/withdrawal or within one month after stopping the offending medication.

Basic criteria

A. The disorder represents a clinically significant symptomatic presentation of a relevant mental disorder (depression, psychosis)
B. There is evidence from history, physical exam, or lab findings of both:
    1. Disorder developed within 1 month of substance intoxication, withdrawal, or taking a medication; and
    2. The involved substance/medication is capable of producing the mental disorder
C. The disorder is not better explained by an independent mental disorder. Evidence of an independent mental disorder could include:
    1. Mental disorder preceded the onset of intoxication/withdrawal or exposure to the medication; or
    2. The full mental disorder persisted for at least 1 month after the cessation of the acute intoxication/withdrawal from the substance or medication. This does not apply to hallucinogens or substance-induced neurocognitive disorders (like Wernicke's Encephalopathy) that persist beyond cessation of acute intoxication/withdrawal
D. Disorder is not exclusively part of delirium
E. Disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Sedating medications are more likely to produce prominent and clinically significant depressive disorders during intoxication, followed by anxiety symptoms in withdrawal. Intoxication with stimulants tends to be associated with psychotic disorders and anxiety disorders, with substance-induced depressive disorders in withdrawal. If delirium is present, other psychiatric syndromes should not be diagnosed (like substance-induced psychosis).

Alcohol-Related Disorders

Epidemiology

- Lifetime EtOH Use Disorder is 10% for women and 20% for men
- Common causes of death include suicide, cancer, heart disease, and hepatic disease
- Drunken drivers are involved in 55% of all auto fatalities and 75% of fatalities in late-evening accidents
- EtOH use is associated with 50% of all homicides and 75% of all suicides.
- Reduces life expectancy by 10 years
- Alcohol-related disorders occur across all socioeconomic classes
- Whites have highest rate of EtOH use
- Men>Women 2:1
- Associated with higher level of education (contrast with illicit drug use)
- 60-80% of EtOH Use Disorder in patients will be missed by their PMD

Comorbidity

- Antisocial Personality Disorder
- Mood Disorders
- Anxiety Disorders
- Suicide

Etiology

- Childhood History: ADHD, Conduct Disorder, and other personality disorders predispose to EtOH-related disorders
- Sociocultural: dormitories/military bases lead to excessive drinking. Some cultures (Asians, conservative religions) are more restrained
- Behavioral/Learning: parental drinking habits may predispose. Positive reinforcement (euphoria) associated with EtOH encourages use
- Genetics: close family members have fourfold increased risk. Identical twins higher risk than fraternal twins. Adopted-away children of alcoholic parents still have fourfold higher risk

Effects of Alcohol

- Absorption: 10% in stomach, 90% in small intestine
- Metabolism: 90% oxidized in liver. Body metabolizes ~1 drink an hour (1 drink = 12 oz. beer = 5 oz. wine = 1.5 oz. 80-proof liquor)
- Neurochemistry: enhances GABA, ACh, 5-HT; inhibits Glutamate
- Gender: women typically are more affected by EtOH than men. The average woman typically has a smaller body size, less blood volume, and more body fat. As body fat has less water, there is less water for EtOH to dilute in; therefore, a higher blood alcohol content (BAC) is achieved. Women also have decreased esophageal and gastric oxidation of EtOH and less EtOH dehydrogenase. Thus, they metabolize EtOH more slowly
- Behavior: a BAC 0.4-0.5 will lead to severe neurological depression, resulting in coma. Higher BACs lead to respiratory depression and death
- Sleep: decreases REM/Stage 4 sleep and leads to sleep fragmentation
- Physical: liver, GI, heart, lipids, cancer, possible death if combined with sedatives

Alcohol Equivalents

- One drink = a 12 oz. beer, 4 oz. wine, or 1¼ oz. of 80-proof liquor
- A standard beer is 4-9% EtOH, which is 8-18 proof (% x 2 = proof). Liquor typically has 40% EtOH (i.e. 80 proof)
- 1 drink is 0.02-0.025% BAC; the legal limit is 0.08% BAC. 1 drink is metabolized each hour; thus BAC drops by 0.02% each hour
- At 0.05% BAC there is exhilaration and decreased inhibition/judgment; 0.10% has slurred speech and staggering gait; 0.3% has confusion and decreased reflexes; 0.4% has stupor/LOC; 0.5% has coma; 0.6% leads to respiratory paralysis and death

Diagnostic Markers

- GGT > 35 is a sensitive marker for heavy drinking, and often is the first abnormal marker. *At least 70% of individuals with an elevated GGT are persistent heavy drinkers* (8 or more drinks daily)
- Elevated MCV is the result of alcohol's toxic effect on erythropoiesis. However, it is a poor method of monitoring due to the long half-life of red blood cells
- Elevated LFTs are the result of toxic injury to the liver as a consequence of heavy drinking

Alcohol Use Disorder

The diagnosis of Alcohol Use Disorder is made by applying the criteria presented above. The symptoms must be present for 12 months, with a minimum of 2 criteria present to diagnose Mild Alcohol Use Disorder. Specifiers for remission exist, with *early remission* being at least 3 months with no symptoms but not yet 12 months in sobriety. *Sustained remission* is when no criteria have been met in 12 months. *Cravings may be present during this time as long as they are the only symptom present***.** Thus, a person may be considered in remission with the presence of cravings still there (a substance use disorder criteria). Another specifier is if the patient is *in a controlled environment* (sober living, jail, locked unit).

Alcohol Intoxication

After ingestion of alcohol, there is clinically significant *dysfunctional behavior*

- Disinhibition
- Agitation/Aggression
- Mood Lability
- Impaired Judgment

One or more of the following

- Slurred Speech
- Incoordination
- Unsteady Gait
- Nystagmus
- Memory/Attention Impairment
- Diminished Consciousness (stupor/coma)

Severe: Hypotension, Hypothermia, Depressed Gag Reflex

Alcohol Withdrawal

After cessation of alcohol use that has been heavy and prolonged, there are two or more of the following

- Autonomic Hyperactivity (Sweating, Tachycardia, HTN)
- Tremor of Tongue, Eyelids, or Outstretched Hands (asterixis)
- Insomnia
- Nausea/Vomiting
- Transient Visual, Tactile, or Auditory Hallucinations, or Illusions
- Psychomotor Agitation
- Anxiety
- Generalized tonic-clonic seizures

Spectrum of withdrawal

- 6-8 hours = tremor/autonomic symptoms
- 8-12 hours = hallucinations
- 12-24 hours = seizures
- 72 hours – 1 week = Delirium Tremens (DTs)

Complications

Withdrawal Seizures: stereotyped, tonic-clonic seizures**.**

- Treatment: BZDs—including Chlordiazepoxide (Librium) PO taper or another long-acting BZD (e.g. Diazepam) or IV Lorazepam. *In patients with liver damage, a BZD without active metabolites (lorazepam) is preferred.*

Delirium Tremens: delirium occurring within 1 week of abstinence

- Symptoms: rapid-onset, clouding consciousness, insomnia, disturbance of cognition *plus* autonomic hyperactivity, hallucinations (usually tactile), and psychomotor activity fluctuation. *Can be fatal*
- Treatment: prevent with BZDs (Chlordiazepoxide PO q4hrs or Lorazepam IV). Avoid antipsychotics (lowered seizure threshold) if possible

Lethal Withdrawal: Both EtOH and BZD/Barbiturate withdrawal can lead to seizures and death. Getting a good history is the most important first step in preventing these complications. Find out the average daily quantity consumed and the time of their last drink, as this will help determine the risk of seizures/complicated withdrawal

- Treatment: use the seizure prevention measures above as well as obtain optimal fluid and electrolyte balance. Patients may require medical inpatient/ICU admission if severe

Wernicke's Encephalopathy: secondary to thiamine deficiency (a cofactor for enzymes involved in axonal conduction). Lesions are seen in the mammillary bodies.

- Symptoms: ataxia, dizziness, confusion, nystagmus/gaze palsy
- Treatment: thiamine (PO/IV), always given before administering glucose

Korsakoff's Syndrome: chronic amnestic syndrome following untreated Wernicke's Encephalopathy

- Symptoms: anterograde memory loss (difficulty forming new memories) with confabulation (made-up memories to fill the gaps). Few patients recover
- Elevated Biomarkers: macrocytosis (2/2 folate deficiency), ↑ GGT, ↑ AST and ALT (AST:ALT ratio of 2:1), ↑ carbohydrate deficient transferrin (CDT)

Fetal Alcohol Syndrome (FAS): inhibition of intrauterine growth

- Symptoms: microcephaly, craniofacial malformations (*thin upper lip with no philtrum*), limb and heart defects. Short adult stature and adult maladaptive behaviors are also associated with FAS

Prognosis

Good Prognostic Indicators

- Absence of pre-existing Antisocial Personality Disorder
- Life stability: having a job, healthy family relationships, and no legal problems
- Full course rehabilitation program (2-4 weeks minimum)

Treatment

The long-term goals of treatment are the same for all substance use disorders: abstinence, relapse prevention, and rehabilitation

- Inpatient Detoxification: prevent seizures (use BZDs) and lessen withdrawal symptoms (ß-blockers and clonidine treat autonomic hyperactivity; antipsychotics treat delirium agitation, and aggression)
- Post-Detoxification Outpatient Treatment: intensive outpatient care with frequent visits or day-hospital treatment in early phases. Multiple studies show that good aftercare following inpatient treatment is associated with the lowest rates of relapse

Medication Management

Treatment focuses on decreasing craving for EtOH through modulation of neurotransmitters (DA, Glutamate) and receptors (NMDA, Opioid). Treatment may also decrease reinforcement of EtOH through inhibition of reward pathways.

Naltrexone

- MOA: competitive antagonist at the mu and kappa opioid receptors. Decreases cravings and blocks dopamine reward pathways, thereby decreasing reinforcing effects of use (i.e. use is less enjoyable)
- Formulations: PO or Depo
- Side Effects: nausea (10%), headache (7%), dizziness (4%), insomnia (3%), anxiety (2%), and sleepiness (2%). Serious side effects include hepatotoxicity (rare). *Check LFTs before initiating*

Acamprosate

- MOA: blocks glutamate NMDA receptors and activates GABA-A receptors. EtOH is inhibitory and chronic use leads to upregulation of NMDA receptors. Withdrawal of EtOH leads to glutamate excitation (i.e. seizures, tachycardia, etc). By blocking NMDA receptors, acamprosate decreases the sign/symptoms of withdrawal as well as decreasing glutamate-driven cravings
- Side Effects: mainly GI in nature

Disulfiram

- MOA: inhibits acetaldehyde dehydrogenase leading to increased acetaldehyde after consumption of EtOH. The increased acetaldehyde leads to symptoms of palpitations, flushing, nausea, vomiting, and headache. It is an aversive treatment
- Side Effects: see above. Rare symptoms of cardiotoxicity, MI, pulmonary dysfunction, and hepatotoxicity. Contraindicated in patients on metronidazole (which has disulfiram like-effects) or patients with cardiovascular, pulmonary, or hepatic disease or with chronic renal failure. *Check LFTs before initiating*

Anticonvulsants

- MOA: inhibition of mesocorticolimbic DA release leading to decreased craving. Topiramate has best studies to date
- Side Effects of topiramate: dizziness, somnolence, cognitive slowing, and weight loss. Rare side effects include metabolic acidosis and renal stones. Be careful with drug-drug interactions

SSRIs: may reduce comorbid psychiatric symptoms (anxiety/depression) that influence drinking behavior

Psychosocial Treatments

- Motivational Interviewing: useful (see above section in Motivation Interviewing)
- CBT: aimed at improving self-control through goal setting, rewards, and learning alternate coping strategies. Uses problem solving instead of using avoidance as a coping strategy
- Behavioral Therapies: combination of disulfiram and behavioral adherence program (EtOH-free social environments, community reinforcement, etc)
- Self-Help Groups and 12-Step Treatment: AA is a "spiritual but nonreligious program requiring belief in something beyond oneself" that provides tools to maintain sobriety. Tools include the 12 steps, group identification, and mutual help. Multiple studies show good support for AA as viable treatment
- Marital and Family Therapy: Elicits support and helps significant others understand illness and treatment
- Ancillary groups: Al-Anon (friends and family of alcoholics), Alateen (teens of alcoholics), and Adult Children of Alcoholics all help family members by teaching to avoid enabling behaviors and improve self-care

The best treatment has been shown to be a combination of therapy/support groups and medication management.

Caffeine-Related Disorders

Epidemiology

- Estimated 85% of adults in USA consume caffeine regularly
- Is the most widely used behaviorally active drug in the world
- Average consumption is 200 mg/day, with 20-30% consuming >500 mg/day (1 cup = 100-150 mg)
- About 2/3^{rds} of those who consume large amounts of caffeine daily also use sedative and hypnotic drugs for sleep and anxiety

Neuropharmacology

- Caffeine is a methylxanthine that has time to peak concentration in 30-60 minutes
- Readily crosses the blood-brain barrier
- Half-life is 4-6 hours
- Antagonizes adenosine receptors leading to an increase in cAMP
- At higher concentrations, caffeine may activate dopaminergic and noradrenergic neurons

Differential Diagnosis of Caffeine Intoxication

Generalized Anxiety Disorder, Pain Disorder with/without Agoraphobia, Bipolar Type II, ADHD, Cocaine/Amphetamine abuse, Hyperthyroidism, Pheochromocytoma, and Sleep Disorders.
There is no Caffeine Use Disorder, only intoxication and withdrawal in addition to Caffeine-Induced Disorders.

Caffeine Intoxication

Recent consumption of caffeine (usually >250 mg) and five or more of the following:

- Restlessness/Anxiety
- Excitement
- Insomnia
- Flushed face
- Diuresis
- GI disturbance
- Muscle twitching
- Rambling flow of thought and speech
- Tachycardia or cardiac arrhythmias (PVCs)
- Periods of inexhaustibility
- Psychomotor agitation

Consumption of >1 gram leads to rambling speech, confusion, cardiac arrhythmias, agitation, tinnitus, and mild visual hallucinations (light flashes).

Consumption of >10 grams leads to generalized tonic-clonic seizures, respiratory failure, and death.
Caffeine Withdrawal

Withdrawal

After prolonged daily use of caffeine, abrupt cessation/reduction in use leads to three or more of the following in 24 hours:

- Headache
- Marked fatigue or drowsiness
- Dysphoric mood, depressed mood, or irritability
- Flu-like symptoms (nausea/vomiting, muscle pain)

Withdrawal occurs within 12-24 hours after last dose, symptoms peak between 24-48 hours, and resolve within 1 week.

Complications

- Possible cardiac arrhythmias in those with pre-existing cardiac disease
- Increased risk of gastric ulcers due to increased gastric acid secretion

Treatment

- Medication Management: analgesics (NSAIDs) for headaches and muscle aches. Rarely BZDs are used for withdrawal anxiety
- Tapering Caffeine Usage: patients keep daily food diary noting all forms of caffeine as well as quantity. The patient and physician can then work on a tapering schedule for consumption, with a 10% decrease every few days. Beverage substitution is recommended. The diary is maintained to track progress. “Cold Turkey” is NOT recommended due to possible withdrawal symptoms, as 50% of users will have headache and other symptoms

Cannabis-Related Disorders

Epidemiology

- Worldwide, cannabis is the most commonly used illicit drug
- According to the National Household Survey of Drug Abuse, the lifetime prevalence of cannabis use increases with age group up until age 34, the decreases gradually. Between the ages of 18-21, 25% had used in the past year and 14% in the past month
- Males > Females (2:1) in those 26 years and older
- Whites > Blacks >> Hispanics (under 35 years old)

Neuropharmacology

- Indian hemp plant *Cannabis Sativa* is an herb known in Central Asia and China for at least 4,000 years
- Hemp is cut, dried, chopped, and rolled into cigarettes called joints
- Common names are marijuana, grass, pot, weed, tea, sticky-icky, and Mary Jane
- Contains the psychoactive substance Δ9-tetrahyrdocannibinol (Δ9-THC), which is most potent in the flowering tops of the plant or from the dried resin exudates from the leaves (hash, hashish)
- Active metabolite is 11-hydroxy-Δ9-THC, which binds to a cannabinoid G_i protein-linked receptor (G_i = inhibitor G protein) that inhibits adenylyl cyclase and affects GABA neurons
- Cannabinoid receptors are most highly concentrated in the basal ganglia, hippocampus, cerebellum, and cortex (lower concentrations than others). Cannabinoid receptors are not found in the brainstem, thus marijuana has minimal effects on respiratory and cardiac function
- When smoked, euphoria occurs in minutes, peaks at 30 minutes, and lasts 2-4 hours

Clinical Features

- Most common effects are dilation of conjunctival blood vessels ("red eye"), mild tachycardia, dry mouth, and increased appetite ("munchies")
- The most serious adverse effect is chronic respiratory disease in heavy chronic users due to inhalation of carcinogenic hydrocarbons (same compounds in tobacco)
- Can precipitate psychosis and is associated with an earlier age of first onset of schizophrenia in males (6.9 years earlier than in non-cannabis users)
- Pregnancy: negative effects on fetal growth, behavioral/cognitive/academic difficulties, impulsivity, and inattention noted as well. *Childhood learning deficits as a result of in-utero exposure*
- High comorbidity of other substance use, including *> 50% meeting criteria for Alcohol Use Disorder*

Cannabis Use Disorder

As with other Substance Use Disorders, cannabis use must be associated with at least 2 symptoms of substance use over a 12-month period of time. Functionally, the disorder is associated with *amotivational syndrome,* manifested by chronic low motivation and reduction in goal-directed activity.

Cannabis Intoxication

During, or shortly after use, there is clinically significant dysfunctional behavior or psychological changes:

- Impaired motor coordination
- Euphoria

- Anxiety
- Sensation of slowed time
- Impaired judgment
- Social withdrawal

Two or more within 2 hours:

- Conjunctival Injection
- Increased Appetite ("Munchies")
- Dry Mouth
- Tachycardia

Cannabis Withdrawal

Cessation of use that has been heavy and prolonged (daily or near daily over months) with *three* or more *within 1 week of stopping use:*

- Irritability, anger or aggression
- Nervousness or anxiety
- Insomnia
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least one of the following causing significant discomfort: abdominal pain, tremors, sweating, fever, chills, or headache

New to the DSM5 is the understanding that daily or near daily use of THC over months can cause withdrawal. This is a factor contributing to difficulty in quitting use. Between 50-95% of heavy users have reported withdrawal symptoms. Onset of withdrawal is in the first 24-72 hours and may last up to 2 weeks.

Treatment

The long-term goals of treatment are the same for all substance use disorders: abstinence, relapse prevention, and rehabilitation.

- Treatment Setting: outpatient setting, either individually or in groups
- Always monitor for an underlying depression (leading to THC use) that may require treatment with antidepressants.

Psychosocial Treatments

- Therapies with the best results combine motivational therapy with coping skills development to promote abstinence and prevent relapse.

- Given the lack of useful pharmacotherapy and high relapse rates (67% by 6 months in one study), additional group therapy and other behavioral interventions are recommended to decrease the rate of relapse.

Hallucinogen-Related Disorders

DSM5 separates hallucinogen disorders into "PCP" and "Other" which include LSD, mescaline, and others.
Phencyclidine (PCP).

Epidemiology

- Prevalence of PCP use is unknown. Only about 2.5% of the population has reported using PCP. Males make up 75% of users
- Phencyclidine (PCP), also known as "angel dust," is a dissociative anesthetic that is no longer used for anesthesia due to disorientation, agitation, and hallucinations on awakening
- Related compound, Ketamine ("special K"), is still used in the US as an anesthetic
- Similar effects as hallucinogens, including LSD
- Easy to synthesize and inexpensive to buy on the streets. Highest use is in Washington, D.C. where PCP accounts for 18% of all substance-related deaths

Neuropharmacology

- Sold as crystalline powder, paste, liquid, or drug soaked paper, and is often an additive in cannabis cigarettes. Can smoke, snort, or use IV. Effects of smoked PCP occur in 5 minutes and plateau in 30 minutes. Half-life is 20 hours
- Primary effect is NMDA antagonism at glutamate receptors. Also affects DA neurons in ventral tegmental area to the cerebral cortex and limbic area
- Detected in the urine up to 8 days after ingestion
- No withdrawal syndrome recognized

PCP Use Disorder

A problematic pattern of PCP use as manifested by 2 criteria for substance use over 12 months. Withdrawal symptoms are not recognized for PCP, so this criterion would not apply toward the diagnosis. Consequences of use include physical evidence of injuries, such as accidents, fights, and falls. Chronic use is associated with memory, speech and cognitive deficits.

PCP Intoxication

Recent use of PCP or similar substance leading to clinically significant problematic behavioral changes developed during or shortly after use:

- Belligerence/ assaultiveness
- Impulsivity/ unpredictability
- Psychomotor agitation
- Impaired judgment

Two or more within one hour (less if snorted, smoked, or used IV):

- Vertical or horizontal nystagmus
- HTN or tachycardia
- Numbness or diminished responsiveness to pain
- Ataxia
- Dysarthria
- Muscle rigidity
- Hyperacusis
- Seizures or coma

Treatment

- For acute PCP intoxication, treatment is symptomatic. DO NOT attempt to talk the patient down. This may lead to significant personal injury as the PCP-intoxicated patient may be agitated or confused, and when combined with increased strength and poor response to physical pain, makes for a very dangerous situation
- Treat acute psychosis/agitation with antipsychotics and BZDs
- Treat medical abnormalities as necessary (including common physical injuries the patient has sustained while intoxicated), monitor BP, temperature, and muscle activity. Respiratory depression may occur, monitor closely
- Ammonium chloride in the early stage, and cranberry juice or ascorbic acid later on are helpful in acidifying the patient's urine, leading to improved elimination of the drug
- Patient may need inpatient psychiatric hospitalization after medical clearance due to persisting psychosis

Hallucinogens

Epidemiology

- Of all substance use disorders, is one of the rarest
- Most common in young white males (whites:blacks = 2:1)
- Highest use in 26-34 y/o (15.5% of this age group have used at least once)
- Western US > Eastern US
- Less morbidity and mortality than other substances (1% substance-related ER visits vs. 40% for cocaine)

Neuropharmacology

- Schedule 1 Drugs: many are naturally occurring in mushrooms (psilocybin), cactus (mescaline), and other plants. Lysergic Acid Diethylamide (LSD) was first synthesized in 1938
- Act on the serotonin system, possibly as a partial agonist on post-synaptic receptors
- Onset of action within an hour, peaks in 2-4 hours and can last up to 12 hours
- Rapid tolerance that reverses quickly. No physical withdrawal

Clinical Features

- Sympathomimetic symptoms: tachycardia, tremors, HTN, hyperthermia, blurred vision, and mydriasis. Death can occur due to HTN, hyperthermia, and physical injury due to impaired judgment
- Synesthesia: colors heard or sounds seen. Can have visual and auditory hallucinations, intense emotional lability, introspective reflection, and heightened suggestibility

Hallucinogen Use Disorder

A problematic pattern of hallucinogen use as manifested by 2 criteria for substance use within 12 months. Withdrawal symptoms are not recognized for PCP, so this criterion would not apply toward the diagnosis.

Hallucinogen Intoxication

During, or shortly after hallucinogen use there is clinically significant behavior or psychological changes:

- Anxiety and fearfulness
- Paranoid Ideation
- Ideas of reference
- Fear of losing one's mind
- Mood lability
- Depersonalization/Derealization

Perceptual changes in a state of full wakefulness and alertness that develop during or shortly after use (may include auditory, visual, or tactile hallucinations, illusions, or synesthesia)

Two or more of the following:

- Pupils dilated
- Tachycardia
- Sweating/Chills
- Palpitations
- Blurred vision
- Tremor
- Incoordination

Hallucinogen-Related Disorders

- Hallucinogen Persisting Perception Disorder: following cessation of the use of a hallucinogen, the person re-experiences one or more of the perceptual symptoms that were experiences while intoxicated with the hallucinogen. May include geometric hallucinations, false perception of movement in the periphery, trails of images, halos around objects, and positive afterimages. These "flashbacks" are experienced by up to 4% of users. Flashbacks are spontaneous, transitory recurrences of the substance-induced experience lasting seconds to minutes, likely due to hallucinogen storage in fat with metabolization at a later time. Can be triggered by stress, EtOH/drugs, *or sensory deprivation (monotonous driving)*
- Hallucinogen-Induced Psychotic Disorder: a "bad trip" with acute panic and psychosis

Treatment

Treatment focuses on abstaining from hallucinogen use, treatment of symptoms, reduce hospital/ER visits, development, preservation of social relationships, and treating co-morbid illnesses (Alcoholism, depression, etc)

- Provide supportive care for the remainder of the intoxication. Use BZDs for acute anxiety if necessary
- Treatment of Hallucinogen Persisting Perception Disorder (flashbacks) includes BZDs or anticonvulsant therapy. Unfortunately, there is no completely successful treatment
- Avoid EtOH, caffeine, or other drugs that may precipitate flashbacks
- Treat psychosis with short-term antipsychotics, with the mainstay of treatment being prevention

Inhalant-Related Disorders

Epidemiology

- Easily available, legal, and inexpensive. Highly used by adolescents and the poor
- About 10% of 13-year-old Americans have used at least once
- Highest use in adolescents (one study showed that at least 18% of high school seniors had used at least once)
- 20% of users develop Inhalant Use Disorder
- Whites more common than blacks or Hispanics
- Males account for 80% of use
- Only 1% of all substance-related deaths and less than 0.5% of substance-related ER visits
- Associated with an increased likelihood of Conduct Disorder and Antisocial Personality Disorder

Neuropharmacology

- Includes solvents, glues, adhesives, aerosol propellants, paint thinners, and fuels. Specific examples include: gasoline, varnish remover, lighter fluid, airplane glue/super glue, rubber cement, cleaning fluid, spray paint, and shoe conditioners
- Active chemicals include toluenes, propanes, ethylenes, and halogenated hydrocarbons.
- Used with a tube, can, plastic bag, or an inhalant soaked rag through which the user can inhale the fumes through the nose or mouth (“huffing”)
- Tolerance can develop but there is no DSM5 recognized withdrawal disorder
- Rapidly absorbed through the lungs and delivered to the brain. Effects appear within 5 minutes and last 30 minutes up to hours based on the substance/dose
- Blood concentration increased when combined with EtOH
- One-fifth is excreted unchanged by the lungs, the rest is metabolized in the liver. Detectable in the blood for 4-10 hours

- Additive effects with other CNS depressants (EtOH, BZDs). MOA may be through enhancing the GABA system

Inhalant Use Disorder

A problematic pattern of use of a hydrocarbon-based inhalant substance meeting at least 2 criteria for substance use within 12 months. No withdrawal is recognized, and this is removed from the substance use criteria. Consequences include toxicity, arrhythmia, and fatality.

Inhalant Intoxication

Recent short-term, high-dose exposure to an inhalant causing clinically significant problematic behavioral or psychological changes during or shortly after use:

- Apathy & lethargy
- Argumentativeness/Abusiveness/Aggression
- Mood lability
- Impaired judgment, attention, and memory

Two or more:

- Dizziness
- Nystagmus
- Incoordination
- Slurred speech
- Unsteady gait
- Lethargy
- Depressed reflexes
- Psychomotor retardation
- Tremor
- Generalized muscle weakness
- Diplopia
- Stupor or coma
- Euphoria

Severe: Hypotension, Hypothermia, Depressed Gag Reflex

Inhalant-Related Disorders

- Inhalant Intoxication Induced Delirium: behavioral disturbance due to hypoxia or interactions with other substances. Treatment: short-term antipsychotics for agitation. Avoid BZDs, which can worsen respiratory depression
- Inhalant-Induced Persisting Dementia: due to prolonged hypoxia, inhalant neurotoxicity, or heavy metals (i.e. lead) uses in inhalants. Dementia is permanent

- Others: Inhalant-Induced Mood Disorder, Psychotic Disorder, and Anxiety Disorder

Adverse Effects of Inhalants

- Short-term symptoms of pulmonary/cardiovascular (chest pain, bronchospasm), GI (N/V, hematemesis), and neurological (peripheral neuritis, headache, and lead encephalopathy)
- Irreversible hepatic or renal damage (including RTA)
- Permanent muscle damage associated with rhabdomyolysis can also cause renal damage as well as long-term motor impairment
- Organic solvents are combined with copper, zinc, and heavy metals, which can lead to brain atrophy, temporal lobe epilepsy, lowered IQ, and EEG changes if ingested
- Congenital and developmental abnormalities that resemble Fetal Alcohol Syndrome if inhalants are used during pregnancy
- If a patient is abruptly startled during intoxication, cardiac arrest and death can occur
- Death is due to respiratory depression, cardiac arrhythmias, asphyxiation, aspiration of vomitus, or accidental injury

Treatment

- Medically treat coma, bronchospasm, laryngospasm, cardiac arrhythmias, trauma, or burns. Provide reassurance, quiet support, and attention to vital signs/LOC
- May require psychiatric hospitalization if inhalant-induced psychosis is severe. Treat with short-term antipsychotics. Sedatives may aggravate the psychosis. Monitor for anxiety, depression, and SI
- Street outreach and extensive social service support for the severely deteriorated/homeless. Family support is crucial

Opioid-Related Disorders

Epidemiology

- Opioids have been used for 3,500 years, and in 1806 morphine was first isolated. Heroin is the most abused opioid in developed countries
- Derived from the opium poppy, *Papavar somniferum*
- Synthetic opioids include meperidine (Demerol), methadone, and propoxyphene (Darvocet)
- Lifetime prevalence of heroin use is 1%, male-to-female use is 3:1, and a heroin habit can cost hundreds of dollars per day, leading to criminal activities and prostitution. This accounts for much of the spread of HIV (prostitution and IV heroin use)
- 90% of patients with opioid dependence have an additional psychiatric disorder, most commonly MDD, ETOH addiction, antisocial PD, and anxiety disorders
- 15% of opioid dependent patients attempt suicide at least once

Neuropharmacology

- Primary effects are on opioid receptors: μ-opioid receptors mediate/ regulate analgesia, respiratory depression, constipation, and dependence; κ-opioid receptors are associated with analgesia, diuresis and sedation; δ-opioid receptors may be associated with analgesia
- Endogenous opioids in the brain include enkephalins and endorphins, involved in neuronal transmission and pain suppression
- The addictive rewarding properties of the opioids are mediated through the activation of the ventral tegmental area with DA neurons projecting to the cortex and limbic system
- Heroin is the most commonly abused opioid and is more potent and lipid soluble than morphine. Crosses the blood-brain barrier faster and has more rapid onset of action than morphine
- Opioids can be taken orally, snorted intra-nasally, and injected IV
- Detected in the urine for 12-36 hours. Fentanyl is not detected in the urine

Tolerance and Dependence

- Long-term use of opioids results in changes in the number and sensitivity of opioid receptors, which lead to some of the effects of tolerance/ withdrawal
- Long-term use is associated with increased sensitivity of the DA, cholinergic, and serotonergic systems
- The primary mediator of withdrawal is opioid effect on noradrenergic neurons. Short-term use decreases noradrenergic neurons in the locus ceruleus (LC), while long-term use leads to gene alteration and increased LC excitability by NE. Tolerance for opioids results from this increased LC excitability. Withdrawal of opioids leads to rebound hyperactivity/ increased NE

Etiology

- Psychosocial factors: children of divorced parents or single parents are at higher risk for dependence
- Biological/ Genetic factors: monozygotic twins > dizygotic twins

Opioid Use Disorder

A problematic pattern of opioid use leading to meeting at least 2 of the substance use criteria within 12 months. Recall that the diagnosis cannot be met if the only criteria present are tolerance and withdrawal within the context of being medically prescribed. Consequences of use include multiple medical comorbidities, increased risk for suicide and association with criminal activity.

Opioid Intoxication

During or shortly after use there is clinically significant problematic behavior or psychological changes:

- Initial euphoria followed by apathy and sedation
- Disinhibition
- Psychomotor retardation
- Impaired judgment

Pupillary constriction (or dilation after severe overdose) *and* one of the following:

- Drowsiness or coma
- Slurred speech
- Impairment in attention or memory

Severe: respiratory depression, hypoxia, hypotension, and hypothermia*. In severe OD anoxia leads to DILATED pupils.*

Opioid Withdrawal

Presence of either: cessation/reduction in heavy and prolonged use *or* administration of an opioid antagonist after a period of opiate use

Three or more:

- Dysphoric mood
- Nausea/ vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

Withdrawal of morphine and heroin occurs within 6-8 hours, and subsides within 7-10 days. The key point is that while opiate overdose or *intoxication* can be fatal, withdrawal is **rarely** fatal (as opposed to EtOH and BZD withdrawal, which can be fatal).

Adverse Effects

- Most common and most serious adverse effect is potential transmission of hepatitis, bacterial endocarditis, tuberculosis, and HIV through contaminated needles
- Combining meperidine (Demerol) and MAOIs can produce coma, seizures, and death
- Chronic abscesses from subcutaneous injections ("skin popping") and visible needle tracks can be noted on physical examination
- Death from opioid overdose occurs through respiratory depression in the brainstem. Consider opioid overdose with clinical triad of respiratory depression, pinpoint pupils, and coma
- Pregnancy: malnutrition/ vitamin deficiency, HIV/ sexually transmitted diseases, HTN, pre-eclampsia, miscarriage, premature rupture of membranes, low birth weight, prematurity, stillbirth, neonatal dependence on opioids (50%), and SIDS. *Buprenorphine and methadone are preferred treatment in pregnant women with opioid dependenc***e**

Treatment and Rehabilitation

Treatment of Overdose: maintain and adequate airway. Mechanically ventilate until naloxone, a specific opioid antagonist, can be administered. Monitor vital signs and stabilize before considering treatment of opioid dependence/ rehabilitation.

Treatment Settings

- Inpatient hospitalization: after overdose, inpatient medical hospitalization is required for stabilization. Reversal of opioid effects through the short-acting opioid antagonist naloxone is needed, and treatment of withdrawal can be done in a medical setting or an inpatient psychiatric hospital
- Outpatient clinics: may use group practices and medication management for the treatment of opioid dependence
- Opioid treatment programs: include methadone maintenance clinics that operate under special federal and state regulations. These programs can be highly effective. A recovering heroin addict must be registered with the DEA in a treatment program to receive opioids
- Self-help programs: Narcotics Anonymous is effective in treating dependence, especially when combined with medication management and other treatment settings
- Therapeutic communities: (like a sober living home) participate in a rigid program with other substance users

Medication Management

- Management of withdrawal: symptomatic, including use of clonidine (central α_2-adrenergic agonist decreases NE by stimulating autoreceptors), anti-nausea medications, NSAIDS for analgesia, muscle-relaxants, and short-term BZDs (for anxiety and insomnia). Methadone and buprenorphine and highly effective in treating symptoms of withdrawal
- Methadone and LAAM: both are schedule 2 full μ-agonists. LAAM is structurally related to methadone but has longer duration of action (taken off the US market due to cardiac arrhythmias). Methadone is currently only available through specially licensed opioid treatment programs that are heavily regulated. Goals of treatment are: suppress withdrawal, decrease craving, blocks illicit opioids, stopping illicit opioid use, and enlist the patient in program designed to promote rehabilitation. Side effects include constipation, sweating, and sexual difficulties. The benefits include reduction in the spread of HIV through IV drug use, gainful employment/ less criminal activity, and produces minimal euphoria or depression. The disadvantages are continued dependence on a controlled narcotic
- Buprenorphine: partial μ-agonist/ κ-antagonist that has higher binding affinity for μ-receptors than illicit opioids/ full agonists (knocks illicit opioids off). It is less addictive due to less agonist/ partial agonist effect (pain management without euphoria or respiratory distress) and enters the bloodstream more slowly than other agonists. Good sublingual bioavailability. Treats opioid withdrawal and chronic pain management. However, it can still be abused if injected. As a result, combination with naloxone (opiate antagonist) leads to less abuse potential (naloxone has better parenteral bioavailability. If the drug is injected to abuse, naloxone blocks the receptor)
- Naltrexone: opioid antagonist similar to naloxone with longer duration of action (72 hours). Blocking opioid agonist effects, particularly euphoria, naltrexone discourages/ deconditions substance-seeking behavior. Similar to disulfram, this medication is used to treat dependence, *not withdrawal*. Side effects include dysphoria, anxiety, GI distress, and in higher doses, elevated LFTs

Psychosocial Treatments

All clinical trials for psychosocial interventions have taken place in programs that also provide opioid agonist maintenance (like methadone) or opioid antagonists (like naloxone or naltrexone). Therapy alone may not be a viable option for treatment.

- CBT: helpful in patients with MDD or other co-morbid psychiatric issues. In addition, may reduce high-risk HIV behaviors and decrease criminal behaviors
- Behavioral therapies: uses reinforcers/ rewards (commonly methadone) contingent on abstinence. Can enhance adherence with naltrexone
- Family therapy: enhances treatment adherence
- Self-help groups and 12-step-oriented therapies: Narcotics Anonymous is beneficial by providing peer support, decreasing substance-abusing peers, providing accountability, confronting denial, and intervening early to prevent relapse

Sedative, Hypnotic or Anxiolytic-Related Disorders

Overview

Includes BZDs, barbiturates, methaqualone (Qualudes), and meprobamate. These drugs are anti-epileptics, muscle-relaxants, anesthetics, and are additive to the effects of EtOH. Sedatives are drugs that reduce tension and induce mental tranquility, synonymous with anxiolytics (i.e. they reduce anxiety). Hypnotics are drugs used to induce sleep. However, at varied doses sedatives can produce sleep and hypnotics can produce tranquility

BZDs: rapid onset is associated with the most addiction potential

- Long-Acting: diazepam (rapid onset), clonazepam, flurazepam, chlordiazepoxide
- Short-Acting: lorazepam (rapid onset), oxazepam, temazepam
- Ultra-Short Acting: alprazolam (rapid onset) and triazolam

Barbiturates: before introduction of BZDs, barbiturates were frequently prescribed, but are highly abused and are much more lethal than BZDs due to respiratory depression, especially when combined with EtOH. May be taken orally (common in middle aged/middle class and prescribed by Family MD for insomnia or anxiety) or IV (more severe form of abuse, usually in young adults, with increased rates of HIV, cellulitis, and infection). The IV form has a rapid and profound tolerance/dependence in addition to severe withdrawal

- Long-Acting: phenobarbital (a common anti-epileptic) and barbital
- Intermediate-Acting: amobarbital (Amytal) use in the "Amytal interview" to aid in conversion reactions, and to differentiate the stupor of depression, schizophrenia, and structural brain lesions
- Short-Acting: secobarbital ("reds") and pentobarbital (Nembutal, "yellow jackets"). In the "Pentobarbital Challenge Test," a test dose of pentobarbital is given orally to determine the extent of barbiturate tolerance in order to adequately treat withdrawal

Epidemiology

- The highest prevalence of sedative abuse is in the 26-34 year old age group
- Female to male ratio is 3:1, white to black is 2:1

Neuropharmacology

- All have primary effects on GABA type A receptors, acting to allosterically strengthen the GABA signal. This leads to more influx of negatively charged chloride, inhibiting neurons. The overall effect is calming
- Tolerance is understood through chronic GABA stimulation on GABA-A receptors, leading to less sensitivity/less chloride influx in the presence of the drug. This "downregulation of receptor response" is not due to decreased receptor number or decreased affinity for GABA. It appears to be due to decreased efficiency of coupling with the chloride channel, leading to tolerance
- May be detected in the urine up to 1 week later in longer acting medications

Sedative, Hypnotic, or Anxiolytic Use Disorder

A problematic pattern of sedative, hypnotic, or anxiolytic use, meeting at least 2 criteria for substance use over a 12 month period. Recall that the diagnosis cannot be met if the only criteria present are tolerance and withdrawal within the context of being medically prescribed.

Sedative, Hypnotic, or Anxiolytic Intoxication

Clinically, the syndrome of intoxication is indistinguishable from EtOH intoxication.

During or shortly after use there is clinically significant maladaptive behavior or psychological changes:

- Abusiveness/Aggression
- Mood lability
- Impaired judgment

One or more:

- Slurred speech
- Incoordination
- Unsteady gait
- Nystagmus
- Impairment in attention or memory
- Diminished level of consciousness (Stupor/Coma)

Servere: Hypotension, Hypothermia, Decreased Gag Reflex

Sedative, Hypnotic, or Anxiolytic Withdrawal

BZD withdrawal occurs within the first 3 days of cessation, with seizures developing on the 2nd or 3rd day. Shorter acting substances have onset of withdrawal sooner. For barbiturates, the symptoms of withdrawal usually don't occur until 2-3 days after cessation (or with longer acting drugs, up to 5-6 days later).

After cessation of prolonged use, there are *two* or more:

- Autonomic hyperactivity (Sweating, tachycardia, HTN)
- Tremor of tongue, eyelids, or outstretched hands (asterixis)
- Insomnia
- Nausea/vomiting
- Transient visual, tactile, or auditory hallucinations/ illusions
- Psychomotor agitation
- Anxiety
- Grand mal seizures

Can be *lethal*, just like EtOH withdrawal

Associated Disorders

- Delirium presents with intoxication or withdrawal, and can be indistinguishable from DTs in EtOH withdrawal (more common in barbiturate withdrawal)
- Psychotic Disorders are more common in withdrawal from barbiturates than BZDs, and may be undistinguishable from EtOH-related DTs
- Sedatives and hypnotics can induce mood disorders, anxiety disorders, sleep disorders, and sexual dysfunction

Treatment

Overdose: treatment focuses on gastric lavage, activated charcoal, and monitoring vitals/CNS activity. OD may require mechanical ventilation due to respiratory distress

- BZDs: much safer in OD than barbiturates due to minimal respiratory depression in BZDs. If combined with EtOH, there is significantly increased risk for lethality. Lethal dose is 200:1. Treat with flumazenil (BZD antagonist) in the ER
- Barbiturates: highly lethal in overdose due to respiratory depression. Like BZDs, have additive lethal effects with EtOH or other sedative-hypnotics. Lethal dose is 3:1 to 30:1

Withdrawal

- BZDs: to prevent seizures, the dose should be gradually reduced. Detoxification generally occurs in an inpatient setting, switching to a long-acting BZD for withdrawal and gradually tapering off. Symptoms of withdrawal are treated with clonidine, and there is some data to suggest carbamazepine may be useful in treating symptoms of withdrawal
- Barbiturates: withdrawal can be highly lethal, requiring inpatient hospitalization. A pentobarbital challenge test is done to ascertain the starting dose of barbiturates required for detoxification. Long-acting barbiturates, like Phenobarbital, are used for detoxification. Tapering off is much more gradual than with BZDs

Psychosocial Treatments

- Outpatient treatment programs focus on rehabilitation in a safe environment, utilizing CBT, behavioral therapies, group therapies, and self-help groups
- Treat any underlying psychiatric disorders (SSRIs for depression, anxiety, panic disorder, etc)
- Family support and education are important
- PMD needs to be actively involved in the treatment plan, as "MD shopping" is common among these patients, leading to relapse

Stimulant-Related Disorders

Pharmacological Preparations

- Major amphetamines in USA: dextroamphetamine (Dexedrine), methamphetamine, mixed detroamphetamine-methamphetamine salt (Adderall, Ritalin), and designer amphetamines like MDMA ("ecstasy"). Nicknames include ice, crystal meth, meth, and speed. Can be smoked, snorted, ingested, or injected
- Cocaine: consumed as coca leaves, snorted or smoked as cocaine hydrochloride, or converted into an alkaloid through "freebasing" to make crack cocaine to smoke

Epidemiology

- Highest use is in persons 18-25 and 26-34
- Males > Females (2:1)
- All races and socioeconomic groups are affected equally

Comorbidity

- Anxiety Disorders, ADHD, and Antisocial Personality Disorder *often precede use*. Often mood disorders and EtOH dependence are the result of result of stimulant abuse
- Commonly associated psychiatric disorders include: MDD (>30% of cocaine users), Cyclothymia (20%), Bipolar Disorder, Anxiety Disorders, and Antisocial Personality Disorder

Neuropharmacology of Amphetamines

- Rapidly absorbed and rapid onset of action (1 hour orally, immediately when intravenously)
- Primary effects are produced through presynaptic release of catecholamines (DA), especially in the limbic and cerebral cortex, which influence the reward pathways. This differs from cocaine, which inhibits the reuptake of DA
- MDMA and other designer amphetamines cause release of catecholamines AND serotonin (leading to hallucinations)
- Detected in the urine 1-3 days, with hair samples able to detect use for up to 90 days

Neuropharmacology of Cocaine

- Alkaloid derived from the South American shrub *Erythroxylon Coca*. It was first used as an anesthetic in 1880 (currently used still in ENT surgeries). Was used by Sigmund Freud and widely used as a "cure-all" until 1914 when its addictive properties were recognized
- Most common method of use is "snorting" (i.e. intra-nasally). Other methods include IV or smoking ("freebasing"). Freebasing mixes street cocaine with pure cocaine alkaloid (freebase) to increase effect. Crack is a smoked freebase form of cocaine and is highly addictive
- Competitive blockade of DA reuptake, thereby increasing DA in synaptic cleft and increased D_1/D_2 receptor activation
- Also has effects on Norepinephrine, Serotonin, cerebral blood flow, and cerebral glucose use
- Behavioral affects are felt immediately and last 30-60 minutes, requiring repeated dosing for continued intoxication. Can stay in urine 1-3 days, and up to 12 days in daily chronic users

Stimulant Use Disorder

A pattern of amphetamine-type substance, cocaine, or other stimulant use meeting at least 2 criteria for substance use within the past 12 months.

Stimulant Intoxication

During or shortly after use there are clinically significant problematic behavioral or psychological changes:

- Euphoria & sensation of increased energy
- Hypervigilance
- Increased sociability
- Abusive/Aggressive behavior
- Mood lability
- Repetitive stereotyped behaviors
- Interpersonal sensitivity
- Impaired judgment

Two or more:

- Tachycardia or bradycardia
- Pupillary dilatation
- HTN
- Sweating/Chills
- Nausea/Vomiting
- Weight loss
- Psychomotor agitation or retardation
- Muscular weakness, chest pain, arrhythmias, or respiratory depression
- Seizures, dystonia, dyskinesia, confusion, or coma

Stimulant Withdrawal

After cessation/reduction of use, there is *dysphoric mood plus at least two* of the following within a few hours to several days:

- Lethargy and fatigue
- Vivid, disturbing dreams
- Insomnia/Hypersomnia
- Increased appetite
- Psychomotor retardation or agitation

Withdrawal peaks in 2-4 days and is usually resolved by 1 week. The most serious withdrawal symptom is depression because it can lead to suicidal ideation.

Adverse Effects of Stimulant Use

- Common: nasal congestion/ulceration/bleeding/perforation of nasal septa (snorting), damage bronchial passages (smoking), infection/embolism/HIV (IV use), acute dystonia, tics, and migraines. Two-thirds of acute toxic events occur within one hour of intoxication, with major complications being cerebrovascular, epileptic, and cardiac
- Cerebrovascular: nonhemorrhagic cerebral infarction most common, TIA, and spinal cord hemorrhages
- Seizures: occur in 3-8% of cocaine-related ER visits. Cocaine is the #1 abused substance associated with seizures, amphetamines is #2. Partial complex status epilepticus is seen
- Cardiac: MI and arrhythmias. Long-term use is associated with cardiomyopathy
- Pregnancy: with amphetamines and cocaine, risk of low birth weight, small head circumference, premature delivery, growth retardation, fetal demise, and *abruptio placentae*. With cocaine in utero specifically, see CNS irritability in the newborn with decreased IQ and attention span deficits
- IV Use: HIV, hepatitis B/C, lung abscess, endocarditis, and necrotizing angiitis.
- Stimulant-Induced Psychotic Disorder: paranoia, hallucinations, hypersexuality, hyperactivity, and confusion. Can be distinguished from schizophrenia in that in amphetamine psychosis has NO alogia, flattening of affect, disorganized thinking (i.e. loose associations). Treatment is short term use of antipsychotics like haloperidol or atypical antipsychotics

Treatment

The long-term goals of treatment are the same for all substance use disorders: abstinence, relapse prevention, and rehabilitation.

Treatment Setting: once medically cleared, inpatient treatment is rarely needed. Most patients can be treated effectively in an intensive outpatient program. For acute psychotic/agitated patients, inpatient care may be necessary to monitor for safety and provide short-term treatment with antipsychotics

Psychosocial Treatments

- Multiple studies show that CBT is one of the most effective treatment modalities
- Family therapy is an essential component of treatment, focusing on the consequences of the patient's use and goals for a healthy future. It empowers families to help the addict prevent relapse
- Participation in NA, Cocaine Anonymous, or other 12-step help groups predicts less stimulant use/relapse

Medication Management

- Treat intoxication symptomatically: α-blockers before ß-blockers to prevent unopposed α activity, BZDs for agitation, antipsychotics for severe psychosis
- Studies for treatment of cocaine dependence: buprenorphine (opiate partial agonist), topiramate, baclofen ($GABA_B$ agonist), tiagabine (GABA reuptake inhibitor). All of these medications have some data to show efficacy in treatment of cocaine dependence/withdrawal
- Bupropion (decreases DA reuptake) has been used after amphetamine withdrawal to reduce dysphoria and produce feelings of well-being
- Treating underlying psychiatric conditions that contribute to stimulant use is also important

Tobacco-Related Disorders

Epidemiology

- WHO estimates 1 billion smokers worldwide; 25% of Americans smoke. Tobacco kills more than 3 million people a year
- Tobacco is the most common form of nicotine. Tobacco can be found in cigarettes, cigars, pipes, snuff, and chewing tobacco
- Over 75% of smokers have tried to quit, and about 40% attempt to quit each year. In attempting to quit, only 30% can remain abstinent for even 2 days
- About 20% of the population develops nicotine dependence at some point, making it the *most prevalent psychiatric disorder*
- Women = Men
- More prevalent in lower socioeconomic groups, the lower educated, and in minorities
- 70% of patients with Bipolar Disorder and 90% of schizophrenics smoke. In patients with schizophrenia, nicotine can reduce their extraordinary sensitivity to outside sensory stimuli and increase their concentration
- Associated with 25% of all deaths in the United States. Deaths occur from bronchitis/emphysema, cerebrovascular disease, cardiovascular disease, and almost all cases of COPD and lung cancer. Chewing tobacco and cigars are associated with oropharyngeal cancer
- Secondhand smoke increases the risk of heart disease and cancer by 30%
- Dependence is enhanced by strong social factors that encourage smoking and the effects of tobacco company advertising. Some studies suggest a genetic predisposition toward nicotine dependence

Neuropharmacology

- Nicotine acts as an agonist at the nicotinic subtype of acethycholine (Ach) receptors. It activates the DA pathway projecting from the ventral tegmental area to the cerebral cortex and the limbic system (i.e. the same areas involved in cocaine/amphetamine dependence), resulting in positive reinforcement and addictive properties
- In addition to activating the DA reward system, nicotine causes increased concentrations of NE, epinephrine, vasopressin, ß-endorphin, ACTH, and cortisol. This results in CNS stimulation
- 25% of the inhaled nicotine reaches the blood stream and brain within 15 seconds. The half-life of nicotine is 2 hours

Tobacco Use Disorder

A problematic pattern of tobacco use, meeting at least 2 criteria of substance use within 12 months. There is no recognized intoxication state for tobacco.

Tobacco Withdrawal

After daily use of tobacco for at least several weeks, within 24 hours of reducing or ceasing use there are at least *four* of the following:

- Dysphoric/depressed Mood
- Insomnia
- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased Appetite/weight gain

Can cause slowing of EEG activity, decreased cortisol, decreased catecholamine levels, and a decline in metabolic rate. Heart rate decreases by 5-12 BPM in the first few days after stopping smoking. Weight may increase an average of 4-7 lbs after cessation. May have increased cravings for sugary foods. Withdrawal symptoms peak 24-48 hours after cessation and may continue for 4 weeks. *Hunger and craving for tobacco can last up to 6 months in some patients.*

Adverse Effects

Adverse effects after withdrawal

- Benzopyrenes in tobacco normally inhibit the hepatic P450 CYP 1A2 system. Medications metabolized by this system (including clozapine, haloperidol, BZDs, TCAs, and propranolol) will increase substantially after smoking cessation. Monitor for medication toxicity after quitting smoking
- Smoking increases caffeine metabolism, thus smoking cessation increases caffeine levels by 50-60%, increasing risk for caffeine toxicity. *Reducing caffeine intake when quitting smoking may be recommended*

Nicotine toxicity: in low doses, the signs and symptoms of toxicity include nausea, vomiting, pallor, weakness, abdominal pain, diarrhea, dizziness, HA, HTN, tachycardia, tremor and cold sweats. High doses of nicotine affect concentration and can lead to confusion

Nicotine is associated with decreased REM sleep

Smoking during pregnancy is associated with increased incidence of low birth weight babies and newborns with persistent pulmonary hypertension. Quitting smoking by the third trimester reduces risk of low birth weight babies to equal nonsmokers

Assessment

- Assessment of degree of dependence is very important, as highly-dependent individuals are more likely to need more intensive therapy, especially pharmacotherapy
- Fagerstrom Test for Nicotine Dependence: widely used assessment tool with proven reliability/ validity. Can predict which smokers are likely to quit smoking and which may benefit from nicotine replacement therapy (NRT). Questions include: cigarettes/ day, morning smoking, how soon after awakening have first cigarette, difficulty to refrain from smoking in places where it is forbidden, smoking when ill/ bedridden. Morning smoking and smoking right after awakening are known to be highly associated with difficulty quitting
- Indicators of use: nicotine levels in blood/ urine/ saliva (detectable for few hours), cotinine (metabolite of nicotine) detectable for up to 7 days, carbon monoxide level (measured by breath) reflects smoking over last few hours and is useful to verify cessation in patients using NRT)
- Assess previous causes of relapse to help prevent future relapse

Treatment

Establishing and maintaining a therapeutic alliance: this is a chronic relapsing disorder with most smokers requiring 5-7 attempts before quitting for good. Most patients are not aware of this, and are easily demoralized by relapse. Good therapeutic alliance is essential in encouraging the patient toward abstinence, using and non-judgmental and empathic approach.

Increasing readiness and motivation for smoking cessation: enhancing motivation and dealing with anticipated barriers to cessation are important, especially in ambivalent patients. Stages-of-change approaches and motivational enhancement models (see Motivational interviewing) help to enhance a patient's motivation and challenge ambivalence. Looking at the patient's consequences of use (health issues, social pressures, and special situations [pregnancy, living with a child with asthma]) can sometimes motivate smokers to quit. During MD visits, frequent revisiting of these issues and evaluating the benefits of quitting is associated with increased readiness to quit.

Overcoming barriers to smoking cessation: addressing the patient's fears related to quitting (weight gain, fear of withdrawal, fear of failure) is important. May need to determine other smoking cohabitating family members 'willingness to quit, as this may be a barrier to the patient's smoking cessation.

Eliciting patient preferences about treatment: includes discussing method of treatment (NRT, various psychosocial therapies, etc.)

Determining timing of smoking cessation: best timing is when patient is psychiatrically stable, no urgent problems, and no recent changes in medications. Smoking-related illness may necessitate more immediate cessation.

Determining whether cessation will be abrupt or gradual: most data shows no difference between abrupt vs. gradual cessation.

Setting a quitting date: even if using gradual quit approach, a date for complete cessation of use is recommended. If patient is not ready to set a quit date, frequent revisiting the issue on subsequent visits is helpful.

Developing a plan of psychosocial and pharmacologic treatment: frequent brief follow-up after the quit date is recommended, especially to identify symptoms of withdrawal, and monitor for exacerbation of psychiatric symptoms.

Providing education and enhancing adherence: key points include informing patients that most smokers try to quit multiple times before succeeding, remaining abstinent for 3 months is associated with low rates of relapse, and education on withdrawal symptoms. Weight gain can be prevented through physical activity and healthier diet choices. Diminishing ETOH intake is recommended as it is a risk of relapse. Praise should be provided even after a relapse for any time remained abstinent.

Determining approaches for patients who do not respond to initial treatment: after a relapse it is important to determine if treatment was appropriate and adequately implemented. If so, then rescreening the patient for co-occurring disorders (other substance use or psychiatric disorders) is indicated. May require trial of different NRT if initial treatment inadequate. If stressful life event lead to relapse, therapy may be indicated.

Medication Management

Nicotine replacement therapies (NRT): 5 current FDA approved are patch, gum, lozenge (these are OTC), nasal spray, and inhaler (prescription). Optimal duration is variable, some patients stay on these agents for >6 months. The easiest NRT to adhere to may be the patch, started at high dose 21 mg. Patients who smoke <15 cigarettes/day may benefit from intermediate patch (11 or 14 mg). Duration of patch therapy should be 6-12 weeks. With the use of gum/lozenges, scheduled dosing with gradual tapering off over 6-12 weeks is most effective. Combination with bupropion or psychosocial therapies may improve outcome.

Bupropion: sustained release bupropion is a first-line treatment for smoking cessation. Doubles quit rates, and use with NRT has even higher rates of success. Increased in a step-wise titration over 3-4 days with a target of 300 mg/day. Mechanism of action is through decreasing reuptake of DA (reward/ seeking system) and non-competitive inhibition of nicotinic acetylcholine receptors (interferes with addictive actions of nicotine). Side effects include jitteriness, insomnia, and GI symptoms. Avoid in patients with history of seizures or an eating disorder (due to higher risk of seizures).

Nortriptyline: second-line treatment that has supportive data in the event the above treatments are ineffective. However, can be toxic in overdose, use with caution.

Clonidine: α_2-adrenergic agonist at the NE autoreceptor decreases sympathetic tone in locus ceruleus to abate withdrawal symptoms. Second-line therapy.

Other agents: acupuncture, naltrexone, buspirone, MAOIs, and SSRIs may be of some use, but efficacy is not well established.

Psychosocial Treatments

- Social support is a recommended treatment for smoking cessation
- Behavioral therapies substitute healthy behaviors (walking, exercising) for smoking
- Brief therapies with motivational approaches are helpful
- CBT are helpful for smokers with co-morbid psychiatric disorders or ETOH/ substance abuse. May also help with weight concerns
- Self-help materials and support groups can aid smoking cessation

Miscellaneous

Anabolic Steroid Abuse

Includes testosterone and synthetic analogues of testosterone that possess anabolic (muscle-building) and androgenic (masculinizing) effects. These drugs are used illegally to enhance physical performance and increase muscle bulk

Neuropharmacology: oral testosterone is metabolized in the GI mucosa and liver, leading to decreased bioavailability. Synthetic androgens are less extensively metabolized. May initially induce euphoria and hyperactivity. However, over time, can lead to increased aggression ("roid rage"), irritability, anxiety, and depression. When users stop taking, they can become depressed and over-concerned about their physical appearance, even when no change can be objectively seen

Adverse Effects: Anabolic steroids lead to rapid enhancement of muscle bulk, but also have acne, premature balding, yellowing of the skin/eyes, gynecomastia, decreased size of testicles/prostate, and stunted growth in adolescents. Women using steroids develop a deeper voice, shrinking breasts, clitoral enlargement, and irregular menses. Also causes abnormal LFTs, decreased HDL/increased LDL, decreased spermatogenesis, and may cause MI/cerebrovascular disease**.** DHEA and androstenedione are OTC adrenal androgen food supplements. They are steroid precursors and are noted to cause increased physical and psychological well-being. Their side effects are similar to anabolic steroids.

Illicit "Club Drugs"

Ecstasy (MDMA = methylene-dioxy-methamphetamine)

- Synthetic methamphetamine popular at clubs and "Rave" parties. Some studies suggest that it leads to permanent serotonin depletion in the brain
- Intoxication: euphoria, hyper-verbal, loss of inhibition, hypersexuality, bruxism, altered visual perception
- Adverse effects: hyperthermia, dehydration, CHF, pulmonary edema, and reported deaths. The user will overexert themselves, unaware of dehydration and hyperthermia, leading to significant morbidity and mortality

Rohypnol (Flunitrazepam)

- A BZD, also known as "roofies," the "date rape drug."
- Used by dissolving the pill into a beverage, Rohypnol causes sedation, amnesia, muscle relaxation, and a slowing of psychomotor responses. Sedation occurs 20-30 minutes after administration and lasts for several hours. Commonly used to commit sexual assault, however, currently GHB is more widely used for this purpose

GHB (Gamma-hydroxy-butyrate)

- Combines GBL (a solvent in floor cleaning products, nail polish, and super glue removers) with NaOH or KOH. It is a clear liquid that is easily mixed into beverages
- Intoxication: euphoria, increased energy, hyper-verbal, increased socialization, disinhibition, hypersexuality, muscle relaxation, and loss of coordination due to loss of muscle tone. Other side effects include nausea/vomiting, amnesia, poor concentration, loss of gag reflex, and even death
- Can also be used as a sedative and has anabolic body building effects. Commonly used as a date rape drug

Commonly Abused Over-the-Counter Medications

Dextromethorphan (DM)

- D-isomer of the codeine analog levorphanol (central acting, however, is not an analgesic) used to suppress cough
- Present in many cough/cold formulations, specifically Robitussin DM and Coricidin HBP (which contains 3x more DM than Robitussin)
- Commonly abused by teens for the "high" of heightened awareness, dizziness, visual hallucinations, altered perception of time and drowsiness. DM is very inexpensive and easy to acquire. Patients with a history of EtOH or substance abuse issues should be monitored for DM abuse
- Symptoms of OD: HTN, tachycardia, hallucinations, slurred speech, sedation, seizures, dilated pupils, temporary blindness, severe flushing, coma, and death

Coricidin

- Cough/cold preparations that contain an antihistamine (Chlorpheneramine), a decongestant (like pseudoephedrine), and/or a cough suppressant (DM)
- Coricidin D, containing pseudoephedrine, is highly abused due to the ease of converting pseudoephedrine to methamphetamine. Any products containing pseudoephedrine are now closely monitored and new decongestants with less addictive properties are being manufactured. Pseudoephedrine is a central nervous system stimulant, which can produce symptoms of shakiness, HTN, and tachycardia

- Coricidin comes in pill formulation, making ingestion of large quantities of DM easier than drinking multiple bottles of Robitussin to get the same effect

Urine Drug Screen

Drug	Length of Time in Urine
EtOH	1 drink metabolized / hour
Amphetamines	2 days
Barbiturates	1 day (short-acting), 3 weeks (long-acting)
BZDs	3 days, longer with long-acting agents
Cannabis	3 days to 4 weeks (chronic use)
Cocaine	6-8 hours, metabolites stay 2-4 days
Codeine/Morphine	2 days
Heroin/Methadone	2-3 days
PCP	8 days

A Ninja s Guide to Evidence Based Medicine

Evidence Based Medicine (EBM) is founded on the hierarchical application of empiricism to guide decision making. We accumulate observable data through structured research, classify it based on the strength of evidence (from meta-analyses down to case reports), and form recommendations. To do this, we need to understand key terms, different organizational systems, and how we analyze results. What follows is a basic guide to EBM for the PRITE, with explanations and examples to clarify.

Epidemiology

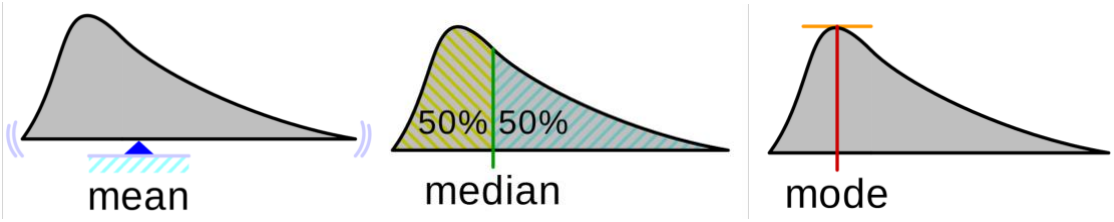
The branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health.

Distribution

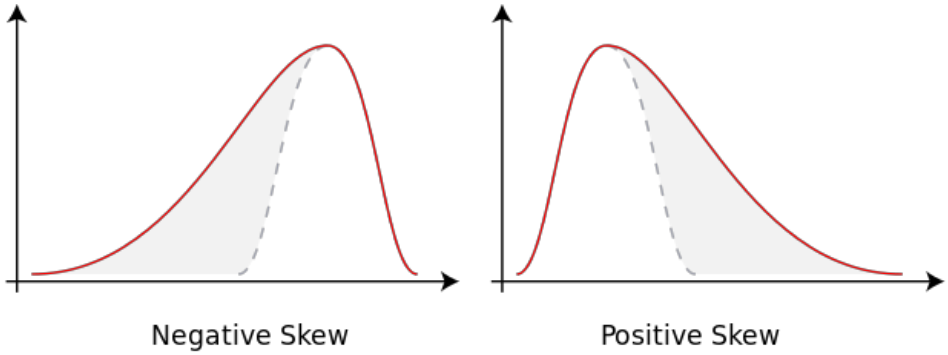
Mean: the sum of values of a data set divided by number of values. *The average.*

Median: the middle value separating the greater and lesser halves of a data set. Useful for skewed data, since a few large outliers impact the mean much more than the median.

Mode: the result that occurs most often in a sample.



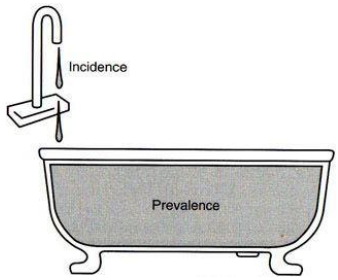
Skew: a measure of the asymmetry of the probability distribution. It is *unintuitive. Think of a negative skew as tacking on results to the left (negative) side of a normal distribution.* Example: Household income data has a positive skew. The x-axis is income, and the y-axis is number of people. There are a few people that make a lot of money. Therefore, the mean will be higher than the median.



Prevalence vs. incidence

Prevalence: the proportion of disease found to have been affecting a particular population. *How many people have it right now.*

Incidence: the probability of occurrence of a given medical condition in a population within a specified period of time. *How many people got it while I was paying attention.* Therefore, chronic ailments have a low incidence compared to prevalence; deadly diseases have similar prevalence and incidence.

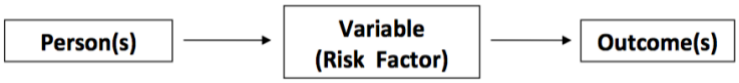


Types of Research

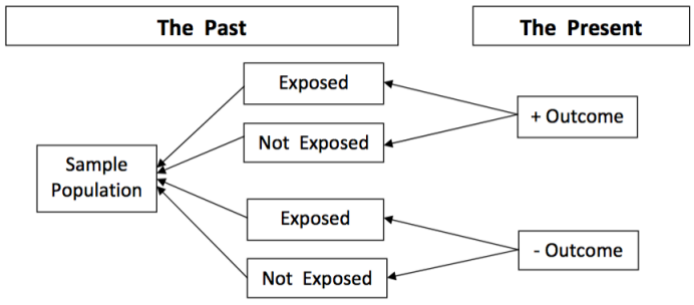
A look at the different levels of studies and how we can organize and make sense of the results.

Study Strength: Low to High

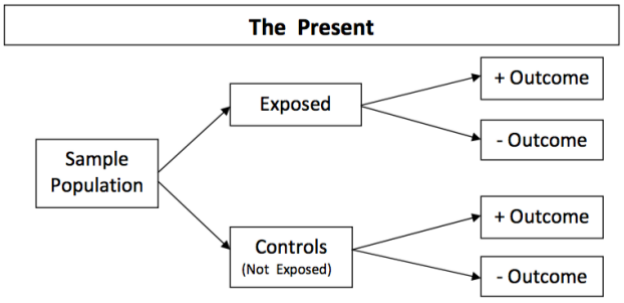
Case reports/series: presentations of individual patients. They focus on rare, unique, or unexpected associations or outcomes which may shine new light on pathogenesis or therapy. **Case series** involve a number of patients that may be related. Remember, *the plural of anecdote is not data,* but they can form the basis of future research. Example: This one guy with lung cancer, he also smoked. Huh. That's interesting.



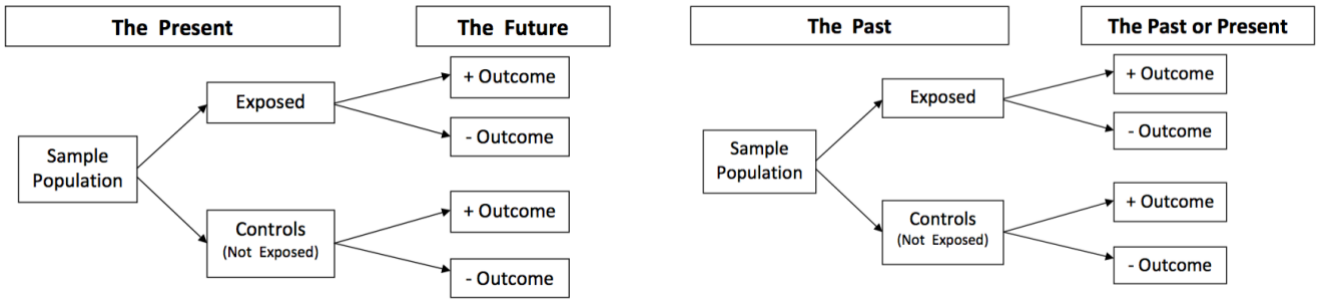
Case control studies: observational studies in which two existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute. Because we don't randomize or look at populations as a whole, we can only calculate **odds ratios**. *Find a group with an outcome, match them as best we can to similar people without the outcome, and go looking for risk factors that differ significantly*. Example: Match people with lung cancer to people without, and we will find smoking rates differ significantly.



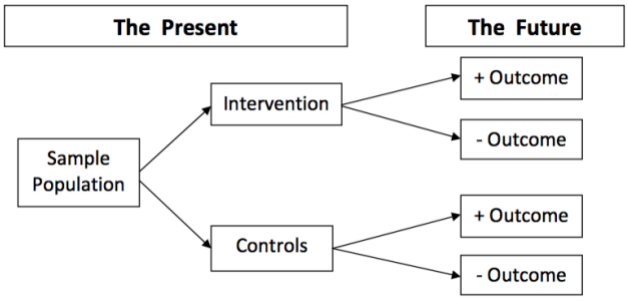
Cross sectional studies: observational studies that analyze data collected from a population at a specific point in time. Example: Look at all patients in a hospital, compare the rates of smoking in the lung cancer group to the ones without lung cancer.



Cohort studies: longitudinal studies that sample a group of people, and perform cross-sections at intervals through time. This can be done retrospectively or prospectively. *Retrospective studies suffer from **recall bias**.* Example: Take a group of people, divide them into two groups based on a risk factor (smokers vs. non-smokers) and track how many from each group contract lung cancer.



Randomized control studies: randomly allocate participants based only on a chosen intervention, and track the outcomes moving forward. *This controls for known and unknown variables.* Example: Take a group of people, randomly assign some to a "smoking group" and another to a "non-smoking group" and measure how many get lung cancer. Then go to jail for an ethics violation.

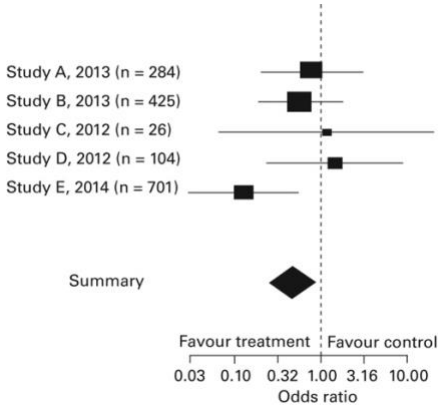


Study Design	Advantages	Disadvantage	Statistics
Case Report/ Series	• Easy • Cheap • Short • Basis of further research	• Lots of bias • No sequence of events	
Case Control	• Useful for rare conditions • Short duration • Inexpensive	• Lots of bias, especially survivor • No sequence of events • Limited to one outcome • Can account for ONLY measured variables (unlike RCTs)	Odds ratio
Cross Sectional	• May study several outcomes • Control over selection of subjects and measurements • Short in duration • Good first step before cohort	• No sequence of events • Bias in measuring predictors • Survivor bias • Not feasible for rare conditions • Can account for ONLY measured variables (unlike RCTs)	Prevalence
Cohort	• Avoids bias in measuring predictors (sampling or selection bias) • Avoids survival bias • Can study several outcomes	• Often requires large sample side • Can account for ONLY measured variables (unlike RCTs) • Prospective can be long and expensive • Retrospective has less control over selection and measurement	Incidence Relative Risk
RCT	• Strongest evidence for cause and effect • Can control for measured AND unmeasured variables	• Costs time and money • Some questions not suitable (ethics, rare outcome) • Too controlled (limits external validity)	Efficacy

Other Types of Studies

Systematic reviews: summarize research and attempt to address a focused clinical question using methods designed to reduce likelihood of **bias**. They explicitly state inclusion and exclusion criteria for evidence to be considered, and then summarize results according to explicit rules. *Cochrane Reviews are systematic reviews.*

Meta analyses: a type of systematic review that utilizes quantitative methods to summarize results from across studies. This increases the **power** of the results; however, it is susceptible to both **selection bias** and **publication bias**. *The results are only as good as the studies chosen*. Usually reported with **forest plots** of **confidence intervals**.



Note that confidence intervals that cross the midline (OR=1 or RR=0) are not significant, but when pooled together, the power is increased and a significant result is seen in the combined result. Square size indicates size of study and lines are the 95% confidence interval.

Ecological studies: analyze risk-modifying factors on health or other outcomes based on populations defined either geographically or temporally. *This is how they found out cholera came from one dirty handle on Broad Street in London.*

Twin studies: comparisons between traits of fraternal twins and identical twins. Results that are present in only one of the twins are said to be **discordant**, or less strongly heritable.

Adoption studies: analyze the role of environment by studying siblings that were separated at birth. *This is how we know that IQ is mostly genetic; twins raised in households with college-educated parents vs. non-college-educated parents have almost equal IQ. Also, IQ tests are overrated.*

Pragmatic studies: use research that is different from the idealized clinical trials which are often used to show **efficacy.** Instead of studies done at a single center, with small numbers of relatively healthy patients, pragmatic studies are done under **real world conditions.** They frequently include complex interventions, sometimes consisting of several interacting components and often involving the skills and experience of multiple health care professionals to deliver the intervention. *STAR-D is the classic example. Lots of things measured, across many sites, while following a very complex (but real world applicable) protocol.*

Analyzing the results

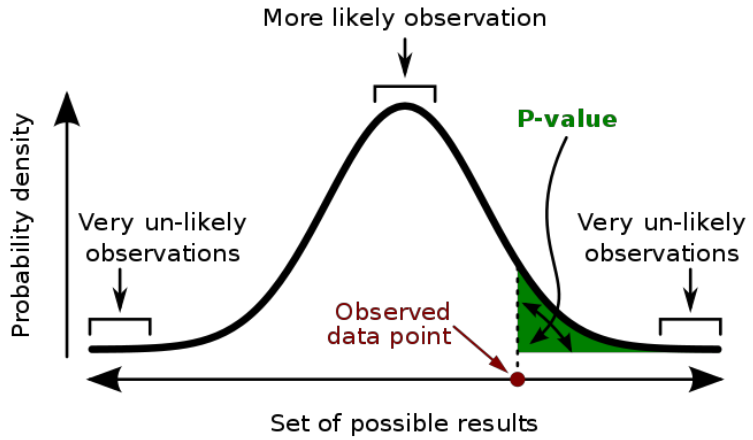
How do we go from measurement to testing for significance?

Hypothesis Testing

Null Hypothesis: the position that there is no difference between two variables. Example: treatment vs. placebo. *If there is not sufficient evidence to reject the null hypothesis, it is retained.*

Alternative Hypothesis: the position that there is a difference between the two variables for the study outcome. This is the negative of the null hypothesis. Example: when we see a result of a drug vs. placebo that has a $p \leq 0.05$, then we reject the null hypothesis. *Literally, there (probably) isn't not a difference. I know double negative.*

***p*-value:** the probability, under the null hypothesis, of obtaining a result equal to or more extreme than what was actually observed, simply by chance. *The smaller the p-value, the larger the significance because it tells us that the null hypothesis may be wrong*. We choose 0.05 out of convenience.



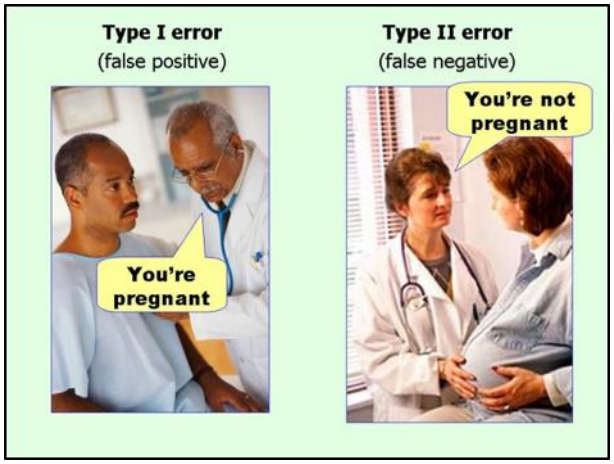
Confidence Interval: a range of values within which we are fairly sure our true value lies. Factors affecting the width of the confidence interval include the size of the sample (**power**) and the variability in the sample. *A larger sample size wil usually lead to a better estimate of the population.* If we hypothesize a true value of 0 (the null hypothesis), and the confidence interval does not contain 0, then the observed result significantly differs and we can reject the null hypothesis. Example: Looking at **forest plot** above, the odds ratio representing the null hypothesis is 1. Therefore, if the 95% confidence interval does not contain 1, such as the Summary result, then we can reject the null hypothesis that there is no difference between treatment and control.

Type I alpha error: occurs when we incorrectly reject the null hypothesis when it is actually true. When interpreting "positive" studies (i.e. when studies have *p*-values < 0.05), two conclusions are possible: either the study conclusion is consistent with reality (correct conclusion or "true positive") or the study conclusion is not consistent with reality ("false positive" or Type I alpha error). *Also known as "seeing something that isn't there."*

Type II beta error: occurs when we accept the null hypothesis (or fail to reject it) when it is actually false. The probability of making a type II error is β (Greek "beta") usually set at 20%. When a study is at risk of making a type II error ($p > 0.05$), we say it has inadequate **power**—or a low probability that it will detect a clinically important difference, if one exists. *Also known as "not seeing something that is there." To increase the power, increase the sample size.*

Type III error: occurs when we forget the difference between Type I and Type II. ☺

	REALITY		
STUDY CONCLUSIONS	**Difference Exists**	**No Difference Exists**	**ROW TOTALS**
Statistical Difference ($p \leq 0.05$)	Correct Conclusion (TP = True Positive)	Error – ***Type I or Alpha*** (FP = False Positive)	All "Positive" Studies (TP + FP)
Statistical Difference ($p > 0.05$)	Error – ***Type II or beta*** (FN = False Negative)	Correct Conclusion (TN = True Negative)	All "Negative" Studies (FN + TN)
COLUMN TOTALS	All of Reality with a difference (TP + FN)	All of Reality with no difference (TN + FP)	**ALL RESULTS**



Multiple hypothesis testing: after the fact ("post hoc") analysis is prone to bias and random error. With a *p*-value cutoff of 0.05, there is a 5% risk of a Type I error *for each test.* Therefore, beware of studies with multiple hypothesis testing, especially if the hypotheses were not established at the start of the study ("a priori"). *Also known as "fishing expeditions", "data mining", or "p-hacking".* Example: In a study of a new drug vs. placebo, the *p*-value for efficacy was > 0.05 and the null hypothesis was retained (drug is no better than placebo). However, the researchers divided the patients up into different groups (by sex, by age, by height, etc.) and found that the drug had a *p*-value < 0.05 for short men over the age of 50. This may be a great starting point for future studies, but should be viewed with skepticism. The more post-hoc analysis done, the greater the probability we will find *something* significant, making a Type I error.

Methods of Analysis

Regression analysis: used to determine how multiple independent variables affect a dependent variable. This is useful when lots of potential causes are measured, but we want to see if they act independently, or are just related to each other. *Detects and corrects for **confounders**.* Example: A recent study looked at the suicidality of adults with respect to their sleep. Participants wore a sleep tracker. Regression analysis showed that increased sleep motion predicted acute suicidal ideation symptom changes, an effect that occurred independent of depressive symptoms at 7- and 21-day follow-up.

T-test: a statistical test that examines whether the population means of two samples greatly differ from one another. It is a tool to analyse whether the two samples are drawn from the same population (which will be the null hypothesis). The most common form is known as the Student's T-test. Example: A study compares a drug to placebo for depression. The null hypothesis is that the drug does not differ from the placebo. If the placebo had a 5% reduction, and the drug had a 7% reduction, the use of the Student's T-test could tell whether that difference is enough to reject the null hypothesis (It will depend on the sample sizes).

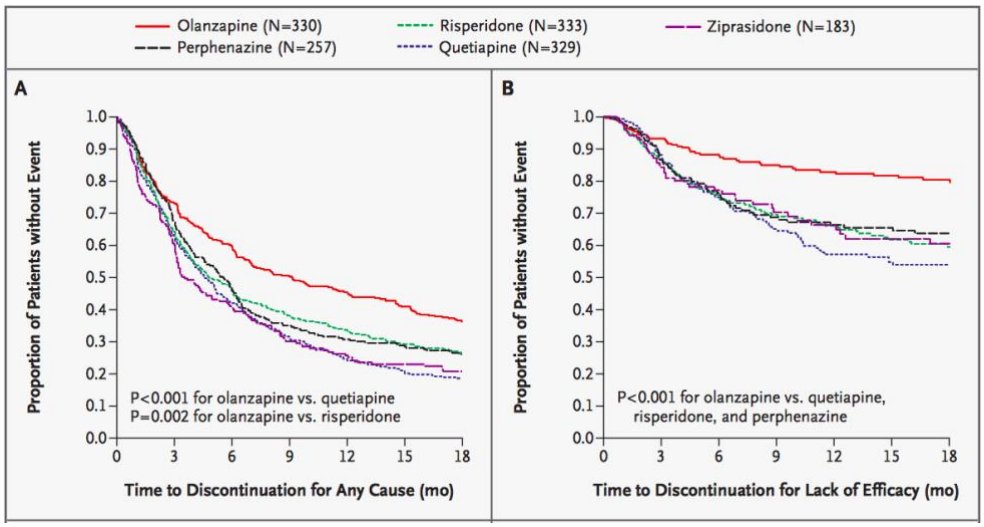
Chi squared (χ^2) test: compares two categorical variables to see if they are related. This is used when variables are *non-continuous* (for instance, height is continuous, but eye color is categorical). Data is usually compared to an expected distribution. Example: We think that admission rates increase towards the end of the month. We collect the data for admissions per day of the month and compare it to the expected distribution of roughly equal admissions per day. A large chi-squared result means that the two sets of data differ significantly, and we would reject the null-hypothesis that there is no difference in admissions.

One-way analysis of variance (ANOVA): used to determine whether there are any statistically significant differences between the means of two or more independent (unrelated) groups. Example: We want to look at factors involved in readmission to the hospital. We create a way to categorize patients into low, medium, and high risk for readmission (independent variables). Then we measure the readmission rates (dependent variable). ANOVA can tell us if we should reject the null-hypothesis that there is no difference between the 3 groups.

Two-way ANOVA: differences between groups that have been divided along two independent variables. It can also compare across the variables, to see if the effect of one of the independent variables is the same for all values of the other independent variable. Example: We want to understand the effect of a medication on hours of sleep for men and women in low, medium, and high anxiety groups. Two-way ANOVA lets us see if there's an effect for each combination. It can also see if there's an effect of anxiety level in just the men or women. *This is often the method used in post-hoc analysis.*

Y	Categorical	χ^2	χ^2
	Continuous	Regression	ANOVA
		Continuous	Categorical
		X	

Survival analysis: looks at the time until an event. Usually represented with **Kaplan-Meier plots** and numerical results are given in **hazard ratios**. Example: Assign schizophrenic patients to different antipsychotics. See how long it takes them to stop. Olanzapine won.



Therapy

Following patients

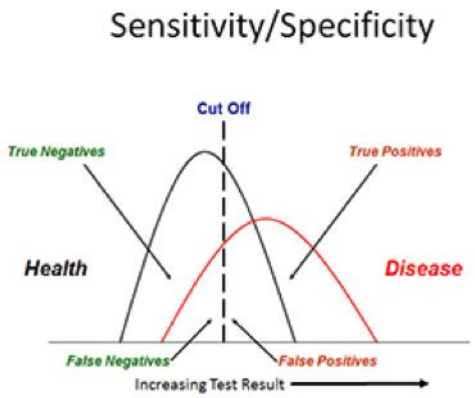
Before looking at a study's results, identify how patients were selected and followed. Depending on the protocol, many patients are excluded, wrongly assigned, or don't complete the study as intended. The results of the study can be biased depending on how we choose to count those patients towards the endpoints.

Intention to treat: analyzes patients within their randomized groups, regardless of whether they received or adhered to the allocated intervention. *This avoids the **bias** associated with the non-random loss of the participants. It also avoids **Type I alpha errors.***

Per protocol analysis: restricts the results to those participants who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It is good for showing efficacy, but may have problems with **generalizability** and real world value. *It tries to avoid **Type II beta errors***. Example: Imagine randomizing 200 patients to two study arms. In one group, patients received drug A. In the other group, they receive Drug B. In the first group, 20 patients drop out, but the drug has a 50% efficacy in the remaining patients. In Group B, no patients drop out, but it only has a 45% improvement. Under per-protocol, the efficacy would be 50% vs 45%. However, in the intention to treat, the dropouts are assumed a failure, and therefore half of the remaining 80 patients in the first group would be counted as successes, leaving group A at a 40% overall efficacy. In intention-to-treat, Drug B actually comes out better.

Epidemiological Statistics

We all remember learning this at some point in medical school. There's going to be math, but only to make things easier to understand. If seeing math is anxiety inducing, cover it up and just learn the concepts.



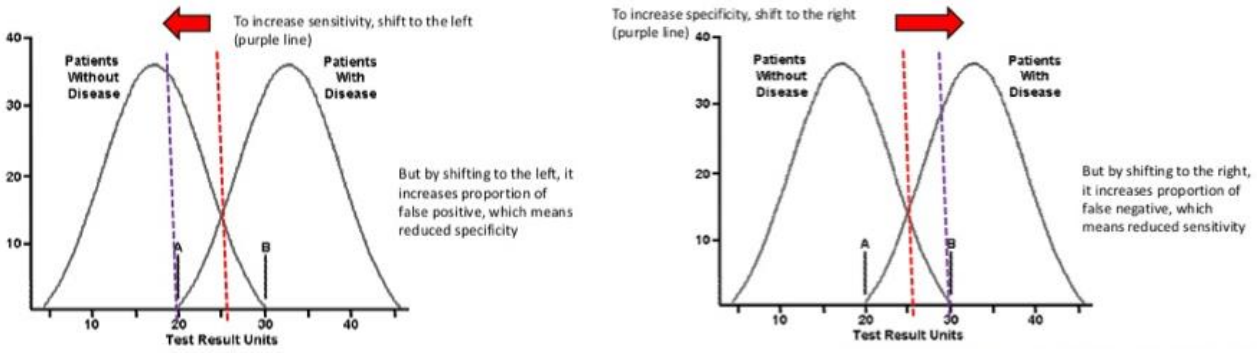
	Reality	
Test	True Positive $\boldsymbol{A}$	False positive (Type I error) $\boldsymbol{B}$
	$\boldsymbol{C}$ False negative (Type II error)	$\boldsymbol{D}$ True negative

Sensitivity: measures the proportion of positives that are correctly identified as such (i.e. the percentage of sick people who are correctly identified as having the condition). *True positive rate.* Use sensitive tests as screening tools, because a perfectly sensitive test would never miss a true positive. It is a good first step, but usually leads to a lot of false positives. *SnOUT=sensitive test to rule out.* Example: D-dimer test is sensitive; sneezing hard will elevate it.

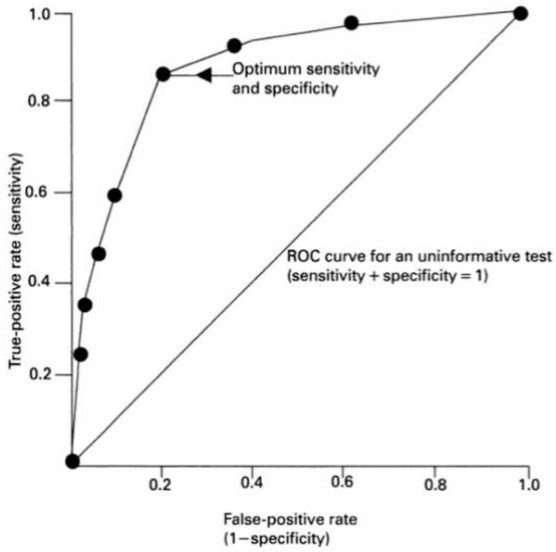
$$Sensitivity = \boldsymbol{A}/(\boldsymbol{A}+\boldsymbol{C})$$

Specificity: measures the proportion of negatives that are correctly identified as such (i.e., the percentage of healthy people who are correctly identified as not having the condition). *True negative rate.* Use specific tests to confirm diagnoses, because a positive result on a perfectly specific test is always correct. But if the result is negative, it doesn't mean the disease is absent. *SpIN=specific test to rule in.* Example: The 4th question in the CAGE questionare; if you're drinking beer and eating cereal in the morning, you might want to talk to someone.

$$Specificity = \boldsymbol{D}/(\boldsymbol{B}+\boldsymbol{D})$$



Receiver Operator Characteristics (ROC): represent the tradeoff between sensitivity and specificity when setting up cutoff points for tests. An ROC curve is constructed for a test by plotting the false positive rate (1-specificity) against the true positive rate (sensitivity) for each cut off point. An ideal test is one that is both highly sensitive and specific, and the curve would follow the path of the upper left hand corner. Example: We design a 20-item questionnaire for parents about their child's behavior to help diagnose OCD, and we compare it to the gold standard of a structured interview. A score of greater than 10 would be positive for the diagnosis. If we lower the cutoff to 8, we are more sensitive but less specific. A cutoff of 12 would be less sensitive, but more specific. So, 10 optimizes for both parameters.



Positive predictive value (PPV): the proportion of positive test results that are true positives. PPV varies with the prevalence of the disease in the population the test is being used on. *The higher the prevalence the higher the PPV.* Rare diseases are hard to test for in a population, because most positive results will be false positive.

$$\boldsymbol{PPV} = \boldsymbol{A}/(\boldsymbol{A}+\boldsymbol{B})$$

Negative predictive value (NPV): the proportion of negative test results that are true negatives. Also varies with prevalence.

$$\boldsymbol{NPV = D/(C + D)}$$

Outcome Statistics

Now with more math!

	Disease	Non-disease
Exposure	$\boldsymbol{a}$	$\boldsymbol{b}$
Non-exposure	$\boldsymbol{c}$	$\boldsymbol{d}$

Odds ratio: a measure of association between an exposure and an outcome. It represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. It is not as intuitive as relative risk! OR is approximately the same as the relative risk (RR) when the outcome is rare (<10% incidence). OR of 1 means no association, and if OR is reported with a CI which includes 1 then the OR is not significant. *Commonly used in meta-analyses and case control studies.*

$$\boldsymbol{OR = \frac{(a/b)}{(c/d)} = \frac{a \times d}{c \times b}}$$

Relative risk: the ratio of the incidence of disease among exposed to the incidence among non-exposed. It is a measure of the strength of an association between groups. *It is commonly used in prospective studies (RCTs and cohort studies).*

$$\boldsymbol{RR = \frac{a/(a + b)}{c/(c + d)}}$$

Relative Risk Reduction/Increase: the proportion of risk reduction attributable to the intervention as compared to a control.

$$\boldsymbol{RRR = 1 - RR}$$

Absolute Risk Reduction/Increase: the change in the risk of an outcome of a given treatment in relation to a comparison treatment (or placebo). Patients understand this better, but it's not as sexy. Example: A new drug is developed to protect against tardive dyskinesia in patients taking an antipsychotic. It has a relative risk reduction of 90%. However, since the incidence of TD is only 1%, the ARR is 0.9%. If the drug caused a lot of side effects, it might not be worth it.

$$\boldsymbol{ARR = a/(a + b) - c/(c + d)}$$

Number Needed to Treat/Harm: the average number of patients who need to be treated to prevent one additional bad outcome. NNH is used when an exposure is harmful (usually reported regarding side effects). Example: in the above drug for TD, the NNT would be 111.

$$\boldsymbol{NNT} = 1/\boldsymbol{ARR}$$

Population attributable fraction: the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced. Basically, within a sample, there's going to be some people that get a disease, but they weren't exposed to the risk factor, and of the people exposed, not everyone got the disease. How much can we blame the risk factor? Example: For lung cancer, we know that smoking has a RR of 20, and that 20% of people smoke. Therefore, 79% of lung cancer is attributable to smoking! (trust me, I did the math).

$$\boldsymbol{PAF} = \frac{\boldsymbol{P_{pop}} \times (\boldsymbol{RR} - 1)}{\boldsymbol{P_{pop}} \times (\boldsymbol{RR} - 1) + 1}$$

Hazard ratio: a measure of an effect of an intervention on an outcome of interest over time. It basically gives the instantaneous risk during a study, and therefore most used in time-to-event analysis or **survival analysis** (i.e. when we are interested in knowing how long it takes for a particular event/outcome to occur).

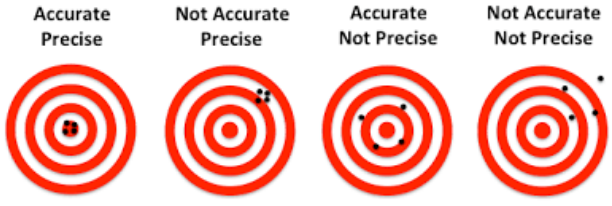
Interpreting Results

How do we know we can trust the results?

Reliability

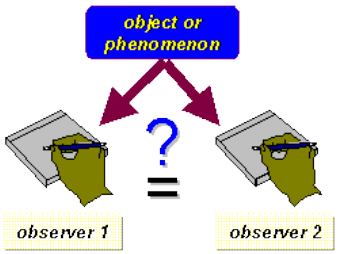
Addresses whether we will obtain the same result when measured by different people or at different times.

Accuracy vs Precision: accuracy refers to a result's relation to trueness. It is a measure of **systematic bias**. Precision is a measure of **random error**, a measure of variability. Example: if in Reality a drug does no better than placebo, a result of OR=1, would be considered accurate no matter what the confidence interval. If the test showed an OR=3 with a very narrow CI, then yes, it is precise, but it is not accurate. This is an example of a Type I alpha error.

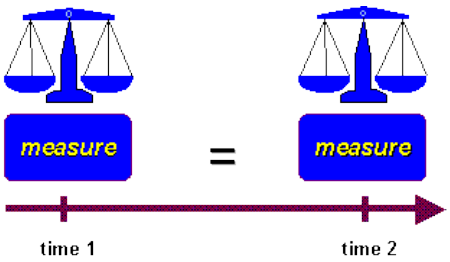


Interrater reliability: is the degree of agreement among raters. It gives a score of how much homogeneity, or consensus, there is in the ratings given by judges. *Measured using kappa; closer to 1*

means better agreement.



Test-Retest reliability: refers to the ability of a test, performed on the same phenomenon, giving the same result.



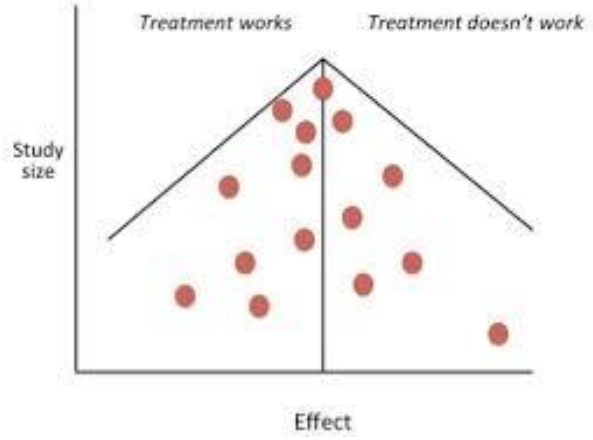
Internal validity: the extent to which a conclusion based on a study is warranted. This is determined by how much the study minimizes **systematic error** or **bias**. *Can I trust these results? Was the study done well?*

External validity: the extent to which the results of a study can be generalized to other situations and to specific patients. *Does this study apply to the patient in front of me?* Example: A new drug is found to significantly decrease symptoms of depression; however, the exclusion criteria screen out patients with any other psychiatric comorbidity or taking any other medication. The study population included mostly Caucasian women of middle to high socioeconomic status. Therefore, can we generalize the results to a poor elderly Hispanic man with co-morbid anxiety?

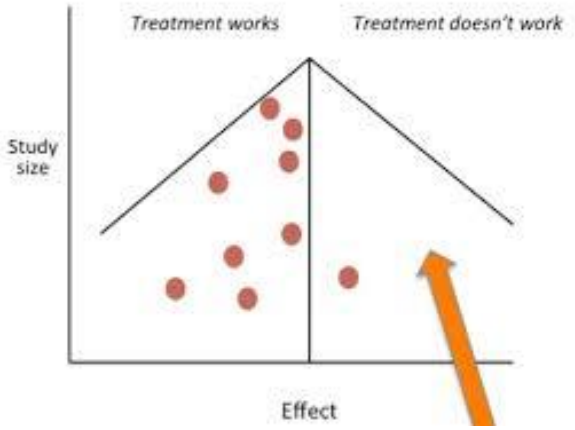
Biases

Systematic error at any stage of a study which produces results that differ from the Truth.

Publication bias: occurs when publication of research depends on direction of the study result. Studies in which the intervention is not found to be effective sometimes are not published (known as the "file drawer effect"). If there is no publication bias, all studies should have a similar effect size, but studies with a large sample size should have a smaller error (confidence interval). *This bias leads to overestimation*. Displayed with a **Funnel Plot**.



No bias



Missing negative studies

Selection bias: selecting patients for a study which do not represent the population as a whole. Also, known as *Berksonian bias*.

Recall bias: caused by differences in the accuracy or completeness of the remembered fact by study participants regarding events or experiences from the past. Common in **retrospective studies**, especially **case-control**. Worse in studies of socially unacceptable topics, life threatening illness, or well-established preconceived prejudices. Example: Study looks at rate of congenital malformations in women who used drugs during pregnancy. If comparing self-reported data vs urine drug screens, mothers of affected children more accurately remember using drugs, and mothers of non-affected children under report their drug usage.

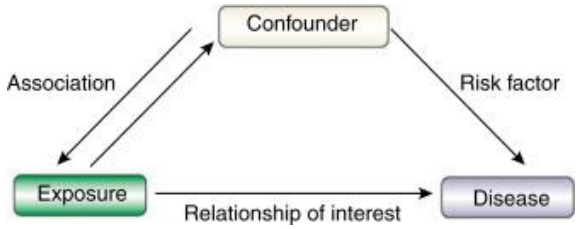
Measurement bias: occurs when information is gathered or measured using a test that distorts the data. Example: A study looks at the relationship between Depakote levels and agitation. Meds are given at 09:00 and 21:00, but blood draws are scheduled for 05:00. The Depakote level will consistently overestimate 12-hour troughs.

Procedure bias: occurs when patients in different arms of a study are treated differently. This is often due to poor randomization or an effect of an intervention triggering more attention and therefore introducing a **confounder**. Example: A double blind RCT compares a drug to placebo for efficacy in depression, however the drug is known to lower platelets and requires frequent monitoring if the level drops. Patients on the drug are more likely to need to see their doctor, and therefore receive more attention.

Observer-expectancy bias: occurs when higher expectations lead to increased performance. Also, known as the *Pygmalion effect* or *self-fulfilling prophecy*. Example: Teachers are told that certain students scored high on an IQ test and are expected to do well in school. In reality the students were chosen at random. They still end up doing better, likely because of unconscious attention by teachers.

Hawthorne effect: a change in behavior as a motivational response to the interest, care, or attention received through observation and assessment. This can occur even in blinded studies and contributes to the **placebo effect.** Example: A study tracks response to a drug vs placebo and tracks social media usage a proxy for mood. However, in both the intervention and control arm, social media usage dropped at the beginning of the study, likely because participants knew their usage was being measured.

Confounders: third variables that can make it appear (sometimes incorrectly) that an observed exposure is associated with an outcome because the confounder is associated with the exposure. They can be adjusted for by *stratifying the odds ratio*, but we have to know the confounder. Example: We find an association between energy drink use and depression. However, we think that lack of sleep is the cofounder, and split the groups based on whether they get adequate or subpar sleep. The association between energy drink usage and depression now disappears in both groups.



Effect modification: commonly confused for confounder, this is a real effect differs depending on a third variable. It is not noticed in crude analysis (all the data mixed together), but becomes apparent in *stratified analysis.* Example: a new medication is developed for ADHD. It shows $p > 0.05$ compared to placebo (crude analysis). However, when stratified according to sex, it shows efficacy with $p < 0.05$ in boys, and no efficacy in girls. Sex was an effect modifier.

A NINJA'S GUIDE TO MATERNAL FETAL MEDICINE

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A Note From Dr. Melissa Pereau, Creator of "The Ninja's Guide to PRITE"

This year, we have done a massive update on the Maternal Fetal Medicine section of the guide to incorporate new treatments and literature. I know that on average, fewer than ten PRITE questions per year focus on Maternal Fetal Medicine. So, why are we updating *this* section to The Ninja's Guide to PRITE? For Dr. Charles Jenson and all our residents, it is because discovering lifelong learning starts right now. Back in 2013, our Chief Resident, Dr. Jenson, approached me about his upcoming Grand Rounds presentation on Psychotropic Medications in Pregnancy. Perplexed, I asked him why he chose this topic when he'd never previously expressed a particular interest in Women's Mental Health. "Because last month, when we saw that Bipolar patient in clinic together, I was terrified," he admitted. I remember her well. A mother of two, Isabella came to the clinic with a singular purpose: she wanted another child. I had treated her in our inpatient psychiatric hospital multiple times in the past during both her peripartum and postpartum courses for severe mania. Each hospitalization was more difficult than the last, requiring extraordinary measures to return her to baseline. At the time of the clinic consultation, she was stable on lithium and quetiapine. We spent the hour discussing ACOG recommendations for the use of lithium during pregnancy, dosing strategies, fetal cardiac monitoring, the risks of taking medication weighed against the risks of stopping medication specifically in her case, and the necessity of working closely with High Risk OBGYN at our university. As the visit concluded and we walked the patient back to the lobby, I recall Charles looking a bit overwhelmed. I whispered reassuringly, "It's ok. This was a hard one."

Dr. Jenson's Grand Rounds on Psychotropic Medications in Pregnancy was exceptional. The knowledge he gained in self-study continued to serve him going forward as an attending physician working in a remote mental health clinic, hundreds of miles from any other psychiatric resources. No matter what setting you work in as a psychiatrist, at some point you will be responsible to manage a patient during or after pregnancy.

Lifelong learning starts now.

A special thanks to the following contributors:

- Jaime Rudyk, MD for compiling the first guide in 2020 & Jo Everett, MD for editing it
- Yifan Lii for the updated version and many painstaking edits with assistance from medical students Karah Sterris, Kaitlyn Fung, Kristen Kim, Akash Patel, Serena Lin and Charlene Wang

ANXIETY DISORDERS

Anxiety in Pregnancy

References: 1-5, 36, 38-42

Pereau's Notes:
A couple years ago, I got a call from our night float resident about a pregnant patient in her second trimester who had presented to labor and delivery with anxiety. The patient was accompanied by her spouse, who noted that the patient was generally worried on most days. She was fearful about the baby's health, the status of the family finances, and other issues despite frequent, repeated reassurance that things were ok. The fear negatively affected her interactions with her family, her coworkers, and her toddler at home. The patient reported sleeping and eating well and was regularly caring for her ADLs. She had no thoughts of suicide or prior psychiatric history. As the resident and I discussed the case, I commented saying, "If this patient wasn't pregnant, we might consider an SSRI for the severity and frequency of the anxiety. However, based on this presentation, I really think a referral for outpatient therapy is warranted first."

About an hour later, the same resident called me about a second patient in labor and delivery. This patient, at a similar stage of her pregnancy, was anxious, tearful, and distraught. She had stopped leaving her home due to fear. She struggled to eat and appeared disheveled. She also denied thoughts about suicide, but frequently had premonitions that the baby was going to die. "In the span of a just few hours," I told the resident, "You have been given the opportunity to learn when to treat and when to refer patients with anxiety during pregnancy to therapy. I couldn't have planned this better. This patient needs an SSRI started today." We started this second patient on sertraline 25 mg and referred her for therapy and medication management in our outpatient clinic.

Up to 14.4% of pregnant women experience pregnancy-related anxiety regarding childbirth, fetal wellbeing, and appearance, the three core dimensions assessed by the Pregnancy Related Anxiety Questionnaire. Meanwhile, 13–21% of pregnant women and 11–17% of postpartum women experience clinically significant anxiety which qualifies for a DSM diagnosis other than adjustment disorder (Thorsness et al. 2018). Parity and perception of parental self-efficacy may be risk factors for first-time mothers for pregnancy-related anxiety (Brunton et al. 2020). Pregnant patients may exhibit both the usual anxiety symptoms and additional symptoms which are relatively unique to pregnancy and can be severe and disabling. These include excessive worrying about causing accidental harm to the baby (leading to hypervigilance and avoidance), intrusive thoughts of harm befalling the baby, and fear of childbirth. Untreated maternal anxiety increases the risk of preterm birth (RR 1.5), low birthweight (RR 1.76) (Ding et al. 2014), and preeclampsia (RR 1.73 for mood/anxiety disorders diagnosed before pregnancy, RR 3.64 if first diagnosed during pregnancy) (Qiu et al. 2009). Mothers with high anxiety are less likely to breast feed (53% vs 65.1% in low anxiety mothers) (Britton 2007). Neonatal effects of untreated maternal anxiety during pregnancy

include elevated infant cortisol levels, disrupted emotional regulation, negative behavioral reactivity, and impaired cognitive performance during infancy (Atkar et al. 2019, Kinsella & Monk 2009). Anxiety in pregnancy may also be associated with an increased risk of hyperactive symptoms (Bolea-Almanac et al. 2019) and other childhood psychiatric/behavioral disorders (Leis et al. 2014).

When evaluating a pregnant patient for new or increasing anxiety, there is a need to rule out thyroid disfunction, anemia, and preeclampsia. In addition, a careful social history should be completed and screenings for domestic abuse should be done.

Pregnancy Recommendations

As with depression, psychotherapy is the recommended first-line treatment for mild to moderate anxiety during pregnancy. Complementary approaches such as acupuncture, massage, relaxation training and yoga can be helpful adjuncts, but data does not support their use as the primary treatment. Medication should be considered if there is little/no response to psychotherapy, if symptoms are severe, or if there is a history of a previous anxiety disorder which required medication.

SSRIs (with a possible exception of Paxil during the first trimester) are first-line treatments for GAD and panic disorder (see the section on Depression for a detailed discussion of SSRIs in pregnancy). Tapering before delivery does not prevent adverse neonatal symptoms and is associated with a high risk of relapse postpartum. Due to the high incidence of anxiety and depression postpartum, it is recommended that patients continue an antidepressant started during pregnancy until 12 months postpartum, followed by a gradual taper.

For episodic, limited anxiety (where an SSRI would be inappropriate or as you await the effects of the SSRI), limited, short term, intermittent use of benzodiazepines is considered safe. Benzos with a shorter half-life are preferred in late pregnancy. Antihistamines, propranolol, and Seroquel are safe alternatives when there are contraindications to benzodiazepines (e.g. history of substance use).

Lactation Recommendations

Non-pharmacologic interventions are first-line treatments (see above), while SSRIs are first-line pharmacologic treatments for generalized anxiety (see section in SSRIs). Propranolol is safe for intermittent anxiety and panic disorder.

Benzodiazepines are associated with infant symptoms (mostly sedation) in 1.6% of cases. Short term, low dose, intermittent use is probably safe, however benzos with shorter half-lives and non-active metabolites are recommended to prevent potential serum accumulation.

A 2021 article (Uguz) published a safety scoring system for psychotropic drugs that assigns a score to six domains which are then totaled for a final score between 0 (lowest safety score) and 10 (highest safety score). The domains are: (1) reported total sample, (2) reported maximum relative

infant dose, (3) reported sample size for relative infant dose, (4) infant plasma drug level, (5) prevalence of reported any adverse event, and (6) reported serious adverse effects. Below is a table of the total score and interpretation. Note that a low total score may indicate high risk of adverse effects or that there is limited or no data on safety. If a safety score is calculated for a medication, the safety profile and comments on usage will be indicated throughout this chapter.

Total score	Safety profile	Comments on usage
≤ 3	Very good	Highly acceptable
3.1–5	Good	Acceptable
5.1–7	Moderate	Possible
7.1–8.5	Low	Possible with caution
8.6–10	Very low	Not recommended

Anxiolytics and Sedative/Hypnotics

Antihistamines

References: 6-12

Most studies on antihistamines focus on use for nausea and vomiting in early pregnancy. Within the medical literature, there is a lack of strong evidence to show there is an association between exposure to antihistamine in early pregnancy and birth defects. A meta-analysis found that H1 antihistamine use is not associated with increased risk for major malformation or other adverse fetal outcomes (Etwel et al. 2017). Extensive studies have failed to show any teratogenic effects. Many antihistamines are highly anticholinergic, and this can cause issues in pregnancy including constipation and orthostatic hypotension. Use of sedative antihistamines in late pregnancy has been associated with neonatal tremor and diarrhea.

All antihistamines are considered safe to use during breastfeeding as transfer into the breastmilk is minimal. However, large doses and prolonged use of sedating antihistamines can potentially cause infant sedation and decrease milk supply (So et al. 2014).

A study from the Slone Epidemiology Center Birth Defects Study analyzed antihistamine use and the presence of congenital anomalies. It demonstrated that 16 previously reported associations were not found within their study population. In addition, they found six associations that had never been reported before, including diphenhydramine and D-transposition of the great arteries (OR 2.3, 1.1–5.0), doxylamine and cystic kidney disease (OR 2.7, 1.3–5.6), chlorpheniramine and neural tube defects (OR 2.6, 1.1–6.1), tetralogy of Fallot (OR 3.1, 1.2–8.4), hypoplastic left heart syndrome (OR 4.9, 1.6–14.9), and great veins anomalies (OR 3.3, 1.1–10.0) (Li et al. 2013).

Diphenhydramine [13-17]

A multi-center case-control study showed no association with birth defects. However, it is not recommended to be taken in the 3rd trimester because it has an oxytocin-like effect and can cause uterine contractions.

Prolonged use at high doses during lactation can potentially decrease milk supply. This is especially true if combined with sympathomimetics such as pseudoephedrine (commonly found in OTC cold medications) or before lactation has been well established.

One randomized clinical trial with 54 patients found that treatment of insomnia with diphenhydramine or trazodone during the third trimester of pregnancy could potentially prevent postpartum depression. Diphenhydramine may also potentially aid in headache relief when administered with metoclopramide during the second and third trimester of pregnancy when acetaminophen fails. One case report also reported that fetal heart rate increased from 155 bpm to 200 bpm 14 minutes after administration of IV diphenhydramine.

Doxylamine [10, 14, 18, 19]

In the late 1970s, there were multiple studies on doxylamine use in early pregnancy for nausea and vomiting that found associations with limb and GI abnormalities. As a result, it was temporarily withdrawn from the market. Later, larger prospective and retrospective studies in the 1990s found no evidence of risk of any congenital anomalies, cardiocirculatory defects, or negative effects if used in pregnancy.

However, prolonged use of high doses during lactation can cause infant drowsiness and decrease milk supply.

Hydroxyzine [5, 7, 10, 14, 20-22]

Exposure to cetirizine, the active metabolite of hydroxyzine is not associated with adverse outcomes above background rates. Around 80 documented cases of use in pregnancy found no congenital anomalies or newborn symptoms.

One case of neonatal seizure was seen in a neonate born at 29 weeks to a woman who took hydroxyzine 150 mg/day for anxiety. The plasma concentration of hydroxyzine in the neonate was identical to maternal serum levels. The neurological development of the infant was normal at 6 months.

Prolonged use of high doses during lactation can cause infant drowsiness and decrease milk supply. However, transfer of cetirizine into human milk seems to be minimal and is unlikely to pose significant risk to the breastfeeding infant.

Benzodiazepines

References: 5, 15-22, 29-36, 43-45

Benzodiazepine use before, during, and after pregnancy is common and has been increasing in the last decades (Bais et al. 2020). Its use as an anxiolytic has been associated with some adverse outcomes, although most studies have not found an association between benzodiazepines and congenital

malformations. Multiple studies have shown that exposure to benzodiazepine was associated with lower gestational age at birth, lower gestational weight, increased risk of preterm delivery, and increased risk of spontaneous abortion. One study showed that the risk of preterm birth was higher in those who were exposed to benzodiazepines late in pregnancy (OR 1.5) compared to those exposed to benzodiazepines early in pregnancy (OR 2.6). The risk of low birth weight was also higher when exposure occurred in late pregnancy (OR 1.9) compared to when exposure occurred in early pregnancy (OR 1.3). One article hypothesizes that low birth weight may be due to the medication causing earlier birth rather than growth restriction (Huitfeldt et al. 2020). Other studies also show that benzodiazepine use concurrent with either an antidepressant or opioid may lead to higher prevalence of adverse outcomes for the fetus (Oato et al. 2021).

The most well-studied benzodiazepine in pregnancy is diazepam, and limited evidence suggests there is no increased risk of major malformations. However, diazepam crosses the placenta, and its concentration in cord blood can be up to 3 times higher than that in maternal serum.

A study from 1998 suggested an increased risk of cleft palate in babies whose mothers took benzodiazepines (Dolovich et al.), but subsequent a meta-analysis of more than 4000 cases (Enato et al. 2011) showed no increased risk of malformations. Another study with similar findings noted that patients taking benzodiazepines are more likely to smoke cigarettes, which may explain the possible association with cleft palate (Wikner et al. 2007).

A small study found a possible association between lorazepam and anal atresia (Bonnot et al. 2003). Another small study described 8 cases where the mothers abused high doses of benzodiazepines (at least 30 mg/day diazepam or 75 mg oxazepam). All 8 newborns developed facial dysmorphia. Some were found to have microcephaly (Laegreid et al. 1989). Other reported negative effects included postpartum apnea and benzodiazepine withdrawal symptoms in the mother, as well as mental retardation and attention problems in the neonate.

Newborns metabolize benzodiazepines very slowly: the half-life of diazepam is 54 hours in a premature infant, compared to 18 hours in a child 3 to 8 years old (Morselli et al. 1973). Newborns born to mothers with short-term use of high dose benzodiazepines before delivery (including for the treatment of eclampsia) often exhibit respiratory depression and decreased Apgar scores. In cases of longer-term use, withdrawal symptoms including seizures, tremor, hypotonicity, poor feeding, lethargy, restlessness and disturbances of temperature can occur (Creeley & Denton 2019). Symptoms can persist for weeks or months in some cases. A large prospective study (n=48,412) found no difference in motor and cognitive functioning at age 3 between controls and children exposed to therapeutic dose of benzodiazepines in utero (Iqbal et al. 2002). Furthermore, benzodiazepines compete with bilirubin for albumin binding, which theoretically can lead to kernicterus in the infant (Schiff et al. 1971).

Overall, short-term or intermittent use of normal doses of benzodiazepines does not appear to be associated with an increased risk of malformations. However, chronic use of high doses of benzodiazepines does increase the risk. Due to the short half-life and extensive study in pregnancy, lorazepam is the most commonly recommended benzodiazepine to use in pregnancy (Bais et al. 2020). For a patient on long-term benzodiazepine therapy, tapering the dosage days to weeks before delivery is recommended to prevent severe acute withdrawal in the postpartum period. For postpartum use of benzodiazepines, arrangements for overnight infant care need to be discussed.

In a study of 124 women taking benzodiazepines while breastfeeding (various doses for various indications), only 2 (1.6%) reported infant sedation (one mother reported use of 0.25 mg alprazolam on occasions and the other reported chronic use of 0.25 mg clonazepam BID and 1 mg of flurazepam daily) (Kelly et al. 2012). According to a 2021 safety scoring system, midazolam has a good safety profile and use during lactation is acceptable. Lorazepam and alprazolam have a moderate safety profile and may be used during lactation. Diazepam, clonazepam, and oxazepam all have low safety profiles, and it is possible to use these medications during lactation but with caution (Uguz 2021).

Benzodiazepine Receptor Agonists

Eszopiclone [36-37]

No studies in humans during pregnancy or lactation have been published on eszopiclone.

Data from the racemate zopiclone suggests it may be of low risk to an older breastfeeding infant. It is considered a pregnancy category C drug based on animal studies.

Zaleplon [22, 36]

A study of more than 1300 women exposed to with zopiclone, zolpidem, or zaleplon found no increased risk of congenital malformations. Zaleplon is considered a safe option for intermittent insomnia during pregnancy.

According to a 2021 safety scoring system, zaleplon has a very low safety profile and use during lactation is not recommended due to the lack of research on its use during breastfeeding.

Zolpidem [23-26, 34, 36]

Zolpidem crosses the placenta (umbilical ratios for n=6 were 0.48–2.75), but is rapidly cleared from the fetal circulation. A study of nearly 2500 women who used zolpidem (more than 500 during the first trimester) found an increase in the risk for low birth weight (OR 1.39), preterm delivery (OR 1.49), small gestational age (OR 1.34) and cesarean delivery (OR 1.74).

Another study of 80,000 women in which more than 600 were exposed to benzodiazepines or z-hypnotics (specifically zolpidem and zopiclone) showed an association between benzodiazepine use and slightly lower gestational age at birth, slightly lower birth weight, and mild to moderate higher risk of preterm delivery. The results may be attributed to earlier delivery rather than growth restriction. The same study did not find any effects on head circumference, APGAR scores, or risk of respiratory distress. However, no increased risk for major malformations have been noted.

According to a 2021 safety scoring system, zolpidem has a very low safety profile and use during lactation is not recommended since there is little research on its use during breastfeeding.

Zopiclone [22, 34]

See studies above regarding zopiclone. According to a 2021 safety scoring system, zopiclone has a moderate safety profile and use during lactation is possible. There are limited studies to date on its use during breastfeeding.

Additional Medications Used for Anxiety

Buspirone [5, 27]

As of 2018, there are no studies of buspirone in pregnancy in humans, although animal data shows no evidence that it causes congenital malformations. One review recommends that unless there is a clear benefit, it should be discontinued in pregnancy.

There is also limited data on its effect on breastfed infants, though it is likely to produce low levels in breastmilk. Buspirone has been shown to increase serum prolactin, but this may not affect a mother's ability to breastfeed if lactation has been well established.

Propranolol [5, 28]

Propranolol can be used to treat physical symptoms of anxiety and panic attacks. It has been studied for treatment of hypertension in pregnancy and one study retrospective study found that chronic use of beta-blockers, including propranolol, may be associated with fetal growth restriction in women with cardiovascular disease as it may cause decreased placental perfusion. Limited studies have been published regarding propranolol's use for anxiety during pregnancy, but doses are usually lower than for HTN and dosing is often intermittent and on a PRN basis. Chronic high doses late in pregnancy have been associated with neonatal apnea, respiratory distress, bradycardia, and hypoglycemia.

Chronic use of propranolol at high doses may decrease placental perfusion and therefore cause decreased birth weight. Chronically high doses late in pregnancy may be associated with neonatal bradycardia and hypoglycemia. However, discontinuing it before birth is not recommended due to exacerbation of hypertension during delivery.

Propranolol likely presents low risk of accumulation in the infant. However, no studies have been done on infant serum levels. Limited studies show no significant adverse effects in breastfed infants. As limited data is available, avoidance of propranolol in perinatal period may be appropriate.

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MOOD DISORDERS IN PREGNANCY

Depression in Pregnancy

References: 1-14, 164, 165, 190, 194

Pereau's Notes:

As a kid in elementary school, we played a game called "Green Light! Red Light!" About 15 of us children would line up at one end of the playground and a child at the opposite end of the

playground would call out commands. When we heard the words, “Green Light!” hollered, we would take off at a sprint, each of us seeing how far we could go before the command “Red Light!” abruptly stopped our progress. Every now and then, for good measure, a “Yellow Light!” was called and each of us was permitted to move in slow motion down the playground before the next “Red Light!” pierced the air. The first kid to reach the end of the playground was declared the winner, earning the right to call out commands when the game began anew.

Over the past ten years, the literature surrounding use of SSRIs in pregnancy has evolved into a giant game of “Green Light! Red Light!” A plethora of observational studies from the 1990s on children who had been exposed to SSRIs were unable to identify any difference in neurobehavioral development compared to unexposed children. Green Light! Over the past decade, a number of studies have been published showing that untreated perinatal depression is associated with increased risks of preterm labor and neurodevelopmental abnormalities in children. Green Light! Then, in November 2011, an article in the Archives of General Psychiatry by Croen et al, cited the risk for autism in children exposed to SSRI in utero to be “2-fold.” Red Light! This was followed by a 2016 study published in JAMA Pediatrics by Boukhris et al, which supported the previously found increased risk. These studies were featured on CBS News, Science Daily, and Time Magazine. Red Light...right? The above medical literature involved large retrospective case control studies where the offspring of normal mothers with no psychiatric history were compared to those of mothers with depression who were treated with SSRIs. Between both studies, only 29 cases out of nearly 150,000 compared offspring of depressed mothers who did not receive an SSRI with those who did get an SSRI. Let’s pause. We are trying to see if SSRIs cause autism; instead, all we really know is that having depression may increase the risk of autism. So, there’s no reason to lock up the Prozac.

Look, I’m awful with numbers, math, statistics, and research methods. I’m comfortable admitting that. “Confounding by indication” is a special type of research error where something vital is overlooked: individuals with a disease who are prescribed a medication are inherently different from the general population who does not take the drug. Even I can see the error in comparing the neurobiology of offspring of completely normal mothers to those whose pregnant mother had depression severe enough to require an SSRI. The only thing that can be assumed from this data is that mothers with healthy brains are less likely to have kids with autism than mothers with depressed brains. It was never about the SSRIs. Take home: we need better studies with proper controls. So here are my thoughts: when CBS Morning News announces that we have a study solely analyzing 145,000 pregnant mothers diagnosed with major depressive disorder and can show that the ones who took the SSRI (more than just picking up a single month’s prescription at the pharmacy—another feature of some studies) had autistic children, I will spit out water properly. Until then, I’m going to keep treating my patients based on the other data we have and the clinical presentation of each individual patient. Green Light!

Interestingly, like the studies linking SSRI use with autism, the problem with much of the safety data on the use of SSRIs in pregnancy is use of healthy controls. Fluoxetine, a commonly used SSRI in pregnancy, is associated with a small risk of congenital abnormalities of the heart. However, in a

2013 study from Denmark (Jimenez-Solem et al.), patients on SSRIs during pregnancy were compared with patients who paused SSRI use 3 months prior to conception. This study was able to compare mothers with depression who received SSRI treatment during pregnancy to mothers with depression who did not. Unlike most studies on the use of SSRIs in pregnancy, all of the patients being evaluated had depression. Their results? There was no difference in cardiac malformations in the infants of those exposed to SSRI vs those who paused their treatment 3 months prior to conception (p=0.95). However, there still was an increased risk of cardiac malformations in these patients as a whole. This could be due to the effect of maternal depression on fetal heart development regardless of depression treatment, or a myriad of other confusing and confounding factors (fun fact: pregnant women on SSRIs had 30% higher utilization of ultrasound during pregnancy). Two things I take away from all of this: 1) most of the data we have on SSRI use in pregnancy is riddled with confounding by indication as there's no way to tell if the underlying mental illness is actually causing the abnormalities; and 2) a twofold increased risk of a disease sounds scary, until you understand that the disease only occurs in 1% of the general population (all fetal cardiac malformations). Green Light!

In June 2018, *JAMA Pediatrics* published an article by Ligonier-Candelas et al. which showed increased amygdala-insula white matter connectivity in infants exposed to SSRI in utero compared with those who were not (n=98). Here's the clencher—the controls were infants of mothers with depression who had NOT been treated with SSRI. Yellow Light! Based on the neuroanatomy cited, I don't think anyone reading this article is worried that pregnant mothers receiving SSRIs are going to have children with Autism. But it does begin to look at the role SSRIs play in altering the structure of a growing fetus' brain in utero, especially with potential risks for anxiety dysregulation in the future. Honestly, this article was a gut punch for me. Not a Red Light, just a "I don't want to play this game anymore. I just wanna go home."

So, what now? Standing at the end of the hallway on the inpatient psychiatric unit is a woman in her second trimester of pregnancy with severe depression. A week ago, she overdosed on 300+ pills of Tylenol and was on the medical floor. She is hopeless, still suicidal, and the life of her child is at risk. In front of me are two distinct brains, each beautiful and in need of protection. I'm treating two patients. To my core I feel morally and ethically responsible for both of them. So, I take a step back.

As clinicians, we are trained to evaluate risk. A history of failed suicide attempts increases the risk of future attempts. Depending on which studies you read, that risk of completed suicide after a prior failed attempt is at least 4x higher. But what does that even mean? As I scroll through this new guide, I see a LOT of numbers. For example, 2.4% of infants exposed to lithium in utero in the first trimester have cardiac malformations, compared with 1.15% of non-exposed infants (Patorno et al. 2017). How does this translate clinically?

Let's consider a patient in her first trimester of pregnancy who has been in acute mania for the past 2 weeks. Her family brought her to the hospital after she was found naked in the back yard trying to punch the "alien baby" out of her. What is the likelihood that without any medication she will

mentally clear and have a normal pregnancy? What are the odds that without any medication she and her pregnancy will be safe and protected? I'm holding a 2.4% risk of cardiac malformations against a much bigger clinical risk. The risk of loss of life, loss of pregnancy, or other adverse outcomes for this patient is certainly greater than 2.4%. And in this case, we're talking about lithium in the first trimester—a medication with one of the most highly documented risks for fetal malformation. Starting an SSRI in a severely depressed woman during pregnancy becomes a no-brainer.

So, when I'm looking at the pregnant woman inpatient in front of me with severe depression, a recent Tylenol overdose, and a continued desire to end her life, I am confident that in terms of treatment with an SSRI, the odds are ever in my favor. This child was wanted. He is my responsibility. I inform my patient that only about 3% of babies in the US are born with major birth defects and adding an antidepressant might slightly increase that number. I inform her that NOT treating her depression could lead to abnormalities in the pregnancy as well. I tell her that there is data, in the form of 98 cases and numerous baby mice in labs around the world, that the medication I will choose will not be without some effect to her developing baby's brain. The data is still up in the air. Her situation is not. More than anything, I assure her that she is not "a crazy person," that she has an illness in her brain that threatens to kill her and the baby, and that I am confident medication will help her. I speak with her spouse and her family, and document my reasoning for this choice. In this moment, my primary goal is to protect the child's existence. Going forward, I will continue to read and learn. It is an experience of lifelong learning.

According to the World Health Organization, 10% of pregnant women and 13% of women who recently gave birth worldwide experience mental illness, with the majority of cases being depression. In developing countries, the numbers increase to 15.6% and 19.8%, respectively, Untreated depression is associated with poor nutrition, comorbid substance use, poor adherence with prenatal care, and is the number one risk factor for postpartum depression. Suicide is one of the leading causes pregnancy-associated death and the cause of an estimated 20% of postpartum deaths. Depression is one of the highest contributors to suicidality (Campbell et al. 2021). A cross-sectional study by Admon et al. found that from 2006–2017, there was a significant increase in suicide ideation and intentional self-harm in the one year before and after giving birth (2021).

There are a myriad of other risks associated with untreated depression in pregnancy including the following:

- Major congenital anomalies (odds ratio of 1.4, which is greater than that of SSRIs)
- Spontaneous abortion (RR 1.1) and stillbirth (OR 1.8)
- Preterm birth (OR 1.3–1.5), low birth weight (OR 1.2–1.4), and postpartum hemorrhage (OR 1.3)
- Excessive crying in the newborn
- Sudden infant death syndrome (OR 4.93)
- Delayed language acquisition (RR 1.83)
- Conditions such as MDD, GAD, ADHD, Conduct Disorder, and ODD in the child

Many women are hesitant to take medication during pregnancy. The decision to treat is a highly individualized one and requires open communication about the risks of both antidepressant treatment and the risks of untreated depression in pregnancy. Ultimately, there are no antidepressants that are considered so teratogenic or fetotoxic that they would be contraindicated in pregnancy or lactation. Even with medications that are considered to have higher risks (such as paroxetine), the absolute risk is still very low.

Here are some thoughts to keep in mind when reading studies and trying to figure out how to help interpret them for your patients.

- The baseline rate of major fetal malformations is low, around 1–3%.
- If the relative risk for a drug is 2, the risk of a major malformation is increased, but the absolute risk is still only 2–6%.
- "Major malformations" are often grouped together because they are *so* rare, and it can be difficult to determine the true clinical significance.

So, what do you actually need to know for treatment? For a woman diagnosed with mild to moderate depression in pregnancy, therapy can be trialed as a first-line treatment to limit medication exposure. However, in severe depression, especially if associated with suicidality, the risks of untreated depression (including suicide completion) far outweigh the risks of medication use. Women who have never been on an antidepressant should be started on an SSRI, typically sertraline followed by citalopram or escitalopram. For women stable on an antidepressant prior to pregnancy, stopping the SSRI on conception is not recommended as the risk for relapse is high during pregnancy. If a patient insists on stopping her antidepressant, a slow taper is recommended. For women with severe depression who do not wish to take medication or do not respond to medication trials, ECT is also an option.

Antidepressants

SSRIs

References; 15-23, 118

All SSRIs cross the placenta. The concentration relationship between cord blood and maternal plasma is between 0.3 and 0.9. Citalopram is transferred the most, followed by fluoxetine. The lowest transfer is found with sertraline, followed by paroxetine. As noted above in Pereau's Notes, SSRIs may have an impact on brain development because embryonic serotonin regulates migration of neural crest cells and axonal growth.

Pregnancy Recommendations

Regarding risk factors associated with SSRIs, multiple studies have failed to demonstrate an increased risk of congenital malformation with most SSRIs except paroxetine, which may be associated with a small increased risk of cardiac defects. Multiple meta-analyses argue against a significant teratogenic effect of SSRIs. Additional increased risks with SSRIs include:

- Preterm birth associated with third trimester exposure only (OR 1.6)
- Postpartum hemorrhage (OR 1.5)
- Neonatal behavior syndrome (restlessness, rigidity, jitteriness, feeding difficulties, respiratory distress). This typically starts on the first day of life and continues for up to two weeks, or rarely up to one month. Most frequently seen with paroxetine, followed by fluoxetine (RR 3)
- Persistent pulmonary hypertension of the newborn (RR 6)
- When combined with benzodiazepines, increased risk of congenital heart defects

Lactation Recommendations

What do you tell new mothers about breastfeeding and antidepressants? If a woman was taking the SSRI during pregnancy and had no issues, there is no need to limit breastfeeding. Beware of depression relapse during the postpartum period if deciding to discontinue SSRIs. Sertraline is considered the antidepressant of choice during breastfeeding due to minimal levels detected in breast milk. It is followed by paroxetine and citalopram. Fluoxetine has a long half-life and potential accumulation in the infant. However, if the mother was stable on fluoxetine during pregnancy, switching to another agent during the postpartum period solely for reasons related to lactation is not clinically recommended.

Pereau's Notes:

A patient I began treating during her first pregnancy while in the inpatient psychiatric hospital was stabilized on sertraline 100 mg. However, in the year following her normal delivery, she continued to show symptoms of worsening depression. She ended up stabilizing on duloxetine 120 mg and bupropion XL 150 mg. She did very well on these medications for two years until she became pregnant for the second time. After consultation with OBGYN, I changed her medication back to sertraline 50 mg and titrated it to 150 mg throughout the course of the pregnancy. Her depression was stable on the medication, although she did have some residual symptoms including amotivation and low energy throughout the pregnancy. After a normal delivery of a healthy infant, she took 3 months off work. During that time, she continued on sertraline 150 mg. On her one month follow up visit, she came to my clinic in tears with a 4-year-old and a wailing infant in tow. She was not able to get out of bed most days, was not tending to the needs of the household, and could barely provide care for her 2 children. Her mother and spouse were supportive with time and aid, but she had ongoing issues with mood lability, tearfulness, and strong thoughts about wanting to pack a bag and take off in the middle of the night. She had passive vague thoughts of suicide. She was barely eating, her hygiene was poor, and she admitted to not feeling emotionally connected to the baby despite breast feeding each day. I consulted a colleague in OBGYN about possible treatment strategies. "What antidepressants was the patient on prior to the pregnancy?" she asked me. I hesitantly told her the patient had done well on duloxetine and bupropion in the past, as the sertraline had never really treated her to full remission. "Then put her back on those," she said. "But she's breastfeeding!" I protested. She directed me to a textbook which has become my constant companion over the years, Drugs During Pregnancy and Lactation, edited by Schaefer, Peters, and Miller. I learned that the amount of duloxetine in breast milk is about 0.25% of the dose taken, and bupropion could not be detected in the baby's serum. While each was supported by a handful of cases, the woman in front of me was in distress and at risk of rehospitalization. I explained my

concerns to her, including not having great safety data on the use of these medications and breast feeding. We discussed stopping breast feeding, but my patient argued that as long as she was producing milk, she wanted to continue to feed her daughter. Within 4 weeks, she returned to the clinic. I was greeted by a huge smile, her well-manicured hands resting softly over the sleeping baby in the carrier fastened on her chest. Her 4-year-old played quietly in the office as we chatted. This was a different person in front of me. She radiated peace, contentment, and connection to her children. I knew I had made the right choice, even though it had been a terrifying clinical decision at the time.

Citalopram [15, 24-26, 126, 141, 142]

Citalopram is considered to be safe in pregnancy and a good second choice after sertraline for the treatment of depression in pregnancy. Several small studies have found an association between first trimester exposure and birth defects. However, the pattern of defects varied dramatically, and it is not likely to be a true teratogen. Larger studies have generally demonstrated safety of use in pregnancy. However, a 2020 case control study including pregnant women on citalopram monotherapy found an association with atrioventricular septal defect (aOR 3.73) and diaphragmatic hernia (aOR 5.11). However, these findings have yet to be replicated.
According to the 2021 safety scoring system, citalopram has a good safety profile and use during lactation is acceptable. There are no major issues when taken during lactation, although some studies have demonstrated some association with colic, irritability, and sleep issues which resolved spontaneously without cessation of breastfeeding.

Escitalopram [27-28, 126, 141-142]

Not as many studies have been done specifically on escitalopram; however, it likely has safety data similar to citalopram. One small study found an increased risk of low birth weight associated with escitalopram during pregnancy (RR 4.7). A large 2020 case control study of pregnant women using escitalopram as monotherapy found that escitalopram had the fewest associations with various major birth defects compared to other SSRIs.

According to a 2021 safety scoring system, escitalopram has a moderate safety profile and use during lactation is possible.

Fluoxetine [25, 28-31, 126, 141-142]

A single study found a slight possible increased risk for cardiac malformations (OR 1.6). This finding was replicated by another study, which found an increased risk of coarctation of the aorta (15 out of 275 patients, aOR 2.06). However, the majority of studies have found no increased risk of any congenital malformations. Another study found that when controlling for depression itself, fluoxetine had no greater risk for cardiac malformations. A single study has found an increased risk of esophageal atresia (12 out of 275 patients, aOR 3.10).

According to a 2021 safety scoring system, fluoxetine has a moderate safety profile and use during lactation is possible. Overall, fluoxetine seems to be safe in breastfeeding, but there is concern regarding

accumulation given the longer half-life compared to other antidepressants. A review of 20 studies found a few cases of adverse events that could possibly be related to fluoxetine including decreased postnatal growth, sleep disorders, colic, irritability, fever, emesis, watery stool, and possible seizure.

Fluvoxamine [25, 140, 141-142]

Use of fluvoxamine during pregnancy has not been found to be associated with an increased risk of major malformations, or pregnancy complications; however, studies are limited due to the relatively limited use of fluvoxamine compared to other SSRIs.

According to a 2021 safety scoring system, fluvoxamine has a moderate safety profile and use during lactation is possible. Breastfeeding appears safe, as studies show only a single case of neonatal jaundice that resolved spontaneously without discontinuation of breastfeeding.

Paroxetine [32-39, 126, 142]

Paroxetine has received the most attention among SSRI due to reports of an elevated risk for cardiac malformations in some, but not all studies. It appears the risk may be greater with first trimester exposure (OR 1.72) and may be dose dependent (higher risk if dose >25 mg/day) (OR 3.07). The most common anomaly found was right ventricular outflow tract obstruction defects. A 2020 study has also found that paroxetine may increase the risk of anencephaly and craniorachischisis (aOR 3.43), as well gastroschisis (aOR 2.11) that persists despite accounting for underlying conditions.

Paroxetine has also been noted to be most frequently implicated in neonatal withdrawal syndrome, possibly related to its short half-life compared with other SSRIs.

Women who are extensive metabolizers for 2D6 have been noted to demonstrate decreasing paroxetine concentrations during pregnancy compared to those women who were poor metabolizers, who demonstrated increased blood levels during pregnancy.

According to the 2021 safety scoring system, paroxetine has a very good safety profile and use during lactation is highly acceptable. For women who are breastfeeding and needing to start an antidepressant in the postpartum period, paroxetine is considered a first-line treatment due to its safety profile.

Sertraline [26, 40-42, 126, 134, 141, 142]

Sertraline is considered a first-line for treatment of depression in pregnancy due to its safety profile, tolerability, and minimal interaction with other medications. A single study found an association between first trimester sertraline exposure and omphalocele (in 3 out of 127 patients, OR 5.7), but later studies found no such association. Another study found a possible increased risk of diaphragmatic hernia when sertraline was used in the first trimester (aOR 2.72). In addition, a 2020 meta-analysis found that sertraline was associated with septal defects (RR 2.07) and respiratory defects (RR 2.65), but concluded that the risk of congenital malformations is still small in women taking sertraline. Thus, caution is advised when deciding whether to continue or discontinue sertraline.

According to the 2021 safety scoring system, sertraline has a very good safety profile and use during lactation is highly acceptable. Sertraline is also considered a first-line treatment for women who are breastfeeding as the amount detected in breast milk is minimal.

Vortioxetine [135, 189]

A 2021 single case series was published regarding the use of vortioxetine in pregnant patients. In this case series, 17 Israeli women with vortioxetine exposure during the first trimester were followed until delivery. 11 out of the 17 women had normal, term, live births with no major fetal malformations noted. One stillbirth at week 22 occurred in a patient who had taken an increased dose of vortioxetine (20 mg QD compared to median dose of 12.5 mg QD) for a longer period of time (gestational age 22 weeks compared to median exposure until gestational age 6 weeks). One patient terminated her pregnancy at week 11 due to acrania but was also noted to be taking daily carbamazepine for trigeminal neuralgia and had persistently low folate levels (<3 ng/ml) despite adequate daily supplementation. The second patient who was found to electively terminate her pregnancy did so due to suspected cystic hygroma in context of daily tobacco use. Two additional patients had spontaneous abortions (at week 7 and 8) but refused further testing. While one patient reported nursing her infant while continuing to take vortioxetine, no data was collected regarding any adverse effects.

A 2021 case study of three lactating mothers taking either 10 mg/day or 20 mg/day of vortioxetine, the levels of vortioxetine in the breastmilk were low and dose-proportional. The relative infant dose was determined to be lower than the theoretical 10% threshold of concern. None of the mothers reported any adverse effects in the infants. However, because this was a small study, vortioxetine should be taken with caution in a breastfeeding mother.

SNRIs

Duloxetine [41, 43-46, 136, 137, 141]

Few studies have been published regarding duloxetine during pregnancy. Most studies which have been published do not suggest an increased risk of congenital abnormalities; however, there may be an increased risk of spontaneous abortion (RR 3), gestational hypertension (RR 1.5–2), preeclampsia (RR 1.5–2), and postpartum hemorrhage. Of note, a later observational study did not find an increased risk of spontaneous abortions in patients taking duloxetine. A 2020 cohort study echoed past data and found an increased risk of postpartum hemorrhage (RR 1.53) and a mildly increased risk of congenital malformation (RR 1.11). No adverse effects have been noted for breastfeeding and transfer into the breast milk is low.

Venlafaxine [20, 22, 42, 45, 47-50, 126, 138, 141-142]

Studies have demonstrated a variety of birth defects including atrial septal defect, coarctation of the aorta, cleft palate, and gastroschisis. However, a later meta-analysis found no significant increase in birth defects. A 2020 case control study including 71 patients taking venlafaxine found that birth defects associated with venlafaxine persisted despite accounting for underlying medical conditions. These birth defects included: anencephaly and craniorachischisis (aOR 9.14), coarctation of the aorta (aOR 4.19), ventricular septal defect (aOR 3.51), left ventricular outflow obstruction (aOR 2.57), atrial septal defect (aOR 2.28). These findings have yet to be duplicated. However, like duloxetine, there appears to be an increased risk of spontaneous

abortion (RR 2), preeclampsia (RR 3), preterm birth (OR 1.6), and postpartum hemorrhage. Venlafaxine appears to be associated with mild symptoms of tachypnea and respiratory distress in the newborn which typically resolve after a few days. In a study of 9 women taking venlafaxine throughout their pregnancy, venlafaxine and its metabolites were found to significantly penetrate into amniotic fluid and cord blood, thus exposing the fetus to relatively high levels of venlafaxine as compared to maternal serum levels. In 3 out of the 9 patients, infants required a brief NICU admission but were discharged without any major complications. Three case reports have been published demonstrating neonatal seizures as possible withdrawal symptoms. When considered together, the data suggests that a thorough risk and benefit analysis should be performed prior to prescribing or continuing venlafaxine, and that other "safer" SSRIs be considered as alternatives.

According to a 2021 safety scoring system, venlafaxine has a moderate safety profile and use during lactation is possible. However, other studies have suggested that breastfeeding is not generally recommended while a mother is on venlafaxine as the transfer of the drug into breastmilk is significantly higher than in other antidepressants. However, no adverse effects have been reported.

Desvenlafaxine [139]

Desvenlafaxine is a metabolite of venlafaxine, so the pregnancy/lactation information for venlafaxine is likely applicable. There is little to no published information regarding desvenlafaxine during pregnancy. In a single study of 10 lactating patients taking desvenlafaxine for postpartum depression, concentrations of desvenlafaxine in breast milk were comparable to those of venlafaxine in prior studies (6.8% of the weight adjusted maternal dose), thus reflecting desvenlafaxine's poor lipid solubility. No acute adverse drug-related effects in infants were noted.

Milnacipran/Levomilnacipran [51, 124, 185-186]

There have been very few studies done on milnacipran, which is a FDA approved drug for fibromyalgia. While studies on the general population have been conducted, pregnant women have been excluded from those studies. The Savella (milnacipran) pregnancy registry is currently enrolling subjects and collecting data regarding its safety in pregnancy and following infants until 12 months of age. The trial is expected to be completed June 2023. A preliminary abstract from 2013 reported two subjects who had preterm births. However, no birth defects were found. Milnacipran is a category C drug.

There is limited data on the use of milnacipran during lactation; thus, it is recommended to be used with caution if breastfeeding. The amount of milnacipran in breastmilk is low. There are no studies on infant serum level or adverse effects in the infant. Although galactorrhea is a side effect of milnacipran, its clinical effects in a breastfeeding mom. There are no studies done on levomilnacipran use during lactation, but since it is the racemic form of milnacipran, it is expected to behave similarly. Use during breastfeeding is also cautioned.

Atypical Antidepressants

Bupropion [26, 52-57, 125, 126]

It is unclear what the risks of first trimester exposure to bupropion are. During the manufacturer trial, 700 pregnant women were treated, and no adverse side effects were reported. However, in a retrospective case-control study there was an increased incidence of cardiac defects with first trimester use. Studies have demonstrated an increased risk of ADHD in children who were exposed to bupropion at any time during pregnancy (OR 3.63), but especially during the second trimester (OR 14.66). A 2021 meta-analysis of 23 different studies on antidepressant use in pregnancy showed a significant odds ratio of 1.23 for bupropion in producing congenital heart defects during first trimester pregnancy. In addition, a retrospective case control comparing antidepressant use and later birth defects showed an association between bupropion and diaphragmatic hernia. Other research studies have also shown that early pregnancy bupropion use is associated with specific heart defects.

Compared with women who continued smoking in pregnancy, it has been noted that women taking bupropion were at decreased risk for premature birth and low birth weight.

There have not been many studies published regarding breastfeeding and bupropion, so using an antidepressant with more data may be beneficial. A single case study has been published regarding a 6-month-old with a possible seizure after the mother started taking bupropion.

Mirtazapine [58-62, 128, 142]

Mirtazapine has been found to be useful for women with hyperemesis gravidarum given its action blocking 5-HT3 receptors which helps with nausea and vomiting. Although the largest review study published found no increased risk of birth defects, smaller studies have demonstrated small increases in the risk for preterm birth as well as a mild neonatal syndrome which tends to resolve after a few days. Further case reports show that patients either suffering from hyperemesis gravidarum comorbid with high anxiety, significant weight loss, or have depression refractory to other treatments should be trialed on mirtazapine.

According to a 2021 safety scoring system, mirtazapine has a moderate safety profile and use during lactation is possible. There is limited published information regarding breastfeeding and mirtazapine. One case report did demonstrate sedation and increased weight gain in an infant, but serum testing revealed that the infant's level was about 37% of the maternal level which was much higher than typically seen (about 1.3%) and was likely due to impaired elimination/metabolism in the newborn.

Trazodone [63-65, 142]

There are limited published studies on trazodone, and none have found evidence of teratogenicity. Data has demonstrated very little transfer of trazodone into breastmilk and case reports have not shown any adverse effects.

According to a 2021 safety scoring system, trazodone has a low safety profile and use during lactation is possible with caution and only when necessary due to the limited data available.

Nefazodone [63, 66, 129]

There are limited published studies on nefazodone, and none have found evidence of teratogenicity. A single case report demonstrated an infant with drowsiness, lethargy, feeding difficulties, and hypothermia, which

resolved 72 hours after discontinuation of breastfeeding. Use during breastfeeding is sometimes avoided due to concerns about hepatotoxicity. However, there is no published data to support this.

In a report based on two nursing mothers, nefazodone, but not its major active metabolites, is shown to pass through breast milk. However, neither exposure came close to the 10% level of concern suggested by other researchers. There were no abnormal development differences; however, the unknown effects on brain maturation prompt caution when prescribing to mothers.

Tricyclic Antidepressants

References; 20, 67-72, 130

Overall, these drugs have been less extensively studied in pregnancy than SSRIs. A potential benefit of using a TCA during pregnancy is the availability of serum testing, which allows for dosing adjustments to accurately compensate for the rapidly changing pharmacokinetics associated with pregnancy. This is especially relevant for treatment-resistant patients.

If a TCA is going to be used, a less anticholinergic one, such as nortriptyline or desipramine, is preferable. These medications have a lower incidence of severe constipation, which can be especially problematic in the 3rd trimester.

Multiple studies with (>2000) pregnancies have not found evidence of teratogenicity of TCAs with the exception of clomipramine, which is associated with an increased incidence of cardiac defects.

Additional issues noted with TCAs in pregnancy include increased risk for the following:

- Preeclampsia, especially with treatment during the second and third trimesters (RR 2.2)
- Postpartum hemorrhage (RR 1.8)
- Neonatal adaptation syndrome similar to that seen with SSRIs but at a higher rate than with SSRIs
- Increased average birth weight when compared to babies exposed to SSRIs

For nursing mothers, the transfer of TCAs into breastmilk is low. Nortriptyline has been the most studied with no noted adverse effects. Doxepin has a case report with adverse effects noted.

As newer and larger studies are published, there are increasing data that demonstrates prenatal exposure to TCAs does not increase the rate of major congenital anomalies or neurodevelopmental problems.

Amitriptyline[131, 132, 142]

While there is no published evidence of teratogenicity, amitriptyline is very anticholinergic which can lead to orthostatic hypotension and constipation, especially during the latter half of pregnancy.

A nested case control study done to determine the association between different antidepressants and duration of use during pregnancy and the risk of gestational diabetes mellitus (GDM) showed that amitriptyline was associated with an increased risk of GDM (OR 1.52, 1.25 to 1.84).

A 2017 cohort analysis showed that antidepressants with serotonin reuptake inhibition effect (amitriptyline) increase the risk of organ specific defects during embryogenesis. This includes defects of of the eye, ear, face, and neck (OR 2.45, 1.05 to 5.72), and digestive tract (OR 2.55, 1.4 to 4.66).

According to a 2021 safety scoring system, amitriptyline has a moderate safety profile and use during lactation is possible.

Clomipramine [69, 73, 133, 142]

Studies have demonstrated an increased risk of congenital anomalies (OR 1.4) and cardiovascular malformations (OR 1.6) as well as an increased risk of preterm delivery (12.1%) and gestational hypertension (3.1%) with use of clomipramine during pregnancy. A study done on 10 neonates to measure clomipramine concentration and withdrawal symptoms showed an elimination half-life of 42 h (compared to 20 h in adults). In 2 of the 10 neonates, tachycardia and cyanosis were seen as serious withdrawal symptoms after maternal use of clomipramine.

According to a 2021 safety scoring system, clomipramine has a low safety profile and use during lactation is possible with caution.

Doxepin [68, 74, 142]

There is one published case of respiratory depression requiring resuscitation in an infant exposed to doxepin through breastmilk. However, in that case, the measured concentration in the infant's serum was very low suggesting other factors may have been involved. A second case study described hypotonia, poor sucking and swallowing, vomiting and weight loss. However, symptoms resolved after 24 hours.

According to a 2021 safety scoring system, doxepin has a very low safety profile and use during lactation is not recommended.

MAOIs

References: 75, 133, 134

Overall, MAOIs have limited data regarding their use in pregnancy and lactation. It has been noted that MAOIs may have pregnancy risks. They can increase the risk for gestational hypertension and may decrease placental perfusion. Hypertension, one of MAOIs most well studied side effects, has been associated with increased morbidity in pregnancy. Due to extremely limited data, it is currently safer to avoid use of MAOIs in pregnancy.

Phenelzine [76, 145-147]

Phenelzine is generally avoided during pregnancy given the extensive medication interactions which can be problematic during delivery. Phenelzine is an irreversible MAO inhibitor, so it requires strict dietary restrictions to prevent ingestion of tyramine, which could lead to hypertensive crisis. Studies have shown the potential of phenelzine to induce hyperprolactinemia and galactorrhea in non-pregnant, non-nursing patients, but it is currently unknown how these findings impact breastfeeding practices.

Tranylcypromine [77, 148-150]

Tranylcypromine is generally avoided during pregnancy given the extensive medication interactions which can be problematic during delivery. Tranylcypromine is an irreversible MAO inhibitor, so it requires strict dietary restrictions to prevent ingestion of tyramine which could lead to hypertensive crisis. Two published cases of high-dose tranylcypromine use in combination with other agents resulted in one fetal death, as well as similar congenital defects found in both babies. These included cardiac defects, hypertelorism, and agenesis of the corpus callosum. In another study, those treated with tranylcypromine had increased levels of prolactin, but the clinical relevance of this information remains unknown at this time.

Selegiline [151-152, 187-188]

A 2017 study of a woman with severe depression who used 6 mg/day selegiline patch found the absence of selegiline or its metabolite in an infant blood sample at 12 days postpartum. The infant was followed until 5 months of age at which time they were developing normally. Another case study reported a woman who took selegiline 10 mg/day along with other agents throughout pregnancy and during the postpartum period in which she breastfed for 3 days. Her child was followed for 10 years had normal development throughout. Although no adverse effects have been reported, research remains very minimal. Other agents should be considered.

Moclobemide [153-156]

Moclobemide is not currently approved by the FDA for use in the U.S. but is used in Canada and several other countries for treatment of depression and social phobias. Two published articles have shown the relative infant doses while breastfeeding to range between 1%–4%. A total of 13 reported infants have breastfed during maternal use of moclobemide therapy with no adverse effects. Limited research and lack of approval from the FDA suggest that other agents should be considered at this time.

Additional Treatments for Depression

Brexanolone [119-123, 157-163]

Brexanolone is indicated for severe, treatment-resistant postpartum depression. It is derived from the progesterone metabolite allopregnanolone. Its use is based on the theory that a major contributor to postpartum depression is the sudden and dramatic decline in progesterone and other reproductive hormones following childbirth. Brexanolone functions as a positive allosteric modulator of GABA-A receptors. Despite the inconvenience of IV administration, its rapid onset makes it a favorable option. Oral and transdermal methods of administration are currently being explored.

It is administered intravenously as a continuous 60-hour infusion at certified inpatient facilities and requires monitoring for excessive sedation and hypoxia. Additional side effects include dry mouth, hot flashes, and sedation in >/= 5% of the population. Severe somnolence and/or loss of consciousness requiring a dose interruption or treatment termination occurs in 4–5% of patients.

Three large clinical trials have demonstrated efficacy with overall reductions in clinical depression scores. Brexanolone resulted in a higher rate of remission in mothers at 4 weeks compared to SSRIs (84.5% vs 16.2%). In another study, clinical response to brexanolone suggested better health-related quality of life, less productivity loss, and less healthcare resource utilization than those who did not respond. When compared to SSRI using an indirect comparison model, brexanolone demonstrated larger improvements from baseline depression scores at day 3. Although the absolute difference between placebo and brexanolone decreased over time, the model predicted brexanolone to be superior in efficacy over time.

Due to the lack of longevity of follow up in clinical trials, questions of remission, relapse, and safety beyond 30 days remain. Randomized controlled trials comparing SSRIs (gold standard treatment) to brexanolone are needed to validate the findings of the indirect comparison model.

Although one cost-benefit analysis showed bexanolone to be more cost-effective than SSRIs at the 11-year mark, the $34,000 price tag (not including the cost of administration and hospitalization) remains a significant barrier to administration. Widespread usage is also prevented by its black box warning and lack of testing on certain patient populations. However, phase III clinical trials are underway for brexanolone use for MDD and postpartum depression in adolescents.

Brexanolone passes in into breastmilk but is theorized to have low oral bioavailability meaning infant exposure is theoretically low. However, clinical trials have failed to study infant brexanolone exposure through breastmilk, resulting in the recommendation that breastfeeding be interrupted for the duration of infusion. Although breastfeeding can be resumed shortly after infusion, another article has pointed to the possible negative implications a 3-day pause in breastfeeding has on breastfeeding practices. Thus, future research on brexanolone in relation to infant exposure through breastmilk and its effect on breastfeeding practices is warranted.

Bipolar Disorder During Pregnancy

References: 191-193

One of the major concerns of treating women with bipolar mood disorder is relapse during pregnancy. In women who discontinue their medication, the relapse rate is 52% (Viguera et al. 2000). Even for those who stay on medication, the relapse rate is still 24%. A later meta-analysis found the rates of postpartum relapse in women with bipolar disorder to be 66% if they were medication-free during pregnancy and 25% if they were on prophylactic medication. Interestingly, patients with bipolar disorder were less likely to relapse (17%) than patients with isolated postpartum psychosis (29%) (Wesseloo et al. 2015). Women with bipolar disorder (treated and untreated) are at increased risk for having babies who are small for gestational age and have microcephaly (untreated OR 1.68, treated OR 1.26) (Boden et al. 2012).

Lithium

References: 78-89, 117, 142

Pereau's Notes:

Lithium is my go-to medication in pregnancy when treating women with Bipolar Mood Disorder, even in the first trimester. As an inpatient psychiatrist, the acuity of the patients I encounter warrants the use of this medication. As I mentioned above, the increased risk of cardiac malformation with lithium, even in the first trimester, can be offset by the risks associated with the clinical presentation. A number of studies have evaluated the relationship between lithium dose and risk for malformations. I think it's safe to say that the lowest effective dose should be used. Personally, I tend to start lithium at 300 BID and titrate up to 1200mg in pregnant patients. While we know that single daily dosing is likely better for patient renal function, for the duration of the pregnancy I prefer BID and even TID. This is based on an informative and compelling study by Horton et al., which recommends keeping average and peak blood levels and as low and as stable as possible. In the treatment of pregnant patients, I often find the question, "How would I feel safest taking this medication if this was me and my baby in this patient's current condition?" to be helpful. If my answer is, "I wouldn't take that medication if I was pregnant, no matter the circumstances," I don't prescribe it. For patients stable on lithium prior to the pregnancy, I may choose to continue the lithium at the same dose and then work closely with OBGYN. The current ACOG guidelines for the continuation of lithium in pregnancy in patients with a history of severe mood episodes are 1) lithium should be tapered off prior to pregnancy and restarted after organogenesis; or 2) lithium should be continued uninterrupted in patients who have had frequent episodes and are at risk for relapse. Patients need to be educated about the risks of stopping the medication (relapse rate >50%) vs continuing it (effects on the fetus). Having a good working relationship with a High Risk OBGYN team is essential in coordinating care for these patients.

Regarding breast feeding, I have read a number of articles about the neonate's poor renal ability to clear lithium. Mechanistically, it makes sense to me. The data on how much lithium actually gets to the baby from the breast milk is inconsistent (0–50%). For that reason, if a patient is stable on lithium, we have a discussion about possibly electing not to breast feed, especially if the patient had a psychiatric hospitalization during the pregnancy. This decision must, of course, also be coordinated with the OBGYN and pediatrician. While a person is pregnant, the decisions I make in her treatment involves two individuals. I don't get a choice in that. Anything affecting the mother may affect the child. Once the baby's born, whether or not to breast feed <u>is</u> a choice. In my mind, stopping the lithium in order to breast feed is not an option. I've seen the plethora of studies showing the value of breastfeeding for both the mother and the child. I've also seen case reports of lithium toxicity in neonates. I'm a huge advocate for breast feeding, especially for patients on SSRIs. Once we are talking about lithium in breastfeeding, I personally tend to avoid it. This is based on my own personal comfort level as a provider and in response to the question, "Would I have breastfed my son, Grant, if I needed to take lithium?" For me, the answer would be no. There's a lot of great infant formulas out there. That said, there's data which implies this is a safe practice if it is closely monitored and done in collaboration with pediatrics.

Lithium can be complicated to administer during pregnancy as renal clearance physiologically increases 50–100% during pregnancy. Serum level monitoring must be done more frequently in

pregnant patients. Moreover, lithium completely equilibrates across the placenta, so fetal levels are similar to maternal levels.

During the first trimester, dehydration in patients with hyperemesis can raise lithium levels to a potentially toxic range. Some studies (but not all) have shown an increased incidence of miscarriage rate (RR 2.6) (Poels et al. 2020). There is conflicting evidence that suggests an association with preterm birth (RR 2.3) (Fornaro et al. 2020). Exposure to lithium during the first trimester has consistently demonstrated an increase in the overall rate of congenital anomalies (OR 2) (Fornaro et al. 2020). Specific malformations include defects in the heart and large vessels, including Ebstein's anomaly (downward displacement of the tricuspid valve), which occurs in about 1/1000 cases (20 times more frequent than the general population). Cardiac malformations appear to be dose dependent (Fornaro et al. 2020). The incidence is 1.1% for a dose of less than 600 mg, but is 3.2% for doses greater than 900 mg. Although the absolute risk of major malformations for lithium-exposed neonates (pooled prevalence 7.4%) may be higher than the general population (4.3%), the risk is smaller than previously thought (Hermann et al. 2019). To screen for cardiac malformations, current ACOG recommendations include fetal echocardiogram for pregnancies exposed to lithium in the 1st trimester.

During the third trimester, there are multiple issues associated with administration of lithium. First, lithium antagonizes ADH, which can cause fetal polyuria and an increased risk of polyhydramnios. For women who develop preeclampsia, a decrease in renal clearance can potentially lead to toxic levels. The initial pregnancy-related increase in lithium clearance declines sharply after delivery. The widely practiced current recommendation to discontinue lithium with the onset of labor and resume at a lower dose postpartum are based on case report and case series studies and have been challenged. A retrospective cohort study from 2021 found no maternal lithium blood level fluctuations surrounding delivery and no association between neonatal blood levels at delivery and neonatal outcomes (Molednaar et al. 2021). Careful monitoring of lithium blood levels is recommended instead of lowering the lithium doses prior to delivery. However, further research is warranted.

Infants exposed to lithium in utero are at increased risk for multiple issues:

- Symptoms correlated to infant serum level at time of delivery: large for gestational age, hypotonia, feeding difficulties, depressed reflexes, cyanosis, apnea, bradycardia, hypothyroidism, diabetes insipidus.
- Floppy infant syndrome: lethargy, poor sucking, elevated respiratory rate, elevated heart rate, difficulty with temperature regulation, and hypotonia. Long-term development tends to be normal.
- Transient hypothyroidism requiring thyroid supplementation for the first few weeks to months of life.
- Case reports of breathing disorders, persistent pulmonary hypertension, atrial flutter, and seizures.
- Increased fetal growth parameters, including head and abdominal circumference, femur length, birth weight. It may be important to consider the risks posed to infants who are large for gestational age

such as shoulder dystocia, asphyxia, hypoglycemia, longer hospital stay, increased risk of obesity, and increased risk of cardiovascular disease when exposed to lithium in utero (Poels et al. 2021).

There are less well-defined side effects for infants exposed to lithium via breastmilk. The transfer of lithium can be significant but varies based on the dose relative to maternal weight (0–30%). Case reports have demonstrated episodes of cyanosis, cardiac murmur, T-wave inversion, hypothermia, hypotonia, lethargy, tremor, and increased TSH. Research suggests that the effects are transient and resolve with discontinuation of breastfeeding and increased age of the infant (Imaz et al. 2019). According to a 2021 safety scoring system, lithium has a low safety profile and use during lactation is possible with caution.

In clinical practice, a physician should have a "risk-risk" discussion with the patient when deciding whether to use lithium while pregnant and/or breastfeeding. Discussions should include risk to the fetus and risk of relapse. Lithium is more effective than no lithium in preventing postpartum relapse and the number needed to treat (to prevent relapse=3) is lower than the number needed to harm (risk of any congenital anomaly at any time during pregnancy=33) (Fornaro et al. 2020). Risks to include in discussion of lithium use in pregnancy include risk of recurrence, the consequence of recurrence, and the possible effects on the developing fetus and baby (Hermann et al. 2019). If a mother decides to use lithium during pregnancy, the risk of adverse effects can be reduced by monitoring symptoms and blood lithium levels, stressing medication adherence, screening for fetal cardiogenic malformations and planning NICU involvement proactively, protecting maternal sleep especially in the postpartum period, reducing maternal stress, and ensuring adequate social support (Hermann et a, 2020).

Anticonvulsants

Carbamazepine [26, 90-95, 142, 166-170, 175]

Carbamazepine induces P450 enzymes which can lower the effectiveness of hormonal contraception.

During pregnancy, carbamazepine crosses the placenta, and fetal serum concentration tends to be 50–80% of maternal serum concentration. During the third trimester, the maternal serum concentration decreases significantly, so dosing adjustments may be necessary.

In the 1980s, a carbamazepine syndrome was proposed which included epicanthus, upward slanting eyes, short nose, elongated philtrum, hypoplasia of the distal phalanges, microcephaly, and developmental delay; however, subsequent larger studies have failed to confirm that this pattern of defects is associated with carbamazepine use during pregnancy. Malformations appear to be dose-dependent. The current estimated rate of major malformations is 3.4% with a daily dose less than 400 mg, 5.3% for daily doses 400–1000 mg, and 8.7% for daily doses above 1000 mg. There is an increased risk of neural tube defects which has been consistently seen but at different rates depending on the study (OR 2.6–5.0). Other defects which have been associated with carbamazepine include cleft palate, heart and limb defects, inguinal hernia, hypospadias, cholestatic hepatitis, and postnatal developmental delay. However, no defect is as reliably shown to be associated as neural tube defects. One study found even small levels of carbamazepine, such as those

consumed when eating produce irrigated with reclaimed wastewater, have the potential to impair morphogenesis of embryos. It is questionable whether carbamazepine is associated with increased risk of spontaneous abortion, as one case study reported spontaneous abortion in mother at 8 weeks 3 days gestation after acquiring TEN from carbamazepine initiation in early pregnancy.

A 2021 study found significant impairment in Sertoli cell function during late puberty in rats born to mothers given carbamazepine during pregnancy and lactation. A Swedish study found associations of carbamazepine exposure during pregnancy with increased risk of development of autism spectrum disorder or ADHD in children born 1996–2011 and followed for 3 years. Although there is no specific correlation between infant and maternal carbamazepine levels, research has shown mean infant carbamazepine serum levels to have reached 20% of maternal value. Exposure to carbamazepine during breastfeeding has demonstrated no adverse neurodevelopmental outcomes. There have been case reports published demonstrating infant seizures, poor sucking, sedation, and 3 cases of hepatic dysfunction, but in these cases, infants were exposed in utero to carbamazepine and/or carbamazepine was taken in combination with other medications. Thus, carbamazepine is not a reason to discontinue breastfeeding, but monitoring of the infant is recommended especially when carbamazepine is used in combination with other antiepileptic or psychotropic medications. According to a 2021 safety scoring system, carbamazepine has a moderate safety profile and use during lactation is possible.

Gabapentin [96-99, 171-172]

Published research on gabapentin is limited. Few studies have found increased risk of pregnancy complications such as increased risk of preterm birth, small for gestational age infant, and infant requiring NICU stay. In one population-based study, there was no association between preeclampsia and gabapentin use. A few cases of congenital malformations have been reported when gabapentin was taken in combination with other anticonvulsants, and a 2020 study found a possible increase in conotruncal defects. There have been cases reported of neonatal withdrawal symptoms with prolonged use of high doses.

Limited data shows no adverse effects for infants during breastfeeding. The average infant plasma concentration is 12% of the maternal plasma concentration and maternal doses of gabapentin up to 2.1 g daily produce relatively low levels in infant serum. However, monitoring of the infant especially in younger, exclusively breastfed infants, or when using in combination with other psychotropic meds, is recommended.

Lamotrigine [100-105, 142, 173-179]

Prior to pregnancy, it is important to be aware of the use of hormonal contraception because estrogen enhances the metabolism of lamotrigine via upregulation of hepatic glucuronidation. Dose adjustments may be needed when starting or stopping hormonal contraception.

Given the fact that lamotrigine metabolism is significantly affected by changes in estrogen levels, careful monitoring is required during pregnancy. During the first trimester, rising estrogen levels lead to decreased lamotrigine levels. After delivery, serum levels can increase by 154% due to decreasing estrogen. It is important to modify doses after delivery to reduce the chance of toxicity.

Data from pregnancy registers have not shown a statistically significant increase in the rates of major malformations or pregnancy complications, but case reports have been published demonstrating various

malformations, especially when the daily dose was greater than 200 mg. Research from Iran showed significantly decreased weight and height as well as increased anatomical anomalies in lamotrigine-exposed mouse fetuses, however further research is needed.

After birth, one case study reported a newborn with seizures attributed to lamotrigine withdrawal as infants can have a precipitous drop in serum levels. Studies from Europe have shown no association between lamotrigine use during pregnancy and hindrance of neuropsychological development, risk of ADHD development, or risk of autism spectrum disorder.

According to a 2021 safety scoring system, lamotrigine has a moderate safety profile and use during lactation is possible. Studies in breastfeeding have shown an average infant dose of 9% of the maternal dose, but transfer into breastmilk is highly variable between individuals. Limited data from case reports have reported episodes of apnea and cyanosis, intermittent skin rash, anemia, and elevated platelet levels and liver enzymes with high maternal doses. However, evidence is limited, and no major studies have demonstrated any issues.

Oxcarbazepine [26, 106-108, 142, 173, 180-182]

Similar to carbamazepine, oxcarbazepine induces P450 enzymes which can potentially lead to hormonal contraception failure. Risk of malformations is unclear—the largest study to date (393 infants) showed no increased risk, but a study utilizing pregnancy registry data found a slight increased risk (2.2% vs 1.1%) of major malformations.

According to a 2021 safety scoring system, oxcarbazepine has a low safety profile and use during lactation is possible with caution. Research is limited regarding breastfeeding. Levels in breastmilk are thought to be low. It is estimated that a fully breastfed infant receives between 1.5–1.7% of weight adjusted maternal dose of oxcarbazepine and its metabolite. The only adverse effect while breastfeeding was reported in a single case in which an infant developed increased excitability, irritably, limb shaking, and increased muscle tone 12 hours after delivery. This was thought to likely be a withdrawal reaction as the condition of the infant subsequently improved with continued breastfeeding.

Topiramate [26, 106, 109-112]

Prior to pregnancy, topiramate can induce liver enzymes and decrease the efficacy of hormonal contraceptives. During pregnancy, serum concentrations decrease 30–40% during the first and second trimester due to increased GFR and enzymatic induction, so dose adjustments are necessary throughout pregnancy and the postpartum period. Multiple studies reported free transport of topiramate over the placenta with umbilical cord to maternal serum ratios close to 1.

Studies have demonstrated the rate of major malformations to be about 4.6% (2.4% in controls). Malformations associated with topiramate use include oral clefts (OR 5.4), hypospadias, and limb defects. Malformations were reported both with topiramate use alone and when topiramate was a component of an antiepileptic medication regimen in early pregnancy. It has been hypothesized that pre-conception folate supplementation may reduce the risk of fetal malformation, but other studies have not found supportive evidence.

At birth, topiramate has been found to be associated with low birth weight (in 21% vs 4.9% of controls). One case report demonstrated seizures in siblings exposed to topiramate in utero. The seizures were thought to be triggered by hypocalcemia caused by adrenal hypofunction due to topiramate. Research on breastfeeding and topiramate continues to be limited and primarily reduced to case studies. The degree of exposure to topiramate during breastfeeding is much less than gestation, with findings of infant serum concentrations reaching only approximately 25% of the maternal serum level. Most infants reported in case studies have had no adverse effects. There is currently only one case with a reported adverse effect in which a breastfed infant of a mother taking 100 mg topiramate daily developed frequent watery foamy stools at 40 days of life which resolved when breastfeeding was stopped. Although additional research is needed at this time, breastfeeding should be supported in mothers consuming topiramate and no routine laboratory monitoring of topiramate levels in infants is warranted.

Valproic acid [26, 94, 104, 113-116, 142, 173, 183-184]

Prior to pregnancy, valproic acid is associated with polycystic ovarian syndrome, menstrual irregularities, and possibly infertility.

Umbilical cord levels of valproic acid have been found to be 1.7 times higher than maternal levels, likely caused by immaturity of fetal liver enzymes required to metabolize valproate. A multitude of malformations have been noted with exposure to valproic acid in utero. The overall occurrence rate is about 18% and can be even higher when valproic acid is taken in combination with other medications. A dose-response relationship has been noted: with a daily dose of <700 mg, the rate of malformations is 5.6%; with a dose of 700-1500 mg, the rate is 10.4%; and with a dose >1500 mg, the rate is 24.2%. If the mother has had a previous child with a valproic acid associated malformation, the risk for abnormalities in subsequent pregnancies increases to 50%. Other associated abnormalities include (rare abnormalities in italics):

- Neural tube: spina bifida, anencephaly
- Heart: ventricular septal defect, atrial septal defect, aortic stenosis, ductus arteriosus apertus, *anomaly of right pulmonary artery*
- Extremities: radial ray deficiency, polydactyly, cleft hand, overlapping toes, camptodactyly, *hypoplasia of ulna or tibia, missing fingers, oligodactyly*
- Urogenital tract: hypospadia, *renal hypoplasia, hydronephrosis, duplication of renal collecting system*
- CNS: *hydranencephaly, porencephaly, arachnoidal cysts, cerebral atrophy, partial agenesis of the corpus callosum or septum pellucidum, aplasia, lissencephaly, Dandy-Walker anomaly*
- Eyes: *bilateral cataracts, optical nerve hypoplasia, anomaly of lacrimal duct, microphthalmia, bilateral iris defect, corneal cloudiness*
- Respiratory: *tracheomalacia, lung hypoplasia, extensive laryngeal hypoplasia, abnormal lobe formation of right lung*
- Abdominal wall: *omphalocele*
- Skin: capillary hemangiomas, *aplasia cutis of scalp*

In addition to the major malformations, valproic acid has also been associated with fetal hypoxia, low Apgar scores, microcephaly, and decreased postnatal growth. Neonatal liver necrosis has been reported, as well as bleeding due to fibrinogen deficiency and disrupted platelet function. A 2019 study found valproate to exert placental-mediated effects on fetal development through downregulation of genes in placentas from early

human pregnancies. Some associations with lower IQ, delays in speech development, learning difficulties, abnormal behavior, and autistic features have been noted as well.

If valproic acid is necessary during pregnancy, it should be at the lowest dose possible, and the dose should be spread out over 2–4 doses throughout the day. To decrease the risk of neural tube defects, folic acid supplementation (45 mg daily) is recommended.

Breastfeeding while using valproic acid is considered safe as there is very low transfer into the breastmilk, only 1% of the maternal dose. Most case reports have shown no adverse reactions with valproate use alone and use of valproate does not seem to impact infant growth or development. One case of infant baldness and one case of petechiae, thrombocytopenia, anemia, and mild hematuria have been reported, although immune thrombocytopenic purpura could not be ruled out as the cause of these findings. Combination of valproate with other sedating anticonvulsants or psychotropic agents may result in infant sedation or withdrawal reactions. Overall, breastfeeding should be supported, but accumulation can theoretically occur in young infants. Therefore, monitoring of platelets and liver enzymes should be considered. According to a 2021 safety scoring system, valproate has a moderate safety profile and use during lactation is possible.

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PREGNANCY AND CHRONIC PSYCHOTIC DISORDERS

References: 1

Pereau's Notes:
Over the past decade, I have treated a large number of pregnant patients with a previous diagnosis of schizophrenia. Many of them required weeks or months of inpatient psychiatric treatment prior to stabilization and transition to a lower level of care. In these patients, risk versus benefit of psychotropic medications must be considered in a population who may not comprehend the informed consent process. Often, legal and ethical advisement is needed. Personally, I have only rarely seen psychotropic medications be able to completely clear psychosis in pregnant patients with schizophrenia. Instead, the psychosis has a tendency to persist until shortly after delivery. As a result, I tend to use more conservative dosing strategies with antipsychotic medications. For me, the goal is to keep the patient safe and stable until the baby can be delivered, and then further management can aim for remission of symptoms. I can think of many cases I have treated where the overall goal was ensuring that the patient was able to care for ADLs, remain in a safe environment with appropriate structure and monitoring, and have the least amount of medication side effects possible. I recall a conversation with a resident one morning, who was trying to understand why a schizophrenic woman in her 26th week of pregnancy did not need her haloperidol increased any further. "I'm not worried about her continued fixed delusion that she is King Soliman's wife," I started. "What matters to me is that she is eating, taking care of herself, able to process her illness and her need for medications, and is working toward a safe discharge plan." I knew that if we increased her haloperidol to 15 mg BID we would not only increase the risk of side effects, but the fetus would also be exposed to a higher medication concentration. I remain unconvinced that any amount of haloperidol would have completely removed her delusion. The patient was able to discharge to a board and care home where she had structured support until the delivery of a healthy child. A few weeks later, her delusion cleared without additional medication increase.

Patients with chronic psychotic disorders tend to have higher rates of unplanned pregnancy. They also have lower compliance with folic acid and increased use of alcohol, cigarettes, cannabis, and other substances. There is an increased risk of placental abnormalities (including placental abruption), antepartum hemorrhage, fetal distress, low birth weight, and cardiovascular congenital anomalies.

Antipsychotics

References: 2-13, 62

Overall, antipsychotics have not been widely studied in pregnancy. A small study found that at 6 months old, infants with intrauterine exposure to antipsychotics had poorer neuromotor performance (posture, reflexes, and muscle tone). Learning and information processing was unaffected (Johnson et al. 2012).

Chronic administration of antipsychotic medications during the 3rd trimester can cause neonatal symptoms including dyskinesia, hypertonicity/hypotonicity, agitation, excessive crying, irritability, restlessness, sedation, hypotension, tachycardia, difficulty breathing, feeding difficulty, and functional bowel obstruction. EPS symptoms were seen more commonly with typical antipsychotics compared to atypical antipsychotics. Neonatal symptoms have been seen in around 21% of exposed neonates. The symptoms typically last hours to days, although there have been documented cases of EPS symptoms persisting several months after birth.

Typical Antipsychotics (1st Generation)

Many typical antipsychotics have been used for decades for treatment of hyperemesis in early pregnancy and have been shown to be safe. However, research on pregnant patients utilizing the higher doses typically needed for treating psychiatric conditions is limited. A meta-analysis completed in 1996 (>25,000 patients) found a small increase in the rate of congenital malformations (OR 1.2). Individual studies have demonstrated mixed results; some show no increased risk, some show an increased incidence (OR 1.52) of cardiac defects (ASD/VSD).

An increased risk of preterm birth (OR 1.7) has been demonstrated with atypical antipsychotic use. Infants exposed in utero to typical antipsychotics weighed less on average than infants exposed to atypical or non-antipsychotic medications and had an increased risk of being small for gestational age.

Prior to pregnancy, typical antipsychotics may interfere with fertility by increasing prolactin, which can interfere with ovulation.

Chlorpromazine [11, 13, 25, 57]

Chlorpromazine can be used to treat nausea in pregnancy at lower doses (10–25 mg q6h). Several small studies (<500 women) with first trimester exposure showed no adverse effects. However, case reports of three infants who developed respiratory distress and subsequent death after they were exposed in utero to high doses (500–600 mg/day) have been published. Case reports of transient neonatal symptoms including jaundice, hypertonicity, lethargy, and EPS have been published as well.

According to a 2021 safety scoring system, chlorpromazine has a moderate safety profile and use during lactation is possible. Chlorpromazine is detectable in the milk of some mothers during therapy, but levels appear not to correlate well with the maternal dose or serum level. Studies show that breastfed infants can become drowsy during maternal chlorpromazine therapy. In addition, therapy can negatively affect development in a breastfeeding infant, especially if the mother is using dual therapy with haloperidol.

Fluphenazine[30]

There is no published data on fluphenazine during breastfeeding. Very limited long-term follow-up data indicate no adverse developmental effects when other phenothiazines are used alone. Because of the lack of published evidence of this medication's effects on the breastfeeding infant, other antipsychotic medications may be preferred.

Haloperidol [17, 19. 24. 25, 57, 63, 66]

Haloperidol exposure has been studied in pregnant women using it as an antipsychotic as well as to treat hyperemesis gravidarum. Placental passage is about 66%. Multiple studies have not shown an increased risk of congenital malformations. However, women with schizophrenia who took antipsychotics (including haloperidol), had an increased risk for preterm birth (aOR 2.46) compared to women with schizophrenia not exposed to antipsychotics.

A study of over 200 patients taking haloperidol or penluridol (a drug similar to Haldol used in Europe) during pregnancy showed 2 cases of limb defects in the exposed group and none in the control. Although the results are not statistically significant, the authors of the study caution that an association between in-utero butyrophenone exposure and limb defects cannot be ruled out.

According to a 2021 safety scoring system, haloperidol has a low safety profile and use during lactation is possible with caution. The infant should be monitored for drowsiness and developmental abnormalities. There have been limited studies on haloperidol use during breastfeeding, but evidence suggests that a maternal dose of 10 mg/day is associated with low levels in milk and is unlikely to affect the breastfed infant. Case studies indicate that there are no adverse developmental outcomes in infants when followed up to 18 months of age. However, when haloperidol is used with another antipsychotic drug, it can negatively affect the infant. In one case, a breastfeeding mother with a history of schizophrenia who was on risperidone 1.5 mg/day plus haloperidol that was titrated up to 1.5 mg/day experienced significant improvement in her psychotic symptoms of reference, persecution delusions, anxiety, and irritability. However, the infant experienced hypersomnia, poor feeding, and slowed motor movements. After discontinuing breastfeeding, the symptoms completely resolved within 5 days.

Promethazine [21, 27, 43, 47-52]

Promethazine is a phenothiazine derivative, as is chlorpromazine, and has antihistaminergic, anticholinergic, and antidopaminergic activity. It is the most common antihistamine taken during pregnancy and is used for nausea and vomiting during early pregnancy. One study found that it is no better than metoclopramide for its antiemetic effects and has a higher risk of adverse effects such as dry mouth, dizziness, drowsiness, and dystonia.

The National Birth Defects Prevention Study found that promethazine exposure during pregnancy was associated with tetralogy of Fallot and craniosynostosis. The same analysis did not find significant associations between oral cleft lip and/or palate and promethazine, contrary to a case-control study that had reported a higher risk in mothers exposed during 2nd and 3rd trimester.

There are no available studies on levels of promethazine in maternal or infant serum or effects in the breastfeeding infant. However, studies show that it may reduce the levels of prolactin and interfere with lactation if given early postpartum.

Thioridazine [9, 17, 44-46]

There are few studies on thioridazine during pregnancy. Use during pregnancy may be associated with extrapyramidal symptoms in the neonate for up to 12 months, as seen in a case of two siblings born to a mother with schizophrenia who had taken thioridazine, chlorpromazine, and trifluoperazine at various stages of pregnancy. Both siblings had subsequent cessation of symptoms and normal development. One case of

cardiac malformations (transposition of great vessels with patent foramen ovale) was discovered in an infant born to a mother given thioridazine and trifluoperazine before conception and during pregnancy.

Since there are no published studies on thioridazine during breastfeeding, an alternate drug may be recommended during lactation. Phenothiazine can increase prolactin levels higher than other phenothiazines; however, it may not affect a mother's breastfeeding if she has established lactation.

Atypical Antipsychotics (2nd Generation)

References: 68

Atypical antipsychotics, especially clozapine and olanzapine, are notorious for causing weight gain, elevated lipids, and metabolic syndrome. Overweight and obese women are at an increased risk of pregnancy complications including gestational DM and HTN, preeclampsia, surgical delivery, postpartum weight retention, congenital anomalies, stillbirth, preterm birth, macrosomia, anesthesia difficulties, and childhood obesity.

If an atypical antipsychotic is used, maternal weight gain and glucose tolerance needs to be carefully monitored. Women who use atypical antipsychotics are at higher risk for diabetes during pregnancy (OR 1.77 for olanzapine and clozapine, OR 1.5 for all antipsychotics).

Changes in liver metabolism during pregnancy can lead to decreased serum levels for medications metabolized by 2D6 (risperidone, aripiprazole, and iloperidone) and 3A4 (quetiapine), but increased levels of medications metabolized by 1A2 (clozapine and olanzapine).

A cohort study of 561 women exposed to atypical antipsychotics found an increased risk of congenital cardiac anomalies (OR 2.17). The authors of this study caution that there may be detection bias for ASD/VSD (OR 3 for ASV/VSD only) as they were specifically screening for cardiac defects and likely identified some which otherwise would have been clinically insignificant. The National Birth Defects Prevention Study did not observe cardiac septal defects but did find association between early pregnancy atypical antipsychotic exposure and conotruncal defects, cleft palate, anorectal atresia/stenosis, and gastroschisis.

Some, but not all, studies found an association between atypical antipsychotic use and increased birth weight and being large for gestational age. However, another study found an association with low birth weight.

Post-natal adaptation symptoms were found in 15.6% of infants exposed to atypical antipsychotics. Symptoms include agitation, increased or decreased muscle tone, respiratory difficulties, and feeding problems. Most cases were mild and lasted only a few days, although in a few cases symptoms lasted up to a few months. Authors of these studies note that similar effects can be seen with psychotic illness alone.

Aripiprazole [5, 14-15, 31-33, 53-57]

Limited studies published on aripiprazole exposure during pregnancy suggest that it is not likely associated with risk of malformations. Thus far, no placebo-controlled trials have been conducted. Nevertheless, data suggests that the benefits of aripiprazole outweigh the risks for use during pregnancy.

According to a 2021 safety scoring system, aripiprazole has a very low safety profile and use during lactation is not recommended. Because aripiprazole is a dopamine partial agonist, it can decrease prolactin during lactation, leading to problems with breastfeeding and infant bonding. A shared-decision making model should be used when discussing use of aripiprazole postpartum. Maternal doses of aripiprazole up to 15 mg/day can transfer into breastmilk, but thus far there is no data on its effects on the infant. Until more studies are produced, an alternate drug may be recommended.

Clozapine [3, 11, 16-18, 36-37, 57-61, 63]

There is limited evidence to show that clozapine has an adverse effect on maternal and fetal health after clozapine is continued after pregnancy is confirmed. It is not shown to be less safe than other antipsychotics. Data from 400 pregnancies (across several studies) has not demonstrated increased incidence of congenital anomalies. Manufacturer data from 523 reports of use in pregnancy found congenital anomalies in 4% with no pattern of defects, which is not significantly above population baseline. Nonetheless, a discussion of risks and benefits are recommended, and mother and fetus should be closely monitored if it is to be continued. The risk of gestational diabetes doubles with use of clozapine. Cases of newborn sedation, jitteriness, floppy-infant syndrome, and seizures have been reported.

According to a 2021 safety scoring system, clozapine has a very low safety profile and use during lactation is not recommended. There is little published evidence on clozapine use during breastfeeding, but some studies have shown that sedation and adverse hematologic effects in breastfed infants. Other cases have not shown any neurodevelopmental disorders or hematologic reactions in infants. Thus, breastfeeding is not recommended, but if it is to continue, the infant should be monitored closely for sedation and agranulocytosis.

Olanzapine [2, 20, 38, 53, 57, 62, 63, 66]

Placental passage of olanzapine is approximately 72%. Studies have shown that olanzapine exposure is not associated with increased risk of congenital malformations. The risk of obesity, gestational diabetes, and increased birth weight are increased with olanzapine use. Cases of neonatal sedation, persistent jaundice, and seizures have been reported.

According to the 2021 safety scoring system, olanzapine has a good safety profile and use during lactation is acceptable. Maternal doses up to 20 mg/day produced undetectable levels in infant serum. Reports show that there were minimal adverse effects and development was normal long-term in breastfed infants, with some reports of drowsiness or somnolence. Olanzapine has minimal effect on prolactin levels and should not affect lactation after it has been established.

Quetiapine [5, 11, 39-41, 57, 62, 63, 67]

Placental passage of quetiapine is approximately 24%. It is the most prescribed atypical antipsychotic among pregnant women. Studies show that quetiapine use during pregnancy is not associated with malformations. During pregnancy, doses should be increased at least 2.5 times baseline during the 2nd–3rd trimester due to increased metabolic clearance, increased circulating volume, and decreased plasma protein binding.

According to a 2021 safety scoring system, quetiapine has a moderate safety profile and use during lactation is possible. Maternal doses up to 400 mg/day produced low levels in milk. No adverse effects were reported in breastfed infants, and development was normal when followed up to several months. A safe breastfeeding strategy includes a QHS medication regimen and discarding of pumped breastmilk for the following 8 hours. Quetiapine has minimal effect on prolactin levels and should not affect lactation after it has been established.

Risperidone [22, 42, 53, 54, 57, 62, 63]

Placental passage of risperidone is approximately 49%. There is mixed evidenced on whether risperidone increases the risk of birth defects. Some studies have shown that risperidone exposure increases risk for congenital malformations, cardiac malformations, gastrointestinal malformations. Other studies show that the risk of congenital malformation was not higher than baseline.

According to a 2021 safety scoring system, risperidone has a low safety profile and use during lactation is possible with caution. Maternal doses up to 6 mg/day produces low levels in milk. Limited data shows that there was no adverse effects in breastfed infants and develop was normal long-term up to 16 months of age. In one case, a breastfeeding mother with a history of schizophrenia who was on risperidone 1.5 mg/day plus haloperidol that was titrated up to 1.5 mg/day experienced significant improvement in her psychotic symptoms of reference, persecution delusions, anxiety, and irritability. However, the infant experienced hypersomnia, poor feeding, slowed motor movements. After discontinuing breastfeeding, the symptoms completely resolved within 5 days.

Ziprasidone [5, 23, 54, 57, 62, 63, 68]

Multiple studies of ziprasidone exposure during pregnancy did not find any association with increased congenital or cardiac malformations. However, a single case report of cleft palate associated with ziprasidone exposure has been reported.

According to a 2021 safety scoring system, ziprasidone has a low safety profile and use during lactation is possible with caution. There is little published evidence on ziprasidone during breastfeeding, thus another antipsychotic may be preferred or breastfed infants should be monitored for sedation, irritability, poor feeding, and extrapyramidal symptoms. Ziprasidone may cause elevation in prolactin levels but should not affect breastfeeding if lactation has been established.

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INSOMNIA IN PREGNANCY

References: 1-10

Sleep disturbance and poor sleep quality is very common in pregnancy and occurs in about 76% of pregnant women, insomnia occurs in about 57%, and sleep-disordered breathing occurs in about 19%. Restless leg syndrome has also been reported. Not all sleep disturbance requires treatment. In a study of 127 pregnant women, 97% reported disrupted sleep, but only one-third identified themselves as having a sleep disorder. Pregnancy-related symptoms can often contribute to insomnia. These include frequent urination (83% occurrence) and difficulty finding a comfortable sleep position (79%). Insomnia tends to become more frequent and severe during the 3rd trimester and can worsen right before labor due to the effects of oxytocin.

Pregnancy Recommendations

Any patient with a chief complaint of insomnia needs to be screened for anxiety and mood disorders. Obese patients or patients with rapid weight gain who begin having disturbed sleep should be screened for sleep apnea. Once those disorders are ruled out, education about sleep hygiene and behavioral interventions are first-line therapies. CBT has also been shown to be beneficial.

If medications are needed, trazodone is considered safe and may be used in patients who struggle with more than just intermittent insomnia. Zolpidem and other similar benzo-receptor agonists are also considered safe. Short term use of a short-acting benzodiazepine may be safe and may be used if absolutely necessary, although a review in the American Journal of Obstetrics and Gynecology (Okun et al. 2015) recommends using benzodiazepine-receptor agonists over a benzodiazepine. Antihistamines are also safe alternatives. See other sections for more information on benzodiazepines, benzodiazepine receptor agonists, antihistamines, and trazodone.

Although no human studies have been published on the use of melatonin in pregnancy, there is a concern that it may interfere with postnatal development of circadian rhythms.

Lactation Recommendations

Due to the necessity of arranging overnight infant care during treatment, management of insomnia in the postpartum period may be complicated. Diphenhydramine may be used as a first-line treatment. Intermittent doses of zopiclone are also well tolerated.

With any sedative medication, infants must be monitored for sedation, weak suckling, and restlessness.

Valerian, an herbal supplement (in a preparation without alcohol) has been suggested as a potential alternative. However, it is not very well studied.

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A CASE FOR ECT IN PREGNANCY

References: 1-3

Over the past 50 years, the safety of ECT in pregnancy has been well documented. Indications include severe depression, suicidality, catatonia, mania, agitated psychosis, and medication-resistant illness. Rates of miscarriage with ECT are no different than the general population. There is no association of ECT with congenital malformations, and the risk of preterm labor is minimal to none. ECT is cited by many articles as "under-utilized" and is considered safe in pregnancy, especially when considering the risks of untreated severe mental illness. Ward et al. proposed a thorough clinical protocol for ECT in pregnancy that is well worth the review.

Pereau's Notes:
I don't think I will ever forget the wild look in her eyes. I imagine if I had a fixed delusion that my left hand belonged to a homeless man and would come alive while I slept to strangle me, I would look exhausted and terrified most of the time as well. Her attempts to cut off her left had had nearly been successful—twice. The orthopedic surgeons did the best they could to repair a hand which had practically been severed, with all of the tendons mangled in the process. The result was a frozen and useless hand, even more the representation of something foreign and alien to this woman. Prior to the pregnancy, Irene had been a high school guidance counselor with no previous psychiatric history. When depression set in during the first trimester, her psychiatrist started bupropion, which is categorized as Pregnancy Class B and was considered safe. The psychosis started within the first few weeks on the medication. I don't know if it was the combination of the

medication and the pregnancy, but I can say that I have now seen 3 cases of psychosis after initiating bupropion in pregnancy. Each of these patients was admitted to the inpatient psychiatric hospital for psychosis. Irene's case was definitely the most heartbreaking. Even after the bupropion stopped, she remained paranoid and fearful. The fixed delusion did not clear, and she continued to display severe symptoms of depression. Despite multiple hospitalizations and countless medication trials including lithium and haloperidol, the patient never returned to her baseline. By the end of her second trimester, she remained fixated on wanting to cut her hand off. My colleague and I both recommended ECT to the patient and her family. For a number of reasons, the patient's spouse did not feel comfortable with this option. He decided to take time off work to stay home and monitor Irene. The family felt that if they could just get her through the last leg of the pregnancy, she would clear and return to normal. The family requested to take the patient home with them. We reluctantly agreed as the patient was not agreeable to continuing to stay in the hospital voluntarily. About six weeks later, a charge nurse came up to me. "Did you hear about Irene?" she asked. As a psychiatrist, this is generally not a question you ever want to hear. Within a month of leaving the hospital, my patient had gotten up in the middle of the night and walked onto the freeway. She was hit by a car and both she and the baby were killed. This was one of the most tragic moments of my career. The helplessness I felt in that moment is indescribable. The only thought in my mind, even to this day, is, "If only she could have been treated with ECT."

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TRANSCRANIAL MAGNETIC STIMULATION

References: 1-4

Transcranial magnetic stimulation (TMS) is a technology approved by the FDA for the treatment of major depressive disorder. It works by using an electromagnetic coil placed against the scalp to generate magnetic fields which stimulate nerve cells in the brain in regions associated with depression, such as the dorsolateral prefrontal cortex. Treatment regimens often include multiple sessions over the course of several weeks. Many studies show its efficacy in medication-refractory MDD, but there is limited research exploring its use specifically in the postpartum period. There is evidence that post-partum depression as a psychiatric illness differs in ways that disallow generalization of results from TMS on all patients with MDD to patients with PPD.

Current research on TMS use for PPD has shown promising results. Most studies have shown a general reduction in PPD symptoms during treatment and either remission or reduction of symptoms months later. Only one study has shown a lesser response to treatment in which only 27% of participants receiving TMS

had a decrease in depression scale scores by the end of the treatment. In addition, treatment of longer duration (7-10 weeks) has proven more efficacious than treatment of 3–4 weeks duration. Most studies have also shown significant improvement in social-relational outcomes, including parental bonding. Remarkably, in one case report, after undergoing TMS treatment, one mother went from attempting infanticide to sharing a close relationship with her child two months later. Although one study reported reductions in cognitive performance for mothers receiving active TMS compared to sham TMS treatment (control), these reductions were not statistically significant. Finally, compared to its counterpart ECT in the treatment of refractory postpartum depression, TMS is less invasive (no anesthesia, no seizure induction) and has fewer side effects (no amnesia). The most common reported side effects to include scalp discomfort and headache. Additionally, research to date has shown no disruption in breastfeeding practices. However, like ECT, TMS remains a time-consuming process and can be relatively inconvenient for mothers in the postpartum period.

Despite the apparent efficacy of TMS in the treatment of PPD, the results stem from case reports and case series which were not blind, had a potential bias, and were composed of small sample sizes. Thus, further research is needed to provide strong support for the findings reported in the current literature.

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ADHD IN PREGNANCY

References: 1-12

ADHD is the most common neurodevelopmental disorder. In 2017, a study reported the prevalence of ADHD in adult patients worldwide was 3% and this number has likely increased since then (Kittel-Schneider et al. 2021). From family, twin, and adoption studies, the heritability of ADHD is estimated to range from 74–80%, higher than any other psychiatric disease (Faraone et al. 2019, Grimm et al. 2020). ADHD can present with inattentiveness, hyperactivity, or impulsivity. Women frequently present with the inattentive type and struggle with concentration, organization, and memory (Rucklidge et al. 2010). Diagnoses in women can be missed due to attributing ADHD characteristics to one's personality. Examples include describing one as "a dreamer or a spacy, forgetful, or chatty" person (Quinn et al. 2014). Others with ADHD who display symptoms of depression and anxiety may be misdiagnosed with other psychiatric illnesses (Young et al. 2020). Perhaps unsurprisingly, the inattention and impulsivity symptoms of ADHD in pregnant women are significant predictors of impairments In professional life, relationships, and daily life (Eddy et al. 2019).

ADHD symptoms in mothers can continue to affect children. Although mothers with ADHD have been found to show more warmth toward their children, ADHD in mothers is linked to increased parental stress in addition to more frequent lax and overreacting parenting styles (Chronis-Tuscano et al. 2013). Increased ADHD symptoms in mothers is associated with increased ADHD symptoms and decreased quality of life in

both children with and without ADHD. In children without ADHD, increased maternal ADHD symptoms were associated with poorer emotional and social functioning (Efron et al. 2018).

In teenage girls, ADHD is a significant risk factor for adolescent pregnancies (Meinzer et al. 2020). In some studies, maternal ADHD is associated with pregnancy and birth complications such as preeclampsia, infection, increased c-section rate, NICU utilization rate, and preterm birth (Kittel-Schneider et al. 2021). Little research exists on the effects maternal ADHD itself has on pregnancy and breastfeeding. Most research focuses on the implications ADHD medication has on pregnancy, infants, and breastfeeding. Further research is needed. To our knowledge, no research has studied lactation practices in mothers with ADHD independent of ADHD medication use.

General Recommendations

1. Consider ADHD diagnosis in women with depression, anxiety, or certain personality types that can be confused with ADHD
2. Provide teen females with ADHD contraception education
3. Provide support and education in parenting skills for mothers or soon to be mothers with ADHD
4. Use risk-benefit discussion when for ADHD meds during pregnancy and while breastfeeding.

ADHD Medications

ADHD medications cross the placenta rapidly. Research suggests the overall risk for adverse outcomes is relatively low. In one study, intrauterine exposure to ADHD medication was not associated with increased risk of ADHD in children (Lemelin et al. 2021) or adverse maternal or neonatal outcomes (Jiang et al. 2019, Li et al. 2020). When ADHD is severe, researchers suggest ADHD medication can often be continued during pregnancy, but further research for ADHD of lesser severity is needed.

Amphetamines [12-15]

Research regarding controlled prescribed amphetamine use during pregnancy is limited. Thus far, two studies have shown no association of amphetamine use and risk of congenital malformations, cardiovascular malformations, or placental abruptions. Single studies have shown no significant association with CNS disorders, SGA, birth weight, or low APGAR scores. It is currently debated whether there is an increased risk of preeclampsia.

While breastfeeding at 2, 5, and 9 weeks postpartum, one study found infant serum levels of amphetamines to be 15%, 7%, and 5% of simultaneous maternal serum concentrations. When using the appropriate prescribed dose, there is currently little evidence to suggest a negative impact on infants while breastfeeding. However, in those using large doses, limited research has shown possible difficulties in lactation initiation. Research on IV amphetamine use has showed mothers using amphetamines to be less likely to be breastfeeding at discharge than mothers who used other drugs. However further research on prescribed amphetamines for ADHD and their impact on breastfeeding is needed.

Atomoxetine [14, 15-17]

Psychostimulant use during pregnancy was associated with a small increased risk for preeclampsia and preterm birth. Absolute increases in risk are small, and therefore women with significant ADHD or other medical needs should be counseled before they suspend their ADHD treatment.

Atomoxetine was given to 453 patients during the first 140 days of gestation and compared to a primary reference group who were not given ADHD medications from 90 days before LMP and 140 days after LMP (n=1,461,493). Unexposed women had a risk of 3.7% for preeclampsia, 1.4% for placental abruption, 2.9% for SGA, and 11.2% for preterm birth. Atomoxetine use was not associated with an increased risk of the adverse pregnancy outcomes studied.

Eight cohort studies used to compare ADHD medications exposure during pregnancy and further adverse pregnancy related outcomes show that the data is too limited to make an unequivocal recommendation regarding the use of ADHD medications. Therefore, physicians should weigh risks vs advantages of using ADHD medications according to the situation of each particular woman.

One study from 2017 showed atomoxetine use during pregnancy in mothers with ADHD to have no association with risk of preeclampsia, placental abruption, preterm birth, or small for gestational age infant.

Bupropion

(See Atypical Antidepressants section)

Guanfacine [18-20]

There has been no research published on guanfacine use in pregnancy. A single study from 1980 studying guanfacine to lower blood pressure in pregnant women with preeclampsia showed that 6/30 infants born were small for gestational age but all developed normally afterward. The low birth weight was most likely secondary to the mother's preeclampsia. Another study showed prolactin levels was reduced in men and non-pregnant women taking guanfacine. However, it is still unclear how medication induced changes in prolactin affect breastfeeding practices if at all.

Methylphenidate [15, 21-22]

With methylphenidate use during pregnancy, there is no evidence of increased risk for congenital malformations or CNS disorders in the fetus. Limited evidence suggests increased incidence of abortions and miscarriages. There is conflicting evidence about the increased risk of cardiovascular malformations, but risk has been identified significant in at least 3 of 5 studies.

It is estimated infants receive between 0.2–0.7% of the maternal weight-adjusted dose when breastfeeding although there are 3 cases of not being found in infant serum. The effects of methylphenidate in milk on neurological development are unknown. Previous research has shown decreased prolactin levels in patients taking methylphenidate, but it is currently unknown how this affects breastfeeding practices. Although further research is needed, methylphenidate use is not a reason to discontinue breastfeeding.

Modafinil [23-25]

Most studies known to date have shown modafinil use to be significantly associated with congenital malformations. In a 2021 study published in *JAMA*, pregnancy and fetal outcomes were explored in mothers using modafinil and armodafinil during pregnancy. Those using modafinil or armodafinil had a rate of 13% congenital malformations compared to 3% in the general population. Of the 13%, there were 4 reports of

torticollis, 2 of hypospadias, and 3 of congenital heart defects. Overall, the cardiac malformation rate was 3% compared to 1% in the general population.

Only one study has investigated infant exposure to modafinil through breastmilk, estimating infant dose to be 5.3% of maternal dose. Minimal research has shown no adverse effects in infants. If used while breastfeeding it is recommended to be used carefully, with monitoring or not used at all until further research is conducted.

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