Psychopharmacology:
The Basics and Beyond

Part I

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Presentation Objectives

- Increase neuroscientific knowledge about brain functioning
- Understand the neurobiological basis for psychiatric disorders and challenging behaviors to help reduce stigmatization
- Comprehend key terms and rationale associated with prescribing
- Understand concepts related to psychotropic metabolization
- Begin to differentiate between psychotropics, starting with antidepressant medications

Test your Knowledge!

TRUE OR FALSE QUIZ

1. ***One out of three people respond to antidepressants.***

2. ***The cause of schizophrenia is generally known.***

3. ***Mood disorders are perhaps a combination of diseases.***

4. ***Medications work by disturbing the natural chemistry in the brain.***

5. ***1 of every 5 prescriptions of anti-psychotic medications is off-label use.***

TRUE OR FALSE QUIZ

6. *50-percent of individual's chance of developing a substance abuse problem is genetic predisposition, rather than inherited traits.*

7. *In addition to alcohol, methamphetamines can be the most addictive.*

8. *To date, the eras of mental health treatment have include asylums, psychodynamic, and psychopharmacologic.*

9. *About 30% of people do not know important details about their treatment.*

10. *Americans spend more on medicines than all the people of Japan, Germany, Italy, and France, combined.*

Bonus Question:

What is the best psychotropic medication to treat an individual diagnosed with developmental disabilities?

- **Psychotropic treatment should proceed as it would for an individual without developmental disabilities.**
- ***Although it can be challenging, particularly in the context of limited verbal abilities, optimal medication selection should always begin by establishing an accurate psychiatric diagnosis!***
- ***Appreciate the need to avoid a broad-brush approach and look at the idiosyncratic dynamics!***

Pharmacoepidemiology

- The first proponent of organic causes to mental illness was Hippocrates.
- Europeans with a health problem often go first to the pharmacy, not to their physician, as pharmacists often diagnose and prescribe remedies.
- In the 1950s, Donald Klein, an American psychiatrist with a background in biology, brought a new rigor to the study of whether some psychiatric problems might have a biological basis that could be treated with drugs. Thereby establishing the field of psychopharmacology.
- The initial psychotropics were Librium and Valium.

Basic Terminology

All medications are drugs,
but not all drugs are medications…

- **Medications or medicines are taken to treat medical conditions.**
- **Drugs are taken for reasons other than treating health issues. Examples are caffeine and nicotine.**

Basic Terminology

- *Illnesses have symptomatology with predictable courses (i.e., states)*
- *Disorders are a system malfunction with characteristics (i.e., traits)*
- *Incidence (new cases) versus Prevalence (existing cases)*
  - *For example, prevalence in the general population:*

psychosis 1%; mental health disorder 5%, personality disorder 15%

Basic Terminology

Psychotropic, Psychoactive, and Psychopharmaceutical are classes of drugs capable of effecting the mind

- **"Psycho" relating to the mind or brain**
- **"Tropic" means to be attracted to or turn toward**
- **Contemporary definition is "mind-nourishing"**
- **Psychotropics describes a small group of medicines intended to treat brain illnesses or mental health disorders.**

Basic Terminology

- **Psychoactive and psychotropic are essentially synonymous terms.** ***A chemical substance that crosses the blood-brain barrier, acts on the central nervous system, and affects consciousness, cognition, mood, and behavior.***

- **The only difference between the two is the working time wherein psychoactives have greater therapeutic utility because they work in 20 to 30 minutes (e.g., anesthetics and analgesics).**

- ***All psychoactives are psychotropics (umbrella term)***

- ***Using the term psychotropic is always correct.***

- ***What are the most common psychoactive drugs?***

Basic Terminology

It's all in the name…

- **Chemical Name: The description for synthesizing used by an organic chemist (e.g., 7-chloro-1,3-dyhydro-1methyl-5-phenyl-2H-1,4-benzodiazepine-2-one)**
- **Street Name: Benzo, Downer, Blue**
- **Generic Name: diazepam (not capitalized)**
- **Brand Name: Valium**

Basic Terminology

Psychopharmacological Error:

- **Any preventable event that may lead to inappropriate use or harm while the medication is in the control of the healthcare professional or client.**

Side Effects (Negative and Positive):

- **An undesired tilting of the body's homeostatic balance and the system's response to self-correct.**

- **Pasteur discovered that drugs have a left and right sides of their molecular structure. The left does what we want and the right causes the side effects, which are often only later apparent. *The medication name often alludes to the particular side!***

- **The basic mechanisms involved in generating the side effects are often the same as those involved in the therapeutic benefits.**

Basic Terminology

Adverse Drug Reactions (ADR):

- A harmful occurrence (e.g., toxicity, anaphylaxis, anemia) that stems from a medicine that is given at the correct dose (either single administration or prolonged delivery).

- Type A reactions are predictable

- Type B reactions are idiosyncratic, bizarre, or novel

Adverse Events versus Side Effects

- Incorrectly used interchangeably; they mean separate things

- ADRs are never desired and require prompt interventions

- Most negative side effects (e.g., upset stomach) spontaneously resolve over time

- Some medications are utilized for their side effects (e.g., Mirtazapine used in elderly or anorexic patients due to the potential to stimulate appetite and cause weight gain)

Basic Terminology

- **Medication Errors: Common causes are poor interdisciplinary consultation, "medication shopping," communication problems, provider knowledge deficits, and inadequate monitoring.**

- **The difference between an adverse drug reaction and a significant medical error may only be a matter of degrees (e.g., dosage)**

- **Black Box Warning: The strictest warning put on a prescription drug label by the FDA when there is reasonable evidence from research studies to indicate the potential of serious health hazards.**
  - **Antidepressants: Suicidality**
  - **Stimulants: Drug dependence**
  - **Atypical Antipsychotics: Mortality; Dementia**

Potentially-Inappropriate Prescribing: Poorly Researched Area

Basic Terminology

- **Medication Wash: Discontinuation of all medications**
- **Drug Holiday: "Creative Non-Adherence" (i.e., Taking the weekend off)**
- **Non-Adherence: 73% is intentional, rather than accidental (e.g., reducing dosage, doubling pills, giving medications away)**
- ***While both medication washes and drug holidays allow brain receptors to reset, these practices are shunned by pharmaceutical companies.***
- ***All medications potentially stop working because the body seeks homeostasis.***
- ***Changes should always be made in isolation (i.e., one at a time)***

Basic Terminology

Off-Label Prescribing: "Clinical Innovation"

- **Prescribing a medication for something not indicated by the FDA.**
- **Safety concerns (e.g., age, dosage, route of administration)**
- **Common (about 30%) but controversial**

Placebo Effect versus Nocebo Effect

- **Antonyms about psychological expectations to heal versus harm**
- **Based on the desire to please**
- **Thinking an inert medicine has a positive effect (placebo) or negative effect (nocebo)**

How can you tell if it's placebo effect?

Prodrug: Medication converted from pharmacologically inactive to active within the body (e.g., liver). It improves bioavailability and reduces unintended side effects, as it selects how the drug interacts.

Iatrogenic Effects: Illness caused by the treatment (e.g., opioid epidemic)

Valid Reasons to Prescribe Psychotropics:

- Treating a clearly diagnosed psychiatric disorder
- For medical conditions with secondary psychiatric features
- When challenging behavior is resistant to environmental interventions and continues to interfere with functioning
- To treat discontinuation symptoms
- Sedation for medical procedures

Questionable Uses of Psychotropics:

- No re-examination of original rationale
- Lack of evidence for continued usage
- Inadequate assessment
- Haphazard prescribing *(the ADHD example)*
- For the convenience of caregivers
- Ignoring the function of behavior
- Pathologizing life events (e.g., grief)
- Limiting autonomy
- To silence complaints
- Exceeding therapeutic range
- Substituting for appropriate supports

Basic Terminology

Polypharmacy

- **Greek words for "poly" (more than one) plus "pharmacon" (drug)**
- **Prescribing more than one drug, but there is no standard definition of a cut off point with regard to number**
- ***Usually the threshold is five or more psychotropics***
- ***In DDS, our threshold for psychotropics is three***

- ***Technically defined as simultaneous or concurrent use of multiple drugs to treat a single condition or a single individual***

- ***Alternate definitions:***
  - ***More medications than necessary***
  - ***Medications that are not indicated***
  - ***Medications that are not effective***
  - ***Duplication of medications***
  - ***Polymedicine (from Oncology)***

- **The opposite is monotherapy**

Basic Terminology

Five-Types of Polypharmacology

- Same-class (intra-class)
- Multi-class (inter-class)
- Adjunctive (i.e., one medication to treat the secondary symptoms of another from a different class, such as Trazodone given with Wellbutrin for insomnia)
- Augmentative (e.g., Depakote with Lamictal; Zoloft with Abilify)
- Total (c.f., pill burden)

- *Most common are antipsychotics, followed by ADHD medications and antidepressants*

Scenarios where Polypharmacy is Acceptable:

- Treating two distinct illnesses (e.g., mood disorder and psychosis)
- Treating an adverse effect from a primary drug
- Provide symptom relief when awaiting the delayed effect of another medication
- To treat different phases of an illness
- To boost the efficacy of primary treatment
- To treat refractory illness
- To decrease the dosage of monotherapy
- Cross-titration of medications

Basic Terminology

Rates of polypharmacy

- Polypharmacy affects approximately 40% of older adults living in their own homes
- About 21% of adults with intellectual disability are exposed to polypharmacy
- In adult outpatient settings, one-third of patients receive three or more medications

Basic Terminology

- ***Negative Effects of Polypharmacy: Individual and Systemic***
  - **Diagnostic inflation**
  - **Increased risk of medical and drug interactions**
  - **Cascade of side effects**
  - **High cost**
  - **Poor quality of life due to decreased cognition and mobility**

- **If an individual is taking seven or more medications, what is the risk of an interaction effect?**

  99.9%

- **Can antipsychotic polypharmacy be reversed?**

  In a 2011 study of 127 individuals, all stable on polypharmacy, over a 12-month period, two-thirds were successfully moved to monotherapy without significant worsening.

Basic Terminology

Pharmacokinetics

- **How the biology of the body affects the chemistry of the medication (what the body does to the drug)**

Key Elements:

- ***Absorption***
- ***Distribution***
- ***Metabolism***
- ***Elimination***

Basic Terminology

Pharmacodynamics

- **How the chemistry of the medication affects the biology of the body (what the drug does to the body)**

Key Elements:

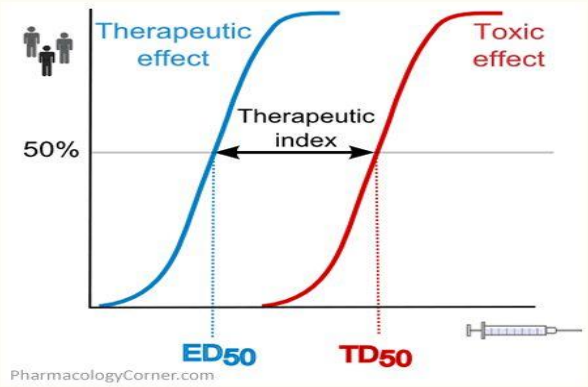
- ***Potency and Efficacy***
- ***Dose Response Curve***
  - ***After IV, inhaling is the fastest route at 8 seconds***
- ***Therapeutic Index (or window) for an effective versus a toxic or a lethal dose***
  - ***Wider is safest. Cannabis is widest.***

Effect = ***the relationship between pharmacodynamics, pharmacokinetics, and biological variance.***

Therapeutic Index

- The ratio of the dose that produces the desired therapeutic effect (ED_{50}) to the dose that produces a toxic effect (TD_{50}).

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$



Basic Tenents

The Ten Rules

1. All drugs are prescribed because they have a mechanism of action

For example, tricyclic (TCA) antidepressants (currently SNRI) :

- **Serotonin Reuptake Inhibitor**
- **Norepinephrine Reuptake Inhibitor**
- **Alpha-1 Agonist (Sympathetic Nervous System)**
- **M-1 Antagonist (Parasympathetic Nervous System)**
- **H-1 Antagonist**
- **Na Channel Blocker**
- **5-HT(2a and 2c) Antagonist**

Basic Tenents
The Ten Rules

2. All drugs have positive and negative side effects

3. Antidepressants will not make you happy (c.f., euphoriants)

4. If one pill works, then two will usually lead to side effects and even medication errors.

5. Drugs interact with each other

Synergistic Effect versus Contraindication

6. Medications will not resolve suffering if they are not preceded by correct diagnosis (i.e., appropriate intervention relies on accurate assessment)

Since the 1970s, across all genre including psychiatry, 40% of diagnoses are misdiagnoses or missed diagnoses.

The Ten Rules

7. Changing one neurotransmitter does more than one thing!

Serotonin 

Dopamine 

Acetylcholine 

Glutamate 

GABA 

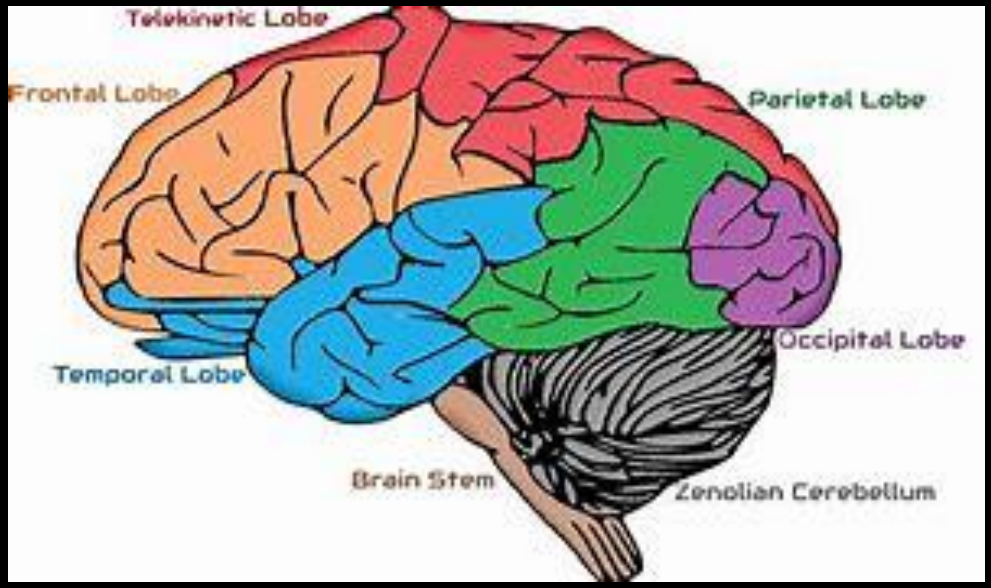
Basic Tenents

The Ten Rules

8. Withdrawal from a drug will often manifest in symptoms that are the opposite of the drug's desired intent

9. Sometimes "no diagnosis" or "no medications" are the sometimes the correct answers

10. Psychopharmacology is far more difficult than some people perceive it to be !



What is the main role of the brain?

Protection!

Front lobes (prefrontal cortex) maturation:

- Females (18 years-old)
- Males (25 years-old)
- Societal Complexity and the Age of Emancipation: In the past it was 19 and now it's 25

- Neuron Organization (Types: Sensory, Motor, and Inter {throughout the body})
  - Soma (body)
  - Nucleus (genetic material)
  - Axon (send info)
  - Dendrites (receive)

- The brain is a collection of billions of cells (i.e., neurons) that are interconnected through networks.

- Neurons are "plastic" (intracellular modifiability) (e.g., new receptors and ion channels)

- The cells communicate primarily by sending (i.e., propagating) nerve impulses from one cell to another by chemical messengers. This process is called neurotransmission.

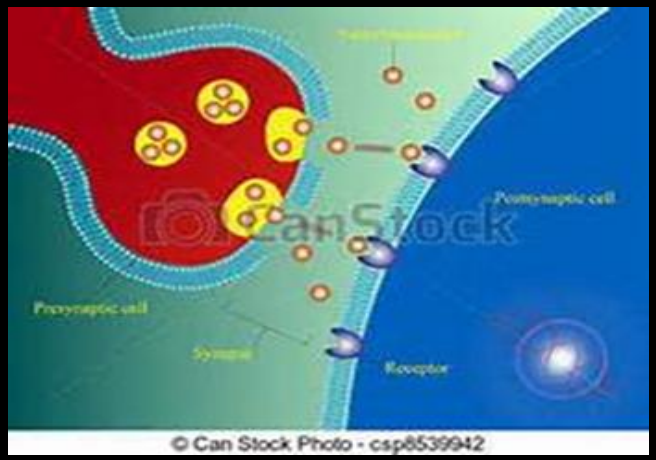
- **Nerve cells tend to be linked based on the neurotransmitter they utilize in common (e.g., dopaminergic network for movement or the serotonergic network for appetite and sleep regulation).**

- **The bucket brigade analogy (intercellular)**

- ***Side effects often generate between networks.*** **For example, an antidepressant acts primarily on the serotonergic system to change mood, but may inadvertently interact with the cholinergic system to cause dry mouth or constipation.**

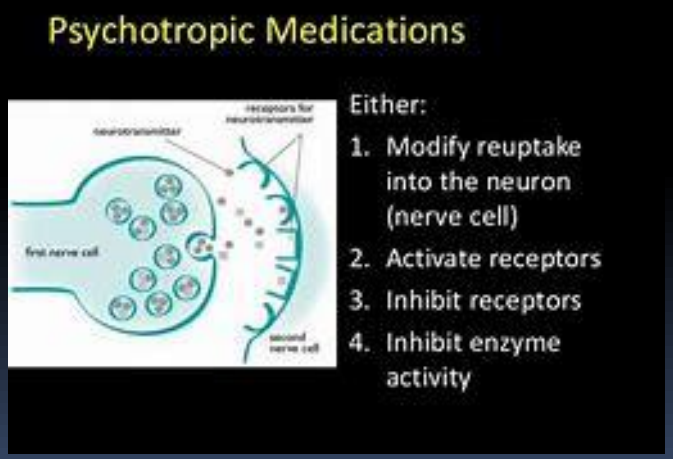
Where medications work:

- **Receptors: Protein molecules with binding (affinity) sites located on the cell membranes.**
- **"Lock and Key" analogy.**
- **Bonds = ligands**



What medications do:

- **Agonist (enhance)**
- **Partial Agonists (diminish)**
- **Antagonists (block)**



Understanding Neurotransmitter Major Functions

While 100 are identified, only 20 are understood

- GABA: Cognition and Inhibition
- Serotonin (5HT): Mood
- Norepinephrine (NE): Motivation and Vigilance
- Dopamine (DA): Reward and "Little" Movements
- Acetylcholine (Ach): Memory and "Big Movements"
- Histamine (H): Sedation
- Glutamate: Excitation (the "master switch" for all brain neurons)

Understanding Neurotransmitters

Serotonin (5HT)

5-hydroxytryptamine

- **Concentrations: 2% Brain, 8% Blood, and 90% GI (Enteric and Peripheral NS)**
- **Regulation of mood, appetite, sleep, pain, and suicidal ideation**
- **Mediates both excitatory and inhibitory activity**

Understanding Neurotransmitters

Norepinephrine (NE)

- Noradrenaline
- Adrenergic system: "Fight, Fright, or Flight"
- Responsible for motivation, fatigue and executive functions (e.g., concentration, problem solving, planning)

Understanding Neurotransmitters

Dopamine (DA)

- Reward and Risk
- Fine motor movements
- Makes work seem effortless
- Peaks at age 16
- "Dopamine hijack"
- Different pathways

Understanding Neurotransmitters

Acetylcholine (Ach)

- Memory
- Cognitive functions
- Movement
- Needs to balance with dopamine

Understanding Neurotransmitters

Glutamate "Gas Pedal" (Sympathetic NS)

- *Excitatory*
- *Memory*
- *Plasticity*
- *Can reach neurotoxicity*
- *Sympathomimetics*

GABA "Brake Pedal" (Parasympathetic NS)

- *Inhibitory (sedatives, hypnotics)*
- *Anticonvulsants*
- *Anxiolytics (anti-anxiety)*
- *Parasympatholytics*

Balance each other out

Half-Life:

- Estimated time for half of the original dose to be metabolized and eliminated from the bloodstream (plasma concentration)

- For example, the half-life of a NSAID is about two hours. If you take Ibuprofen 400 mg at 12:00, then half of the dose (i.e., 200 mg) will have been eliminated by 2:00. By 4:00, 100 mg will have been eliminated.

- Those with a short half-life become effective more quickly, but are harder to withdraw from and can lead to dependency over a period of time (e.g., Paxil is highly prone to serotonin discontinuation syndrome because its half-life is 15 hours)

- Generally it is considered that it takes 5.5-to-6 half-lives for a drug to no longer have a clinical effect or to clear the body.

Steady-State:

- The dose that stays at therapeutic level
- The goal of any medication (e.g., antidepressant) is to achieve a point where the amount that goes into the body is equal to the amount that is eliminated.
- It takes about four times the half-life for the concentration of a drug to reach a steady-state in the body.

The Implications of the Cytochrome CYP450 Enzymes for Psychopharmacology

(Detoxification, cellular metabolism, and homeostasis)

Drug-Metabolizing Enzymatic Genes

- **Pharmacogenomics (i.e., drug-gene testing) study how genes affect the body's response to medication**
- **Tests search for genetic variations (e.g., related to ethnicity) to determine whether a medication could be an effective treatment or whether side effects are likely to occur from a specific medication.**
- **Thus far, about 12 genes measured for about 50 drugs**
- **Hope versus Hype**

Function: Narrowing the Operational Parameters of the Prescribing

The Implications of the P450 Enzymes for Psychopharmacology

Examples:

- **3A4 breaks down most medications**
- **2D6 breaks down most psychotropics. Specifically, this enzyme primarily metabolizes fluoxetine, paroxetine, venlafaxine, and nortriptyline**
- **2C19 primarily metabolizes citalopram, escitalopram, clomipramine, and amitriptyline**

When metabolism is reduced, high blood levels of medication may cause negative side effects.

When metabolism is rapid, lower blood levels may result in poor therapeutic benefit.

Genetic Enzyme Testing

genesight

GeneSight Psychotropic Results

assurex health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9299
Report Date: 1/24/2014

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**citalopram** (Celexa®) [2,4]	**amitriptyline** (Elavil®) [1,6]
desvenlafaxine (Pristiq®)	**clomipramine** (Anafranil®) [3]	**imipramine** (Tofranil®) [1,6]
levomilnacipran (Fetzima®)	**desipramine** (Norpramin®) [1]	**paroxetine** (Paxil®) [1,4,6]
vilazodone (Viibryd®)	**doxepin** (Sinequan®) [3]	**selegiline** (Emsam®) [2]
vortioxetine (Brintellix®)	**duloxetine** (Cymbalta®) [1]	
	escitalopram (Lexapro®) [2,4]	
	fluoxetine (Prozac®) [3,4]	
	fluvoxamine (Luvox®) [1,4]	
	mirtazapine (Remeron®) [1]	
	nortriptyline (Pamelor®) [1]	
	sertraline (Zoloft®) [2,4]	
	trazodone (Desyrel®) [3]	
	venlafaxine (Effexor®) [3]	

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
asenapine (Saphris®)	**aripiprazole** (Abilify®) [1]	
clozapine (Clozaril®)	**chlorpromazine** (Thorazine®) [1]	
fluphenazine (Prolixin®)	**iloperidone** (Fanapt®) [1]	
haloperidol (Haldol®)	**perphenazine** (Trilafon®) [3]	
lurasidone (Latuda®)	**risperidone** (Risperdal®) [1]	
olanzapine (Zyprexa®)	**thioridazine** (Mellaril®) [3,8]	
paliperidone (Invega®)		
quetiapine (Seroquel®)		
thiothixene (Navane®)		
ziprasidone (Geodon®)		

Report will be different for each person

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[8]: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

CONFIDENTIAL HEALTHCARE INFORMATION

The Value of Pharmacogenetic Testing

Consider the context:

- **Psychotropics are metaboliozed based on individual factors (age, race, ethnicity, and physical condition)**
- **About 50% of patients respond poorly to first antidepressant attempted**
- **Reduces frustration, time consumption, financial expense, and debilitation.**
- **Medicare and Medicaid no cost; Commercial insurance $330**
- ***Best in complex cases (e.g., dysfunction in serotonin receptor gene 5HT2C relates to weight gain when using antipsychotic medications)***

Case Example:

- **15 year-old female**
- **History of ineffective SSRI and SNRI usage**
- **Hospitalization for major depression, suicidal ideation, and a new medication trial**

GeneSight® Psychotropic

Pharmacogenomic Test

genesight

Date of Birth:
Clinician:

Order Number:
Report Date: 3/5/2024
Reference:

Questions about report interpretation?
Contact our Medical Information team:
855.891.9415 | medinfo@genesight.com

Antidepressants

Non-Smokers Smoking is defined as the daily inhalation of burning plant material (cigarettes, marijuana), and **excludes** vaping and e-cigarettes. This is used to determine medication results.

Use as Directed

desvenlafaxine (Pristiq®)	
levomilnacipran (Fetzima®)	
vilazodone (Viibryd®)	

Moderate Gene-drug Interaction

sertraline (Zoloft®)	4
citalopram (Celexa®)	1,4
escitalopram (Lexapro®)	1,4
selegiline (Emsam®)	1,7
trazodone (Desyrel®)	1,7

Significant Gene-drug Interaction

bupropion (Wellbutrin®)	1,6
fluoxetine (Prozac®)	1,6
venlafaxine (Effexor®)	1,6
mirtazapine (Remeron®)	1,6,7
amitriptyline (Elavil®)	1,6,8
clomipramine (Anafranil®)	1,6,8
desipramine (Norpramin®)	1,6,8
doxepin (Sinequan®)	1,6,8
imipramine (Tofranil®)	1,6,8
nortriptyline (Pamelor®)	1,6,8
vortioxetine (Trintellix®)	1,6,8
paroxetine (Paxil®)	1,4,6,8
duloxetine (Cymbalta®)	1,6,7,8
fluvoxamine (Luvox®)	1,6,7,8

Antipsychotics

is defined as the daily inhalation of burning plant material (cigarettes, marijuana), **udes** vaping and e-cigarettes. This is used to determine medication results.

Moderate Gene-drug Interaction

fluphenazine (Prolixin®)	1
quetiapine (Seroquel®)	1
asenapine (Saphris®)	3
chlorpromazine (Thorazine®)	3
olanzapine (Zyprexa®)	3
clozapine (Clozaril®)	3,8
haloperidol (Haldol®)	3,8

Significant Gene-drug Interaction

thiothixene (Navane®)	2
thioridazine (Mellaril®)	3,9
aripiprazole (Abilify®)	1,6,8
brexpiprazole (Rexulti®)	1,6,8
iloperidone (Fanapt®)	1,6,8
perphenazine (Trilafon®)	1,6,8
risperidone (Risperdal®)	1,6,8

Patient Genotypes and Phenotypes

PK

Pharmacokinetic Genes

CES1A1 — **Extensive (Normal) Metabolizer**

GLY/GLY

CES1A1 - Gly allele enzyme activity: Normal
CES1A1 - Gly allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. This patient is expected to have normal enzyme activity.

CYP1A2 — **Non-smoker: Extensive (Normal) Metabolizer**
Smoker: Ultrarapid Metabolizer

-163C>A - C/A

CYP1A2 -163C>A - C allele enzyme activity: Normal
CYP1A2 -163C>A - A allele enzyme activity: Highly inducible

This genotype may be consistent with either the extensive (normal) metabolizer phenotype or the ultrarapid metabolizer phenotype. If the patient is a non-smoker (see pg. 1 for definition), the presence of the highly inducible 'A' allele and non-smoker status indicates an extensive (normal) metabolizer phenotype. If the patient is a smoker, the presence of the highly inducible 'A' allele and smoker status indicates an ultrarapid

CYP2D6 — **Poor Metabolizer**

*4/*9

CYP2D6*4 allele enzyme activity: None
CYP2D6*9 allele enzyme activity: Reduced

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

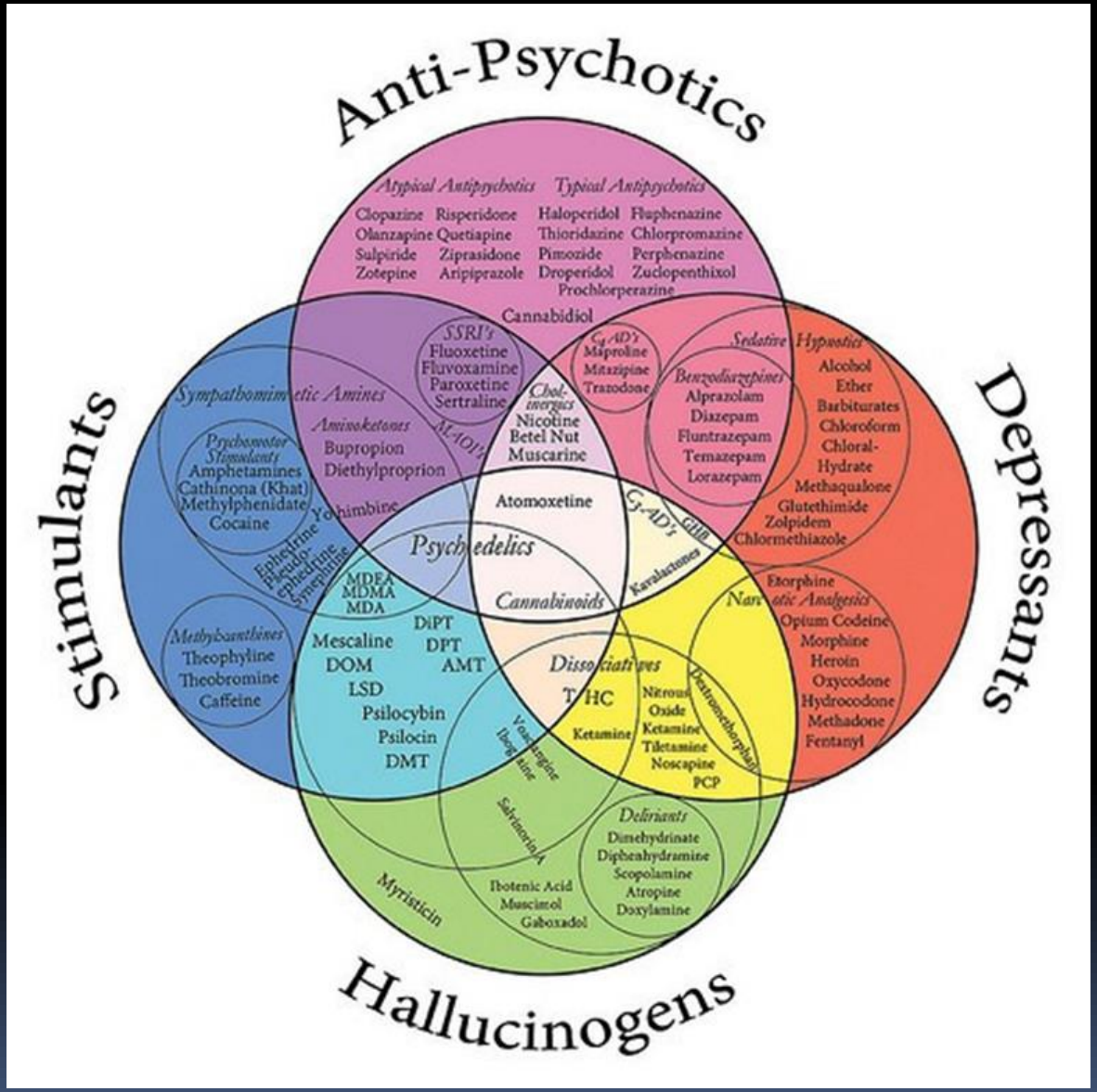
CYP3A4 — **Extensive (Normal) Metabolizer**

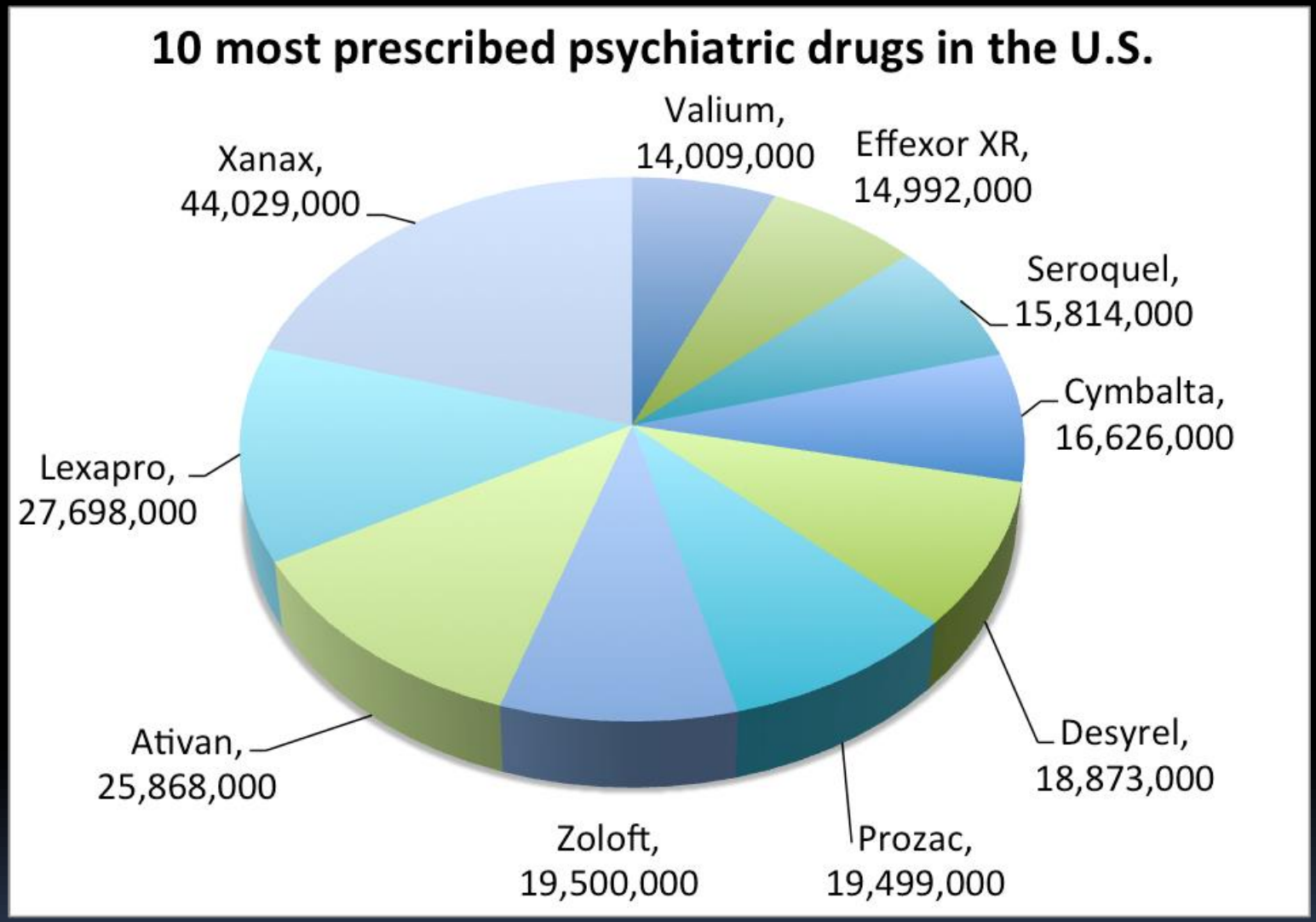
*1/*1

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*1 allele enzyme activity: Normal

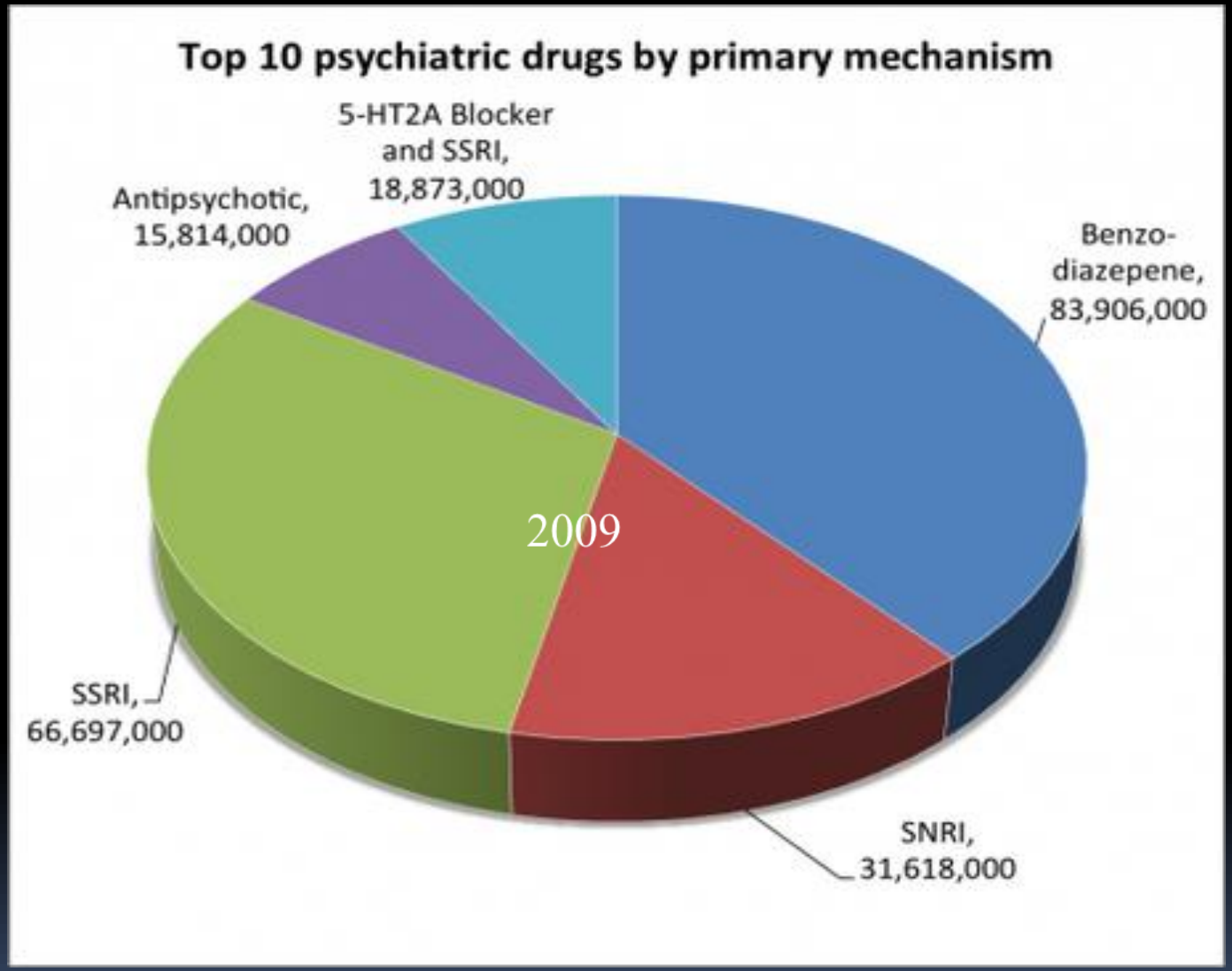
This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CARE INFORMATION
siness as Myriad Neuroscience.


Anti-Psychotics
Stimulants
Depressants
Hallucinogens
Atypical Antipsychotics
Clopazine
Olanzapine
Sulpiride
Zotepine
Risperidone
Quetiapine
Ziprasidone
Aripiprazole
Typical Antipsychotics
Haloperidol
Thioridazine
Pimozide
Droperidol
Prochlorperazine
Fluphenazine
Chlorpromazine
Perphenazine
Zuclopenthixol
Cannabidiol
SSRI's
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
GABA's
Maproline
Mirtazipine
Trazodone
Sedative Hypnotics
Benzodiazepines
Alprazolam
Diazepam
Fluntrazepam
Temazepam
Lorazepam
Alcohol
Ether
Barbiturates
Chloroform
Chloral-Hydrate
Methaqualone
Glutethimide
Zolpidem
Chlormethiazole
Sympathomimetic Amines
Psychomotor Stimulants
Amphetamines
Cathinona (Khat)
Methylphenidate
Cocaine
Aminoketones
Bupropion
Diethylproprion
Yohimbine
Ephedrine
Pseudo-ephedrine
Synephrine
MAOI's
Cholinergics
Nicotine
Betel Nut
Muscarine
Atomoxetine
Psychedelics
Cannabinoids
GABA's
GHB
Karalactones
MDEA
MDMA
MDA
DiPT
DPT
AMT
Mescaline
DOM
LSD
Psilocybin
Psilocin
DMT
Dissociatives
THC
Ketamine
Nitrous Oxide
Ketamine
Tiletamine
Noscapine
PCP
Dextromethorphan
Narcotic Analgesics
Etorphine
Opium Codeine
Morphine
Heroin
Oxycodone
Hydrocodone
Methadone
Fentanyl
Methylxanthines
Theophyline
Theobromine
Caffeine
Yohimbine
Ibogaine
Salvinorin A
Myristicin
Ibotenic Acid
Muscimol
Gaboxadol
Deliriants
Dimehydrinate
Diphenhydramine
Scopolamine
Atropine
Doxylamine


10 most prescribed psychiatric drugs in the U.S.
Valium, 14,009,000
Effexor XR, 14,992,000
Seroquel, 15,814,000
Cymbalta, 16,626,000
Desyrel, 18,873,000
Prozac, 19,499,000
Zoloft, 19,500,000
Ativan, 25,868,000
Lexapro, 27,698,000
Xanax, 44,029,000

2009


Top 10 psychiatric drugs by primary mechanism
5-HT2A Blocker and SSRI, 18,873,000
Antipsychotic, 15,814,000
Benzo-diazepene, 83,906,000
2009
SSRI, 66,697,000
SNRI, 31,618,000

2011

Treatment of Depression

- Symptoms are out of proportion for the circumstances and persistent

- Rule-out medical causes:
  - Sleep disorders
  - Gastrointestinal (e.g., leaky gut, poor diet, vitamin D or B12 deficiency)
  - Hypothyroidism (20% of depressive cases)
  - Urinary Tract Infection
  - Low testosterone
  - Mild cognitive disorder

- Consider depressive equivalents (e.g., irritability, aggression, conflicts, somaticizing, brooding)

- Mild-to-moderate depression: psychotherapy is indicated

- Moderate-to-severe depression: combination of psychotherapy and medication

Treatment of Depression

Hypotheses Across Time…

- Catecholamine hypothesis (1965), particularly related to norepinephrine. ***No evidence to support the neurotransmitter deficiency or chemical imbalance theory.***

- Cortisol hypothesis: Stress response

- Down-regulation hypothesis: Auto-receptors

- Neurotropic hypothesis: New discoveries
  - Existing neurons are able to repair through homeostatic equilibrium (drugs "insult" the brain which tries to protect and compensate)
  - Neurogenesis

Treatment of Depression

Tricyclic Antidepressants

- Three ring molecular structure
- Mechanism of action (if released today) is SNRI
- Narrow therapeutic index: lethality
- Often prescribed for their side effects (e.g., imipramine [enuresis] and amitriptyline [sedation, pain management)

Treatment of Depression

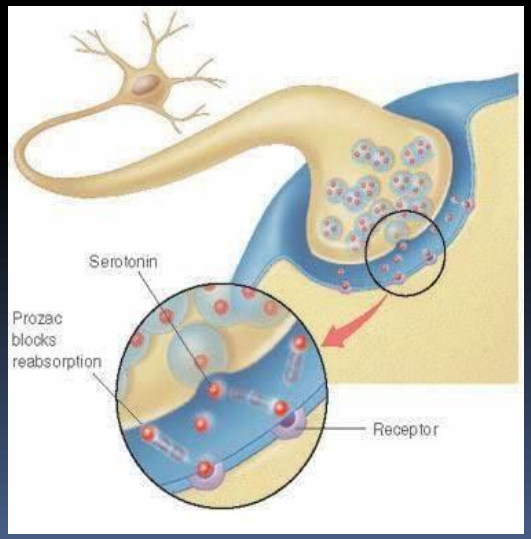
Monoamine Oxidase Inhibitors

- First discovered as an anti-tuberculosis drug
- Blocks breakdown of neurotransmitters
- More effective than tricyclics for atypical depression
- Nardil is the gold standard; now Emsam as a transdermal patch
- Common adverse drug reactions: dietary restrictions (food with tyramine), anticholinergic effects, and hypotension

Treatment of Depression

Selective Serotonin Reuptake Inhibitors

- They are intended to have little effect on NE, DA, GABA, glutamate, and Ach; hence the term "selective"
- Typical point of maximum benefit is 35 weeks



Treatment of Depression

Selective Serotonin Reuptake Inhibitors

Fluoxetine (Prozac)

- The "grandfather " (1986)
- Indicated for major depression, OCD, PMDD, bulimia, and panic disorder
- Positive for childhood depression
- 7 day half-life (no withdrawal syndrome)
- Weekly doses as Serafem
- Marketed as Symbyax (combined with Olanzapine) for bipolarity and treatment resistant depression

Fluvoxamine (Luvox)

- FDA approved for OCD and social anxiety disorder
- Up to 4 weeks to generate good effect
- 17 hour half-life

Treatment of Depression
Selective Serotonin Reuptake Inhibitors

Sertraline (Zoloft)
- The "grandmother" (1987)
- FDA approved for MDD, PMDD, panic disorder, PTSD, OCD and Social Anxiety
- Mild antipsychotic properties
- Most potent SSRI, but also most dangerous
- Safe for pregnancy

Citalopram (Celexa)
- FDA approved for depression
- 36 hour half-life with few side effects
- Doses not greater than 40 mg
- Safe for elderly; unsafe for pregnancy
- Antihistamine effect (sedating)
- Left and right sides of molecular structure

Escitalopram (Lexapro)
- Indicated for major depression and generalized anxiety
- Best tolerated antidepressant and most effective at lower doses
- About 30 hour half-life
- Only the left side of the molecular structure (cleanest)

Treatment of Depression

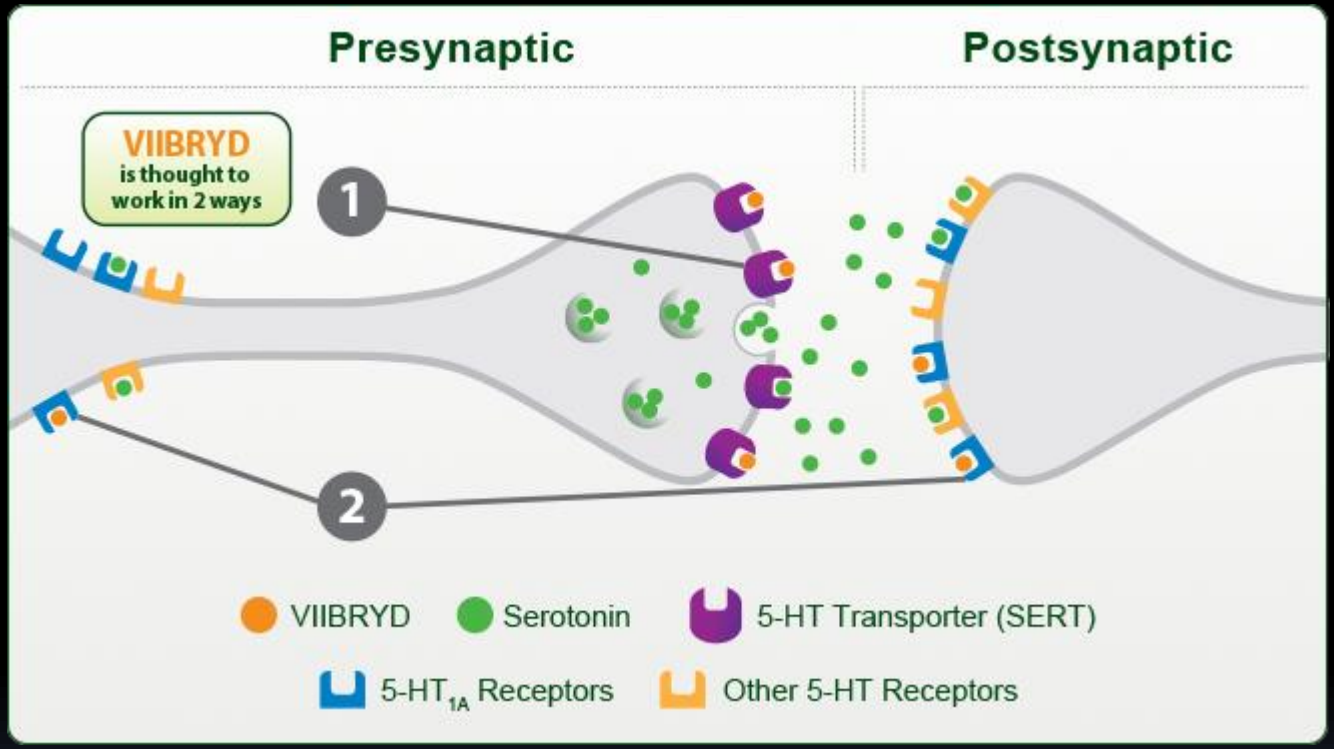
Serotonin Modulators and Stimulators

Vilazodone (Viibryd)

- Indicated for major depression (2011)
- Why the double "I" in the spelling?
- Multimodal or two mechanisms of action
- Serotonin reuptake inhibitor and 5-HT1A receptor partial agonist
- An antidepressant and anxiolytic in one pill
- Fewer sexual side effects and weight gain liability

Vortioxetine (Trintellix) ***formerly Brintellix***

- "Me-Too Drug"
- FDA approved for major depression with a new mechanism of action
- Agonist of 5-HT1A and antagonist of 5-HT3 and 5-HT7
- Causes nausea
- Expensive at $200 monthly (versus generic SSRI at $20)



Presynaptic: Sends Impulses
Postsynaptic: Receives Impulses

Treatment of Depression

Common SSRI Adverse Drug Reactions:

- Insomnia
- Sexual dysfunction
- Restlessness
- Gastrointestinal symptoms
- Suicidal (disinhibiting effect)
- Apathy or amotivation (affects DA)

Serotonin Discontinuation Syndrome

- **Autonomic Nervous System Dysfunction**
  - Dizziness
  - Anxiety
  - Muscle aches or spasms
  - Fever
  - Tachycardia
  - Nausea

- ***To be expected with Paxil and Luvox!***
- ***Watch for polypharmacy effects (e.g., Need "wash-out" period switching MAOI to SSRI; Caution using with other 5-HT agonists, such as St. John's Wort, TCAs, Decongestants)***

Serotonin and Norepinephrine Reuptake Inhibitors
The Dual Agents

Venlafaxine (Effexor)
- Indicated for MDD, generalized anxiety, social phobia and panic disorder
- Half-life up to 13 hours
- Initiation and withdrawal issues
- Contraindicated with hypertension and cardiac history

Desvenlafaxine (Pristiq)
- Metabolite of Venlaflaxine
- Fewer side effects
- Most can metabolize it

Duloxetine (Cymbalta)
- Depression plus treats fibromyalgia, neuropathic and musculoskeletal pain
- Originally a bladder stabilizer
- 12 hour half-life (offers 30% pain reduction but many discontinue due to side effects)

Levomilnacipran (Fetzima and Savella)
- Depression with fibromyalgia
- Strong NE Inhibitor

Atypical Antidepressants

Mirtazapine (Remeron)

- Tetracyclic antidepressants (TeCA)
- Noradrenaline and Serotonin Antagonist
- Sedation and weight gain ("Big Benadryl")

Bupropion (Wellbutrin)

- NE and DA reuptake Inhibitor
- Amphetamine derivative
- Activating and stimulating effects
- Nicotine cessation
- Few side effects as it's not serotonin based

Desyrel (Trazodone)

- Developed in 1982
- Serotonin antagonist reuptake inhibitor (SARI)
- Sedating Antidepressants (treats depression and insomnia)

Other Treatments

- Transcranial Magnetic Stimulation
- Electroconvulsive Therapy
- Cardiovascular Exercise
- St. John's Wort

Treatment of Depression

Esketamine (Spravato)

- For treatment resistant depression (20-70%) and suicidal thoughts
- Those who fail to respond after two trails of medication regimen

- Plant-based spray
- PCP analog with possible psychotomimetic effect
- Relief in hours-to-days

- Different than oral meds, as unique MOA rapidly targets glutamate pathways
- Antagonist inhibits N-Methyl-D-aspartate (NMDA) receptors (for synaptic plasticity and memory)

- Twice weekly for one month along with two hours of monitoring
- After eight weeks tapering required
- Combine with conventional meds and psychotherapy

*Star*D Study:*

- **The largest real-world study of treatment-resistant depression sponsored by NIMH and published in 2006**
- **Sequenced Treatment Alternatives to Relieve Depression**
- **47% response rate to SSRI, but the odds of beating the depression diminish as additional treatment strategies are needed**
- **Boosting agents (e.g., Abilify and Lithium)**

Psychopharmacology:
The Basics and Beyond

Part II

Peter Tolisano, Psy.D., ABPP
Board Certified in Clinical Psychology

Director of Psychological Services
Connecticut Department of Developmental Services

Presentation Objectives

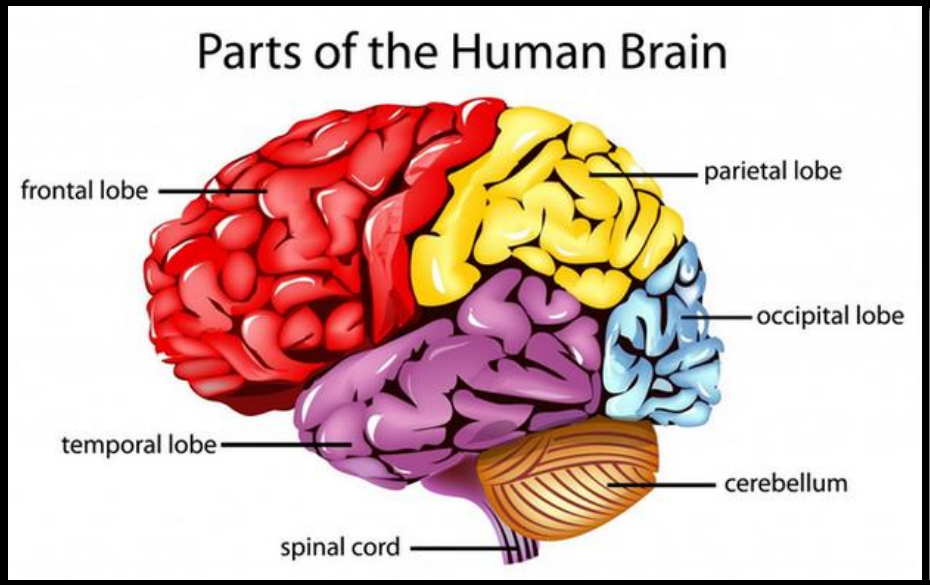
- Continue to differentiate between psychiatric medications, such as mood stabilizers, anxiolytics, antipsychotics, and somnolents
- Recognize side effects associated with the psychotropic medications
- Learn ways to assess medication usage and seek psychiatric consultation
- Better understand prescribing with special populations
- Identify current and future trends in psychotropics

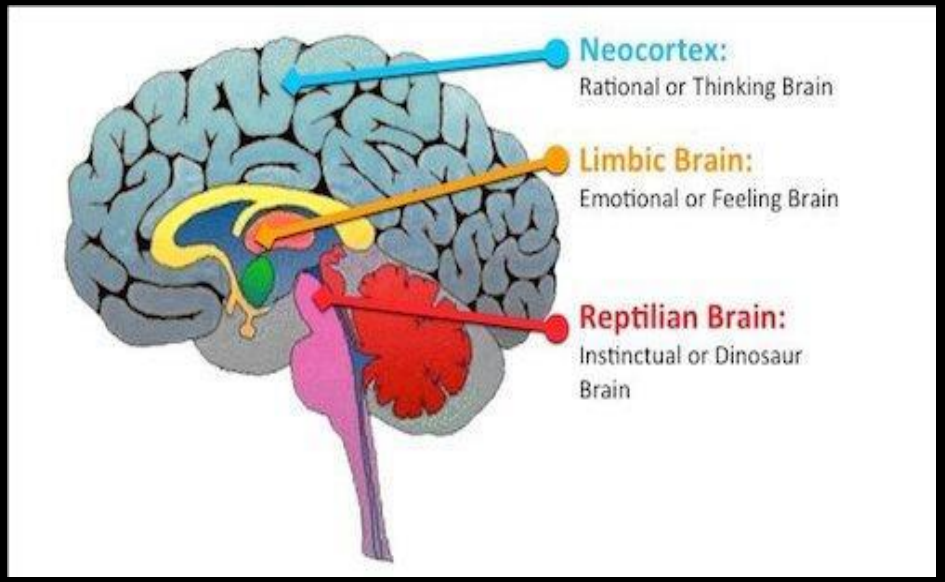
Anxiety-Based Disorders

- ***Anxiety is the most ubiquitous symptom***
- ***Autonomic Nervous System: Sympathetic vs. Parasympathetic***
- ***Diagnoses include the following:***
  - ❖ ***Generalized Anxiety***
  - ❖ ***Panic Disorder***
  - ❖ ***Social Phobia***
  - ❖ ***PTSD***
  - ❖ ***OCD***

The anxiety and trauma-response systems in the brain are overlapping

Integration of Brain Regions



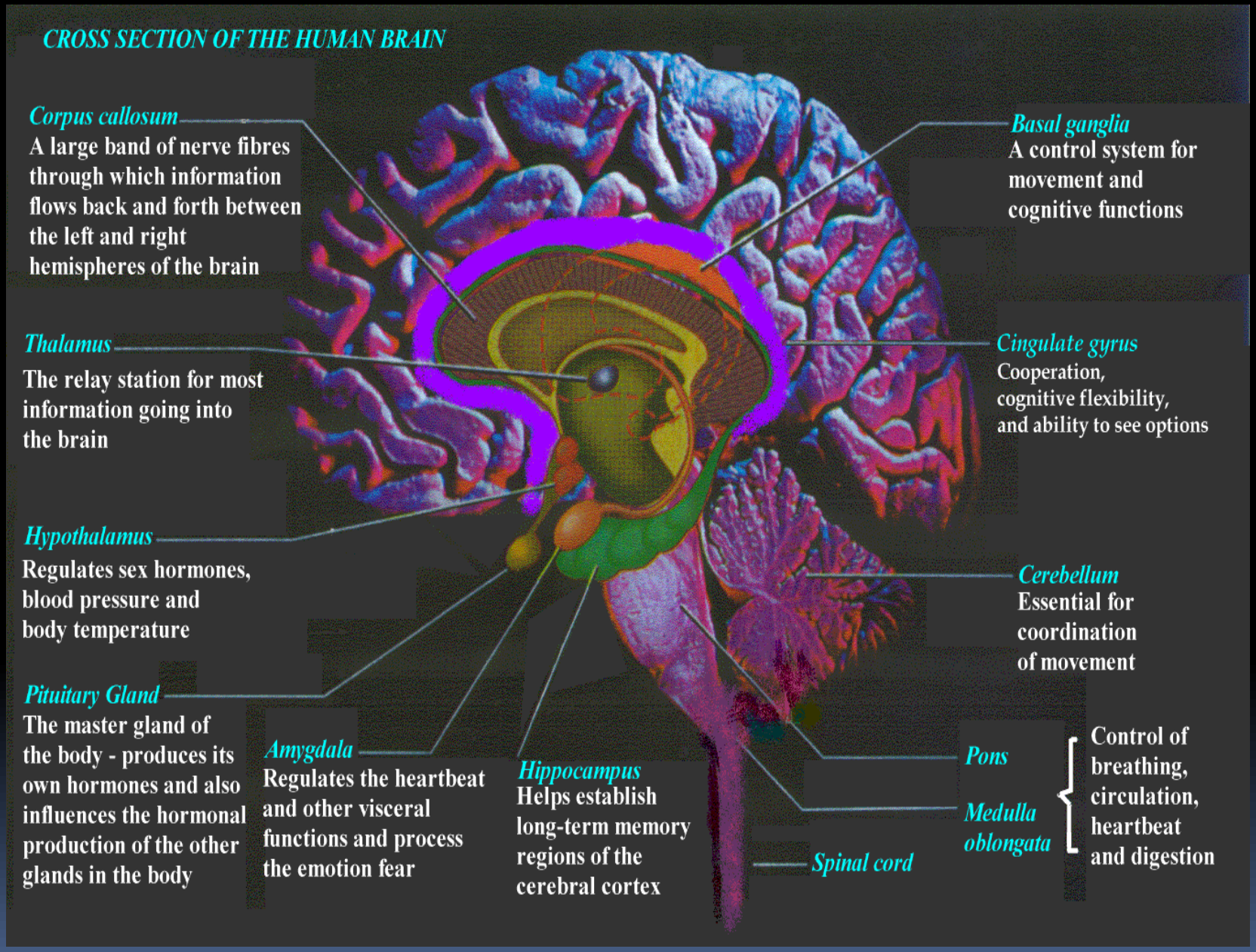


Limbic System

- **Amygdala that detects threat (fight, flight, and freeze reactions)**
- **Hippocampus for memory storage**
- **Hypothalamus relays sensory information and activates the autonomic nervous and endocrine systems**

Frontal Cortex

Responsible for planning, emotional control, thinking flexibly, self-monitoring, and decision-making.


CROSS SECTION OF THE HUMAN BRAIN
Corpus callosum
A large band of nerve fibres through which information flows back and forth between the left and right hemispheres of the brain
Thalamus
The relay station for most information going into the brain
Hypothalamus
Regulates sex hormones, blood pressure and body temperature
Pituitary Gland
The master gland of the body - produces its own hormones and also influences the hormonal production of the other glands in the body
Amygdala
Regulates the heartbeat and other visceral functions and process the emotion fear
Hippocampus
Helps establish long-term memory regions of the cerebral cortex
Basal ganglia
A control system for movement and cognitive functions
Cingulate gyrus
Cooperation, cognitive flexibility, and ability to see options
Cerebellum
Essential for coordination of movement
Pons
Medulla oblongata
Control of breathing, circulation, heartbeat and digestion
Spinal cord

Two Pathways to Anxiety:

Bottom-Up: ***A swift triggering of emotions that links senses and/or perceptions with the "igniting" of the amygdala, which then activates the sympathetic nervous system. You react in milliseconds even before your cortex can think!***

Top-Down: ***Negative cognitive interpretations of stimuli (e.g., catastrophizing, pessimism, perfectionism, guilt) trigger the amygdala and then the autonomic nervous system.***

- ***Ways to create anxiety:***
  - ***Frontal lobe anticipates***
  - ***Right hemisphere produces images***
  - ***Left hemisphere worries and ruminates***

Presentation Exercise: Activating the Amygdala

Anxiety-Based Disorders

- ***One amygdala on each side of the brain, but they work as a unit.***
- ***The amygdala has hundreds of cellular circuits dedicated to different purposes and timetables (e.g., aggression, fear, attachment, etc.). It "pairs" information for "relevance."***
- ***Amygdala has many connections <u>to</u> monitor and influence the cortex; it controls the reaction (i.e., fight, flight, freeze, etc.) where some are preprogrammed and others are "trained."***
- ***The amygdala is irrational (it errs toward caution) and learns from experience through neuroplasticity ("exposure versus avoidance")***
- ***Aerobic exercise and REM sleep reset the amygdala (e.g., completing the circuit).***

Why do first responders react different to threat or athletes differently to stress?

They train in safe environments to quiet the amygdala…

Anxiety-Based Disorders

Anxiolytics or Antianxiety Medications

- ✓ **Benzodiazepines**
- ✓ **Antidepressants (SSRI or SNRI)**
- ✓ **Beta Blockers**
- ❑ **Buspar**
- ❑ **Monoamine Oxidase Inhibitors (MAOIs)**
- ❑ **Anticonvulsants**
- ❑ **Atypical Antipsychotics**

- ✓ ***…Plus Psychotherapeutic Approaches (we can quiet the amygdala with medications, but not necessarily the negative thinking)***

- ✓ ***Individuals with anxiety and depression who engage in forms of self-mutilation (e.g., hair pulling, nail biting) are most vulnerable to endorphin and dopamine "rush"***

Benzodiazepines (Mild Tranquilizers)

A benzo is a benzo…it's all about half-life and potency

Ativan → Xanax → Klonopin → Valium

- Inhibit GABA by opening chloride channels
- Produce widespread sedation in the body
- Reduce anxiety by inhibiting the neural process
- Temporary solution that doesn't rewire the brain

Pros

- Rapid psychoactive effects (fast relief)
- Only intended for time-limited use (2-4 weeks)

Cons

- Highly addictive (tolerance and dependence)
- Risk for fatal overdose from respiratory suppression, especially with alcohol
- Prone to paradoxical reactions: Disinhibition and Impulsivity
- Side effects include emotional blunting and memory problems
- Depression and even seizures with abrupt withdrawal
- Poor sleep agents because they decrease REM

Rebound Effect: Benzodiazepines and the Amygdala

Anxiety-Based Disorders

Beta Blockers:

- **Inderal (Propranolol)**
- **Lopressor (Metoprolol)**
- **Terormin (Atenolol)**

- **These drugs reduce palpitations, sweating, and tremors**
- **Often are prescribed for individuals with social phobia, panic, and essential anxiety**
- **Works from keeping epinephrine related neurotransmitters (e.g., adrenaline) from binding to receptors**
- **They keep the body from responding with fight or flight (reduce the sympathetic response)**
- **They interfere with the effectiveness of exposure-based psychotherapy**

Bipolar Disorder

- **Bipolar I, II, and III subtypes (e.g., mania, hypomania, cyclothymia, mixed episodes, and rapid cycling)**

- **Watch for irritability, increased energy, the amazing reversal, and awareness of effects of destructiveness as risk factors for suicide, especially during inpatient admissions and post-discharge from hospitalizations.**

Differential Diagnosis between Bipolar Disorder and Borderline Personality Disorder

- *Comorbidity only 18%*
- *Mood Swing Triggers: Bipolar Internal and Borderline External*
- *Depression: Bipolar disabling and borderline still impulsive*
- *Thinking: Only borderline is dichotomous*
- *Affect: Bipolar lacks intensity*
- *Care-seeking: Higher with borderline diagnosis*
- *Conflicts: Bipolar ignores realities, whereas borderlines split*
- *Mood states: Bipolar enduring and borderline few hours/days*

Treatments for Bipolar Disorder

- **Mood Stabilizers (term comes from pharmaceutical companies) and neuromodulators**
- **Primary side effect is cognitive dulling (e.g., anticonvulsants can lower IQ testing by one standard deviation in children)**
- **Mechanism of Action: Increase GABA or Decrease Glutamate**
- **Traditional Medications:**
  - **Lithium (suicide and self-harm preventative)**
  - **Depakote**
  - **Tegretol**
  - **Lamictal (Stephens-Johnson Syndrome)**
  - **Topamax**
  - **Neurontin**

Psychotic Disorders

- **Etiology: Dopamine hypothesis to Schizophrenia (1963)**

First Generation (1960s):

- **Neuroleptics and Phenothiazines**
- **Typical Antipsychotics (Positive Symptoms)**
  - **MOA: D2 Antagonist**
  - **Thorazine and Haldol**
  - **Prolixin Decanoate (Injectable)**
  - **Deinstitutionalization Movement**

Psychotic Disorders

Second Generation (1990s): Atypical Antipsychotics

- Treat Positive and Negative Symptoms
- MOA: Serotonin-Dopamine Antagonist
- Primary risks include movement disorders, metabolic syndrome, and cardiac arrhythmia

Mechanisms of Action of Antipsychotic Drugs

- Major action is to block receptors for dopamine
- Typical antipsychotics are potent antagonists for dopamine receptors D2, D3, and D4
- As a result, they are powerful in treating target symptoms but also producing extrapyramidal side effects.
- Newer atypicals like Clozaril are relatively weak blockers of D2, which lowers the incidence of EPS.
- Atypicals also inhibit reuptake of serotonin that helps to treat the depressive features of schizophrenia.

Common Atypical Antipsychotics

- Zyprexa (Olanzapine)
- Risperdal (Risperidone)
- Geodon (Ziprasidone)
- Seroquel (Quetiapine)
- Saphris (Asenapine)
- Clozaril (Clozapine)
- Latuda (Lurasidone)

Third Generation Antipsychotics (with adjunctive mood treatment)

- Abilify (Aripiprazole)
- Rexulti (Brexpiprazole)
- Vraylar (Cariprazine)

Approximately 20% of antipsychotics are prescribed in primary care settings

Risks with Antipsychotic Medications

- Black box warnings for dementia-related psychosis and suicide risk
- Dystonia (involuntary muscle movements)
- Akathisia (mental and physical restlessness)
- Extra-Pyramidal/Extra-Parkinsonian Side Effects (neurons in the brain for movement are affected causing rigidity, tremors, and swallowing problems)
- Tardive Dyskinesia
  - Usually abnormal movements of the mouth and face; may also include rocking of the trunk and irregular breathing
  - Lower dose, change medications, or administer anticholinergic medication
  - The body always tries to balance acetylcholine and dopamine
  - Tongue is most sensitive to acetylcholine issues
  - Abnormal Involuntary Movement Scale (AIMS) used to detect and track the severity of tardive dyskinesia
  - Treated with Cogentin (Benzatropine) and Ingrezza (Valbenazine)

Risks with Antipsychotic Medications

- Cardiac arrhythmia (i.e., polarization changes cause elongation of the Q-T interval or the approximate time for the heart ventricles to start contracting to finish relaxing)
- Metabolic Syndrome (Cluster of cardiovascular and diabetic risks especially with Zyprexa and Clozaril) such as glucose intolerance and poor lipid metabolism
- Weight Gain Liability
- Neuroleptic Malignant Syndrome: Dopamine blockade can cause potentially lethal effects. Fatal in 11% of cases. Higher risk with typical antipsychotics. Creatine phosphokinase (CPK) blood marker.

Weight Loss Pharmacology

- Weight loss involves complex interactions among numerous factors: metabolism, genetics, evolution, biology, societal influences, culture, individual factors, and behavioral changes
- All meds require behavioral interventions (exercise) and dietary modifications for weight control

Amphetamines

- ✓ Used for over a century to suppress appetite
- ✓ Noradrenergic properties and includes medications like bupropion and topiramate
- ✓ 60 million scripts in 2020
- ✓ short and long term effects like dependency, insomnia, and irritability

Lipase Blockers: Orlistat (Xenical)

- ✓ Promotes weight loss by blocking pancreatic lipases needed to absorb fats in the digestive tract; thereby, fats are excreted unchanged

Weight Loss Pharmacology

- Emergence of Glucagon-Like-Peptide 1 (GLP-1) agonists like liraglutide (saxenda), semaglutide (ozempic and wegovy) and tirzepatide (mounjaro)
- Medications mimic the hormone GLP-1 that we produce in our intestines and signal fullness.

- Weight-loss effects: It blunts hunger signals and slows gastric emptying, thus, reducing appetite, giving the sensation of satiety (i.e., feel fuller faster), and making people feel indifferent to food (liberated; not ruminating)

- Possible ramifications of stopping:
  - Glucose in blood surges and may require metformin and insulin
  - Rebound weight gain after discontinuation (Novo Nordisk stated that one year after stopping, following 68 weeks of treatment, participants gained back two-thirds of weight they lost)
  - It's an amphetamine alternative, but risks include kidney disease, pancreatitis, and GI discomfort
  - The cognitive effects dissolve quickly after stopping

Posttraumatic Stress Disorder

- Pre-existing vulnerability
- Becoming symptomatic versus resiliency development
- Zoloft and Paxil
- CBD
- Eye Movement Desentization and Reprocessing (EMDR) Therapy

Attention-Deficit/Hyperactivity Disorder

- Previously Attention Deficit Disorder
- Evidence before the age of 12
- Three Types: Inattentive, Hyperactive, and Combined
- Most common in children (up to 18%)
- Risk Factors: low birth weight, malnutrition, fetal alcohol exposure, lead poisoning, acetaminophen use during pregnancy
- Heritability factor
- Hypoactivation of prefrontal cortex and parietal network
- Disruption in synaptic pruning

Attention-Deficit/Hyperactivity Disorder

- Psychostimulants: Paradoxical mechanism of action on sympathetic nervous system toward “freeze”
- Increasing Dopamine raises risk of cardiac event
- Methylphenidate: Ritalin, Concerta, Quillivant , and Focalin
- Amphetamine: Dexedrine, Adderall, Aptensio, Adzenys, Mydayis, and Evekeo
- Methamphetamine: Desoxyn; highly addictive
- Vyvanse: Drug of choice for Adult ADHD (lisdexamfetamine for the prodrug of dextroamphetamine)

Attention-Deficit/Hyperactivity Disorder

- Strattera: NE and DA reuptake inhibitor; up to 8 weeks before results
- Antihypertensives: Blocks sympathetic nervous system to decrease energy; dosed at night
  - Guanfacine: Tenex and Intuniv
  - Clonidine (Catapres and Kapvay)
- Nutritional approach: Vayarin and Accentrate
- In those without ADHD, stimulants are used for euphoriant properties and increased mental acuity ("Academic Doping")

Anti-Dementia Medications

1. Actelycholinesterase inhibitors are prescribed for mild-to-moderate symptoms. They are intended to *preserve* functioning or delay worsening. These include Aricept, Cognex, and Exelon.

2. Other medications that regulate glutamate can be prescribed to treat moderate-to-severe symptoms. For example, Namenda.

Unfortunately, dementia is typically not detected and diagnosed until the middle-to-late stages, especially for individuals with I/DD.

Sleep Disorders

- *One-third of adults in US report insomnia*
  - *Insomnia Severity Index*
    - *CBT-I protocol*
- *Always need to rule-out Sleep disorders (e.g., OSA)!*

Two-Process model of Sleep Regulation: *Sleep drive and Circadian rhythm*

Sleep medications include both prescription and over-the-counter choices with various mechanisms of action

Hypnotic Medications:

- *Intended to initiate and maintain sleep*
- *Benzodiazepines and non-benzodiazepines, histamine antagonists, melatonin agonists, and orexin antagonists (e.g., suvorexant and daridorexant)*

Sedating Medications:

- *Trazodone, mirtazapine, quetiapine, and gabapentin (all off-label use)*

Sleep Aids

Benzodiazepine-Based:

- Most commonly used treatment of insomnia, but only recommended for short-term usage by AMA and FDA.
- Safer than older sleep medications such as the barbiturates
- Should only be used on short term basis since psychophysiological dependence can occur.
- Can produce a "hangover" effect the following day.
- Concerns about REM suppression leading to poor restorative sleep
- Examples include Halcion (Triazolam), Restoril (Temazepam), and Klonopin (Clonazepam)

Sleep Aids

Non-Benzodiazepine Sedative-Hypnotic Drugs

- **Better safety profiles and less adverse effects**
- **Ambien (Zolpidem)**
  - **Helps fall and stay asleep**
  - **Half-life is two hours**
- **Sonata (Zaleplon)**
  - **Fast-acting**
  - **Half-life is one hour**
- **Lunesta (Eszopicione)**
  - **FDA-approved in 2004 as a longer-lasting sleep agent**
  - **Six-hour half-life**

Wakefulness Promoting:

- **Provigil and Nuvigil**
- **Hypothetical mechanism of action: dopamine reuptake inhibitor**

Cannabis

- Limited research
- 70 unique compounds ("it hits everything") with multiple MOA.
- CBD and THC are substances found in cannabis plants. Tetrahydrocannabinol is the primary psychoactive compound that's lipophilic.
- Endocannabinoid System (ECS) involved in an array of processes from reproduction to memory
- Increases need for cognitive effort (memory, processing speed) especially for those under 17 years-old. It slows reaction time, concentration, and memory, even after the high wears off.
- CBD
  - Cannabidiol is not psychoactive and has medicinal properties
  - About 40% of the plant's extract (THC below 0.5)
  - Treats multiple issues (e.g., seizures, neuropathic pain)
- Epidiolex
  - Investigational drug
  - Liquid formulation of highly purified CBD
  - Remarkable effects for epilepsy
  - Approved for seizures related to Dravet and Lennox-Gestaut syndromes

Cannabis

- As with any drug, the dose and frequency often drive the health risks
- When smoking marijuana the high hits immediately and then fades within hours.
- Edibles take time to absorb because they travel through the GI tract (30 minutes-to-several hours for effects). The timing varies even for experienced consumers, as stomach contents affect it.
- An extra amount of cannabinoid taken before full effect, may end up with the person taking too much, and in turn lead to paranoia, delusions, and panic.
- No matter the administration route, cannabis increases HR and BP, which potentially damage blood vessels. Edibles are associated with more adverse outcomes medically, especially cardiovascular and psychiatric symptoms.
- Edibles have more potent effect; induce more intense and intoxicating high because how the body metabolizes THC.

Opiates and Opioids

- Analgesic: Relieve pain without unconsciousness
- Historical events: World War I, Hospice movement, Perdue Pharma, and "Pseudo-addiction"
- Epidemic: Opioid Triad (coma, pupil constriction, and depressed respiration)
- Diversion by healthcare professionals
- Opiate Receptors: Naturally occurring Endorphins, Enkephalins, and Dynorphins
- Addiction (Tolerance, Withdrawal, and Compulsion)
- Chronic Use: Decreases in testosterone, estrogen, melatonin, and adenosine

- Natural Narcotics: Morphine and Codeine
- Semisynthetic Narcotics: Heroin, Dilaudid, Oxycontin, Percocet
- Totally Synthetic Narcotics: Demerol, Fentanyl, Methadone

- Partial Agonists:
  - Butrans (patch) and Belbuca (film)
  - Potentially lower abuse potential due to ceiling effect
- Antagonists: Narcan (Naloxone)
- Mixed Agonist-Antagonist: Suboxone (Buprenorphine and Naloxone) for medically-assisted treatment

U.S.A. Drug Schedule Chart

As Defined by the U.S. Controlled Substances Act

Classification	Description	Drug Examples
Schedule 1	No current legal medical use High potential for physical and/or psychological dependence High risk for addiction/abuse	• Heroin • GHB • LSD • Marijuana • MDMA/Ecstasy • Mescaline • Methaqualone • Peyote • Psilocybin
Schedule II	Restrictive legal medical use High potential for physical and/or psychological dependence High risk for addiction/abuse	• Adderall • Cocaine • Codeine • Crystal Meth • Demerol • Morphine • Opium • OxyContin • PCP • Percocet
Schedule III	Accepted legal medical use Low/Moderate potential for physical dependence Moderate/High potential for psychological dependence Moderate risk for addiction/abuse	• Anabolic Steroids • Ketamine • Lorcet • Aspirin (w/codeine) • Testosterone • Vicodin
Schedule IV	Accepted legal medical use Low potential for physical and/or psychological dependence Low risk for addiction/abuse	• Ambien • Atvian • Equanil • Rohypnol • Talwin • Xanax • Valium
Schedule V	Accepted legal medical use Limited potential for physical and/or psychological dependence Low risk for addiction/abuse	• Codeine-based cough medicines (Robitussin) • Cannabidiol (CBD) - 2018 Update
Schedule VI (Unscheduled)	Over-the-counter availability Legal without a prescription	• Alcohol • Aspirin • Caffeine • Nitrous Oxide • Nyquil • Tobacco

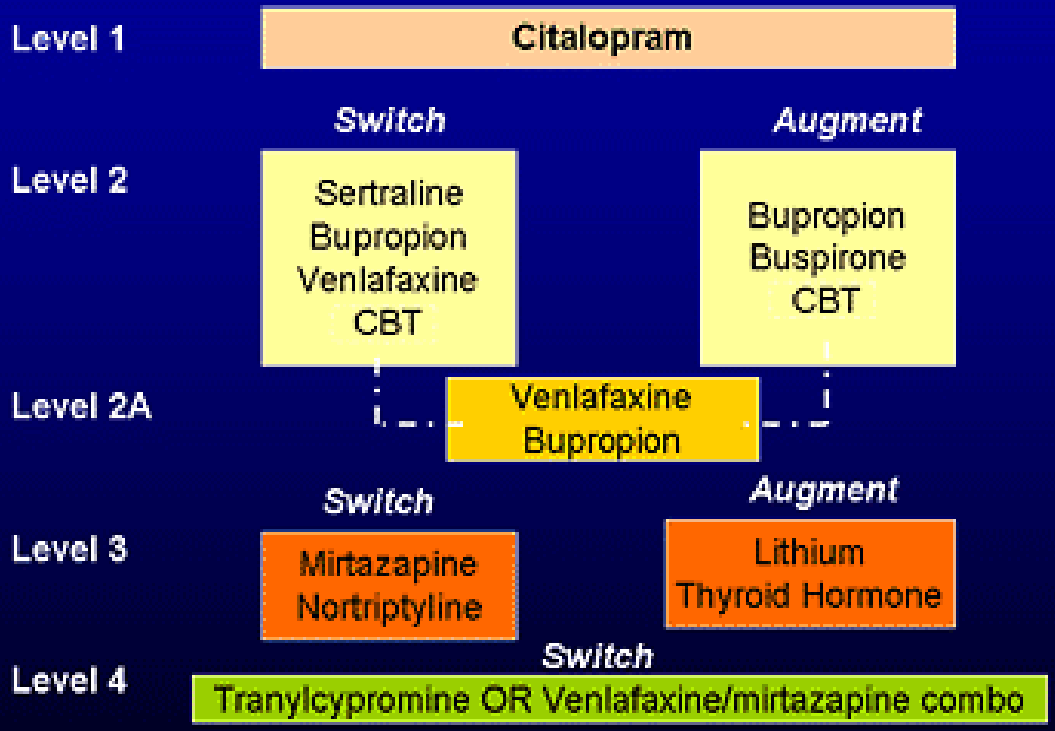

CURRENTLY ON
EXIT 58A-B
95
1
Zoloft
9
Prozac
Paxil
LAST EXIT BEFORE TOLL
Buspar
Wellbutrin
Celexa
Xanax

When are Psychotropics Appropriate?

- Failure of non-psychotropic based interventions, rather than an inadequacy or unavailability of services
- Risk of harm to self or others
- High intensity and frequency of challenging behaviors
- Presence of a accurately diagnosed psychiatric disorder
- To stabilize an individual in order to implement non-medication-based interventions
- Favorable past response to psychotropics
- Individual/Guardian preference as part of their person-centered plan (risk-to-benefit profile as part of informed consent)

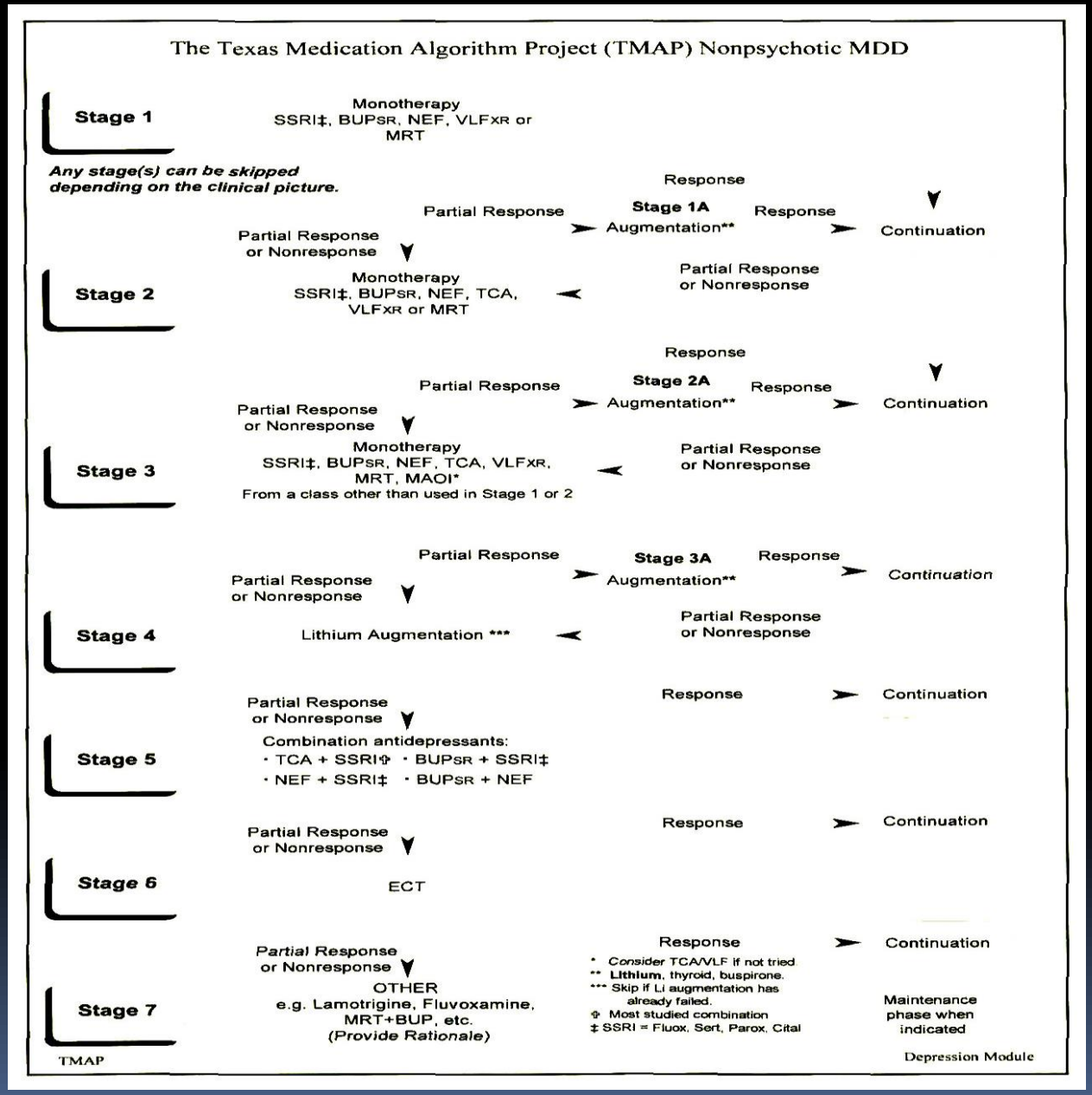
** Start low and go slow…lowest possible dose and minimum duration*

STAR-D† Algorithm for Depression



†Sequenced treatment alternatives to relieve depression, target enrollment N=4000

Rush AJ et al. *Control Clin Trials*. 2004;25:119-142.


The Texas Medication Algorithm Project (TMAP) Nonpsychotic MDD
Stage 1
Monotherapy
SSRI‡, BUPSR, NEF, VLFXR or MRT
Any stage(s) can be skipped depending on the clinical picture.
Response
Partial Response
Stage 1A
Augmentation**
Response
Continuation
Partial Response or Nonresponse
Stage 2
Monotherapy
SSRI‡, BUPSR, NEF, TCA, VLFXR or MRT
Partial Response or Nonresponse
Response
Partial Response
Stage 2A
Augmentation**
Response
Continuation
Partial Response or Nonresponse
Stage 3
Monotherapy
SSRI‡, BUPSR, NEF, TCA, VLFXR, MRT, MAOI*
From a class other than used in Stage 1 or 2
Partial Response or Nonresponse
Partial Response
Stage 3A
Augmentation**
Response
Continuation
Partial Response or Nonresponse
Stage 4
Lithium Augmentation ***
Partial Response or Nonresponse
Response
Continuation
Partial Response or Nonresponse
Stage 5
Combination antidepressants:
· TCA + SSRI✞ · BUPSR + SSRI‡
· NEF + SSRI‡ · BUPSR + NEF
Response
Continuation
Partial Response or Nonresponse
Stage 6
ECT
Response
Continuation
Partial Response or Nonresponse
Stage 7
OTHER
e.g. Lamotrigine, Fluvoxamine, MRT+BUP, etc.
(Provide Rationale)
* Consider TCA/VLF if not tried
** Lithium, thyroid, buspirone.
*** Skip if Li augmentation has already failed.
✞ Most studied combination
‡ SSRI = Fluox, Sert, Parox, Cital
Response
Continuation
Maintenance phase when indicated
TMAP
Depression Module

Psychotropic Medications and Special Populations

- **Developmental Disabilities**
- **Elderly**

Developmental Disabilities

- There was an expectation that psychotropic prescribing for those with I/DD would eventually decrease just like institutionalization, but it never fully materialized.

- In the area of I/DD, currently only two psychotropic medications are FDA-Approved. That is, Risperdal and Abilify to treat "irritability" (i.e., aggression, tantrums, SIB) in children and adolescents with autism spectrum disorder.

Developmental Disabilities

Why is there so much polypharmacy with IDD?

- **Albeit difficult to diagnose, multiple studies reflect that those with I/DD have a higher prevalence of mental illness when compared to the general population and that they can suffer from the entire range of psychiatric diagnoses.**
- **The diagnostic prevalence rate of psychotic disorders in the I/DD population is 3-5%. However, 30-50% of psychotropics prescribed to those with I/DD are antipsychotics.**
- **Psychiatric misdiagnosis: One issue is providers "working backwards" by using the response to prescribed medications as the guide to arrive at a working diagnosis.**
- **"Inherited" prescribing combined with poor advocacy**
- **Developmental disabilities is a marginal area of training in psychiatry and psychology**
- **Staff and caregiver attitudes about destabilizing or worsening**

Developmental Disabilities

Concerns about Psychotropic use for those with I/DD

- Higher than recommended doses
- Excessive reliance on medications
- Unknown long-term effects
- Lack of compelling evidence to support effectiveness
- Use of medications without informed consent
- Difficulty determining and communicating adverse effects

Unknowns…

- Individuals with I/DD are a heterogeneous group with complex and fragile neurological profiles, which makes them more vulnerable to adverse effects (e.g., metabolization and tolerability issues).

- Growing neurological evidence (e.g., fMRI) suggests that those with developmental disabilities (i.e., ID and ASD) experience problems with synaptic pruning and dendrite malformation. Medications may help to "fertilize" synaptic connections.

Developmental Disabilities

Mistaken Belief in the Power of Psychotropics to Manage Challenging Behaviors

- **Although often used beyond their FDA indications, psychotropic medications are regularly used to manage behaviors of concern among those with I/DD.**

- **In general, approximately 20-45% of those with I/DD receive psychotropic medications, many of whom to treat problem behaviors in the absence of a psychiatric diagnosis.**

- **Medication trials should be:**
  - **Targeted at *specific* symptoms (e.g., irritability)**
  - **Monitored for effectiveness using data collection**
  - **Regularly evaluated for risk versus benefit of continuation**

Developmental Disabilities

- We need to thoroughly investigate medical conditions, environmental contributions, emotional issues and psychiatric disorders that influence a behavior of concern before giving consideration to a trial of medication.
- Mental health issues might not be recognized and are attributed to the I/DD (i.e., diagnostic overshadowing bias).
- Adults with I/DD have higher rates of sensory impairments, cardiovascular disease, and gastrointestinal problems—all of which can influence prescribing and metabolization.

DDS Program Review Committee
Changes in 2018

1. ***Individuals below the statewide average (currently 2.87) complete a psychiatric medication data entry form.***

2. ***Individuals above the average (i.e., 3 or more) with no additions of new medications or aversives, submit a PRC packet for paper review.***

3. ***Additions of new medications and/or new aversives require a full (in-person) PRC presentation.***

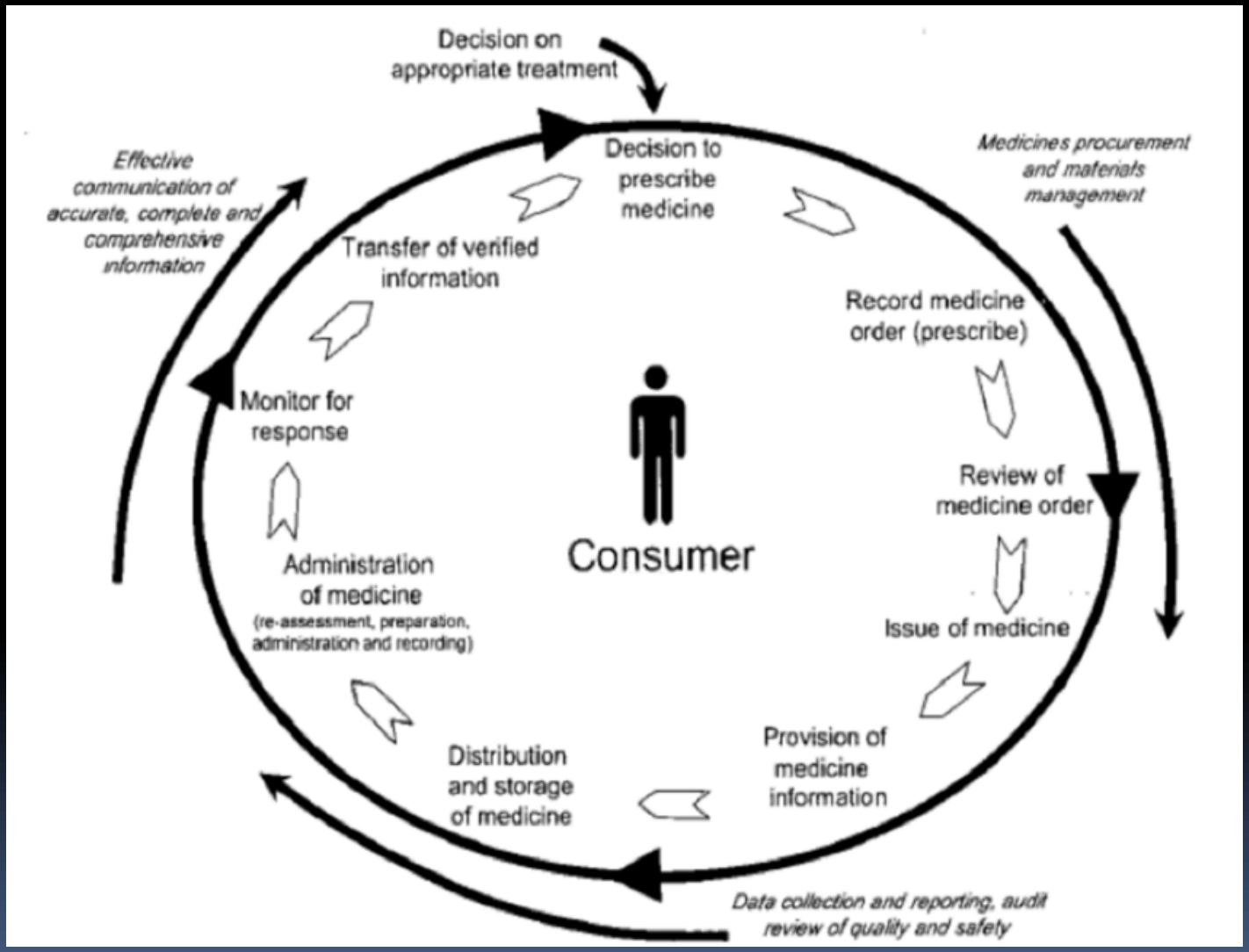
A number of challenges exist in determining the average number of psychotropic medications per individual-served due to the following:

- **Newer psychotropics might not be in our database**
- **Medications could falsely be entered as non-psychotropic**
- **Anti-seizure medications used for mood might be listed as non-psychotropic.**

Elderly

- Poorly researched group. Avoided due to confounds from medical illnesses.
- Beers Criteria (for Potentially Inappropriate Medication Use in Older Adults)
- Every year past 30, we lose up to 0.76% of liver and kidney functioning, so lower doses of medications may be most appropriate for this population.
- High-Risk Psychopharmacology
  - Tricyclic antidepressants
  - Benzodiazepines
  - Antipsychotics
  - Anticholinergics

Psychiatric Consultations



Helpful Tips for Psychiatric Consultations

- Identify the specific symptoms and behaviors to target (e.g., insomnia and low motivation)
- Saying anxiety or depression is too generic
- Limiting to 3 or 4 symptoms helps reduce polypharmacy
- Focus on symptoms rather than sources of psychosocial and emotional distress (e.g., loneliness and sadness)
- Reducing intensity of symptoms (e.g., making affect manageable) might warrant consideration of PRN instead of a standing order

Areas for Medication Evaluation

Risk

- Developmental factors
- Education and language
- Gender and sex
- Culture and Ethnicity
- Weight (gained or lost)
- Allergies
- Addictions
- Health Status and Medical Conditions (e.g., diabetes, seizures)
- Past drug interactions

Risk-to-benefit analysis: Why expose someone to risk of adverse side effects if we are not getting a symptom reduction?

Areas for Medication Evaluation

Knowledge and Monitoring

- Informed consent versus assent
- Educate which medications do what
- Diagnosis and Treatment Plan?
- Dosages and Appearance of Drugs?
- Side Effects?
- What to do if a dose is missed?
- What OTC medications are taken?
- At minimum, select one valued outcome that can be operationally defined, measured, and observed as a clear indication of improvement.
- Baseline versus interventional data collection (e.g., blood pressure)

Areas for Medication Evaluation

Communication

- Why are you taking these medications?
- Do they work? Validate concerns about medications.
- Any recent medication changes?
- Are you comfortable discussing medications with your provider?

Adherence

- Have you stopped taking medications on your own?
- Are you afraid of your medications?
- Do you know the potential risks to your medications?
- Do you do things to make the medications last longer?
- Are the medications that you are taking cause problems?

Areas for Medication Evaluation

- If a combination of medications is effective, then try to reduce or remove the first medication (i.e., return to monotherapy as soon as possible)
- Studies suggest that a reduction in polypharmacy improves quality of life
- Psychotropic medications should be used to treat specific psychiatric disorders, rather than symptoms, and be just one part of treatment along with behavioral and psychosocial supports.

Keys to Informed Consent
Prior to Initiation

- **Medications are not dispensed without thorough evaluation**
- **Discussion of the specific condition to be treated**
- **Alternatives to medications are considered**
- **Risks and benefits associated with each medication are identified**
- **Least restrictive interventions primary**
- **Proper administration is ensured**
- **Monitoring safeguards**
- **Withdrawal strategies**
- **Drug tapering plan**

It's never inappropriate to inquire as to why a person is receiving overlapping medication treatments because the risk of negative side effects increases with the addition of each new drug.

De-Prescribing Protocols:
Concept from Geriatric Medicine

- **Ascertain all the drugs the person is currently taking and the reasons for each one**
- **Consider the current and future benefit compared to harm potential**
- **Prioritize drugs for discontinuation starting with those that have least benefit, lowest adverse withdrawal reactions, and lowest disease rebound effect**
- **Monitor closely for improvement or adverse effects**

Current and Future Directions in Prescribing

- Faster-acting (e.g., melt-away Xanax, Zuranolone)
- The era of molecular neurobiology (e.g., receptor specificity)
- The role of inflammation (e.g., corticotropic-releasing antagonists)
- Neurogenic Theory of Depression Treatment (i.e., *Neurogenesis: medications stimulate changes in the brain, especially neural integration*)
- Poor profitability for affective spectrum medications
- Focus on early stages of diseases
- Elective or Enhancement Psychopharmacology

It is an art of no little importance to administer medicines properly, but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them."

-Philippe Pinel 1809