Introduction to Psychopharmacology or, "9,999 Simple Rules for Prescribing Psychotropics"

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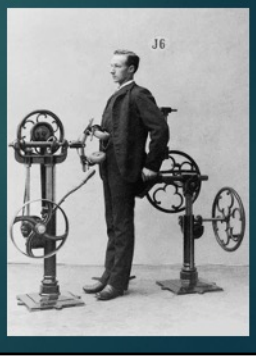
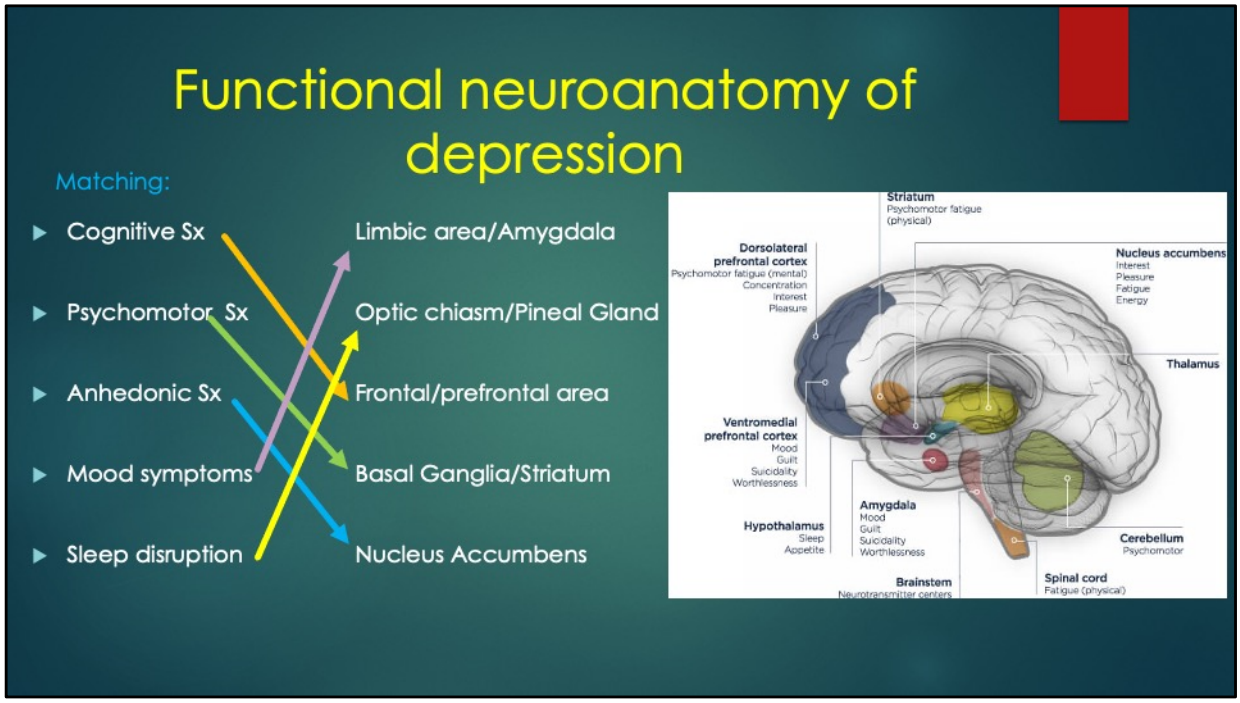
Part 1: Neurotransmitters (NT's): the brain's chemical messengers

EFFECTS OF SPECIFIC NT'S ON SPECIFIC BRAIN FUNCTIONS

UNDERSTAND - DON'T MEMORIZE - SIDE EFFECTS

4 IMPORTANT SIDE EFFECT SYNDROMES (MEMORIZE THESE)





We're all accustomed to the fact that different brain regions are concerned with different mental and bodily functions. Let's do a little matching test to refresh out memories about what brain regions are associated with various components of clinical depression.

If we could remove the burnt-out part of the brain and replace it, like replacing a burnt-out fuse from the fuse box, that would solve the problem. But we don't generally do brain surgery for depression, so we're left with giving medicines that increase the neurotransmitter molecules that are associated with each brain region, in the hopes of re-activating – or inhibiting – the malfunctioning brain region (next slide).

Symptom categories for depression:

Cognitive Sx = poor concentration, negative cognitive bias (filtering), Attribution bias, "negative cognitive triad"

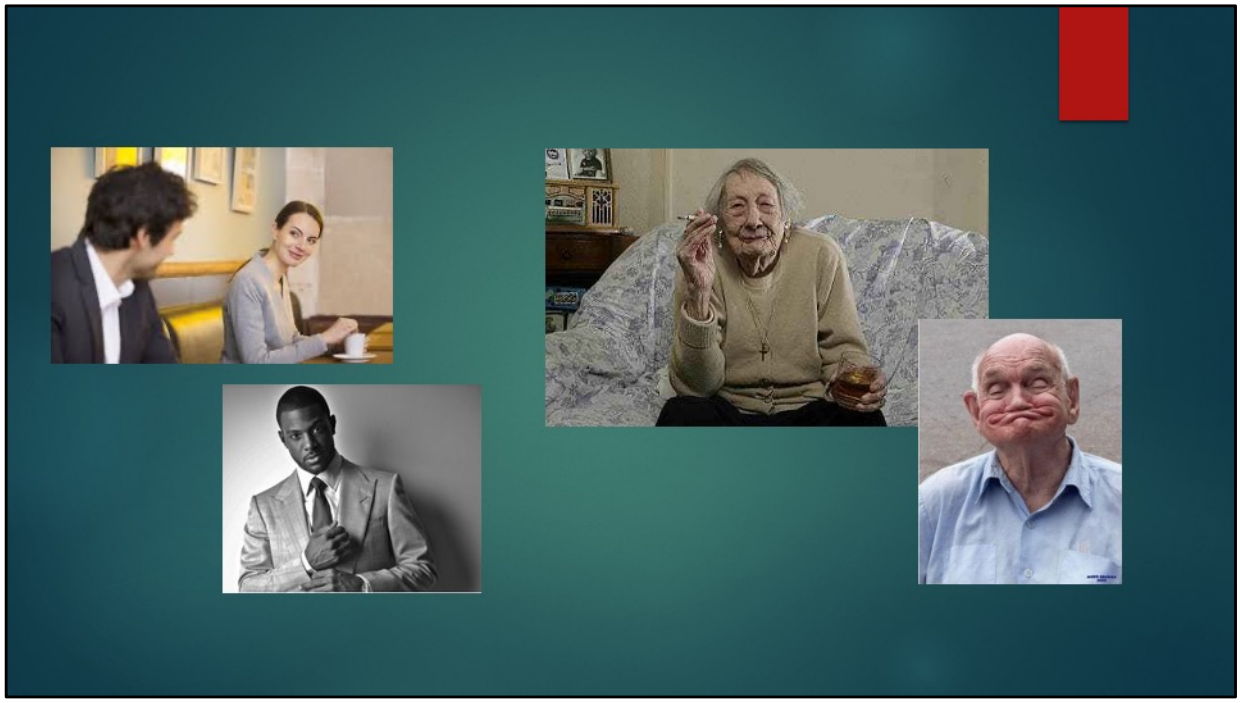
Somatic Sx = pain, fatigue, HA, stomach upset, sensory changes, heightened pain perception, psychomotor slowing

Anhedonia = favorite meal tastes like cardboard, no interest in favorite activities, loss of sex drive

Mood symptoms = sad, irritable, angry, insecure, guilty, worried, fearful

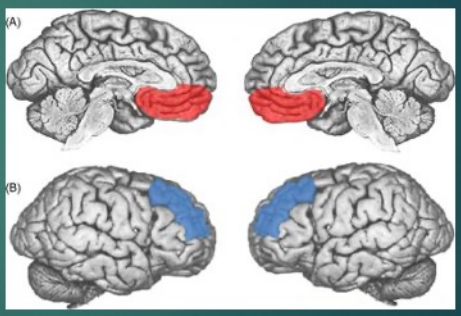
Sleep disturbance = insomnia or hypersomnia

Overall, it seems short-sighted and limited to call Major Depression a “mood disorder”



Functional neuroanatomy of depression

- DL-PFC
  - Attentional control, cognition
  - Regulation of negative affect
- VM-PFC
  - Negative affect
  - Hyperactive in depression
- Refractory vs. non-Refractory depression



- From "The Functional Neuroanatomy of Depression: Distinct Roles for Ventromedial and Dorsolateral Prefrontal Cortex", Koenigs et al., Behav Brain Res 2009 Aug 12:201(2): 239-243

Review slide.

What is the purpose of the brain, anyway? E.g., the lungs are the organ of oxygen exchange, the kidneys are the organ of filtration, so what is the primary function of the brain? If you said something along the lines of "control and integration center" I couldn't fault you, but I would agree with those who call the brain the organ of "threat detection". What's the real purpose, the survival value, of storing memories, interpreting visual data, generating strong emotions, and so forth, if not to remember to avoid the pile of sticks near the water's edge because that's where the rattlesnake lives, or that the bright red, small berries will make you really sick and kill you, etc.?

The brain as the organ of threat detection makes a lot of sense, from the evolutionary point of view, with all the billions of neurons and trillions of synapses as a kind of complex, giant ciphering machine, that all boils down to a basic, binary decision: approach or avoid, walk toward or run from, seize an opportunity or stay safe.

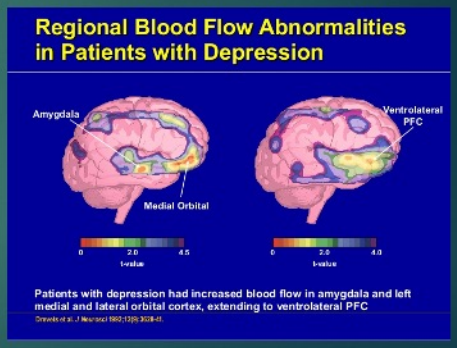
Because avoiding danger has more survival value than seizing opportunity, the brain has what we all know as – what – the brain's "inherent negativity bias" – that's why

worry and anxiety are normal emotions and not only clinical disorders. Depression and anxiety disorders can be thought of as exaggerations of the brains normal, inherent negativity bias. The negativity bias refers to the fact that we – i.e., our brains – respond more strongly to a bit of negative news then we do to an equivalent bit of positive news. Eg., we had a lot of positive feedback about something we did, but the one or two little bits of negative feedback are what we zero in on and fixate on. Or, something we said or did years ago that was erroneous or mildly embarrassing comes back to haunt us again and again.

Negativity bias has survival value. After all, which is more important, reaching out and plucking a tasty little berry with healthy carbohydrates and anti-oxidants, or avoiding eating a poisonous little berry that will make you puke and go into muscle spasm and make you lose control of your bowels and bladder before dying a sickening, painful death? Obviously there's more survival value in avoid mortal danger than in securing momentary pleasures. A lot of the field of positive psychology has to do with overcoming the brain's inherent negativity bias, for example, through exercises like savoring, appreciating, looking for the positives, and journaling about the positives. This is especially helpful for patients in treatment for depression, whose brain's are hyperalert with negativity bias, always wondering, "what will go wrong next?"

How psychotropics affect brain function

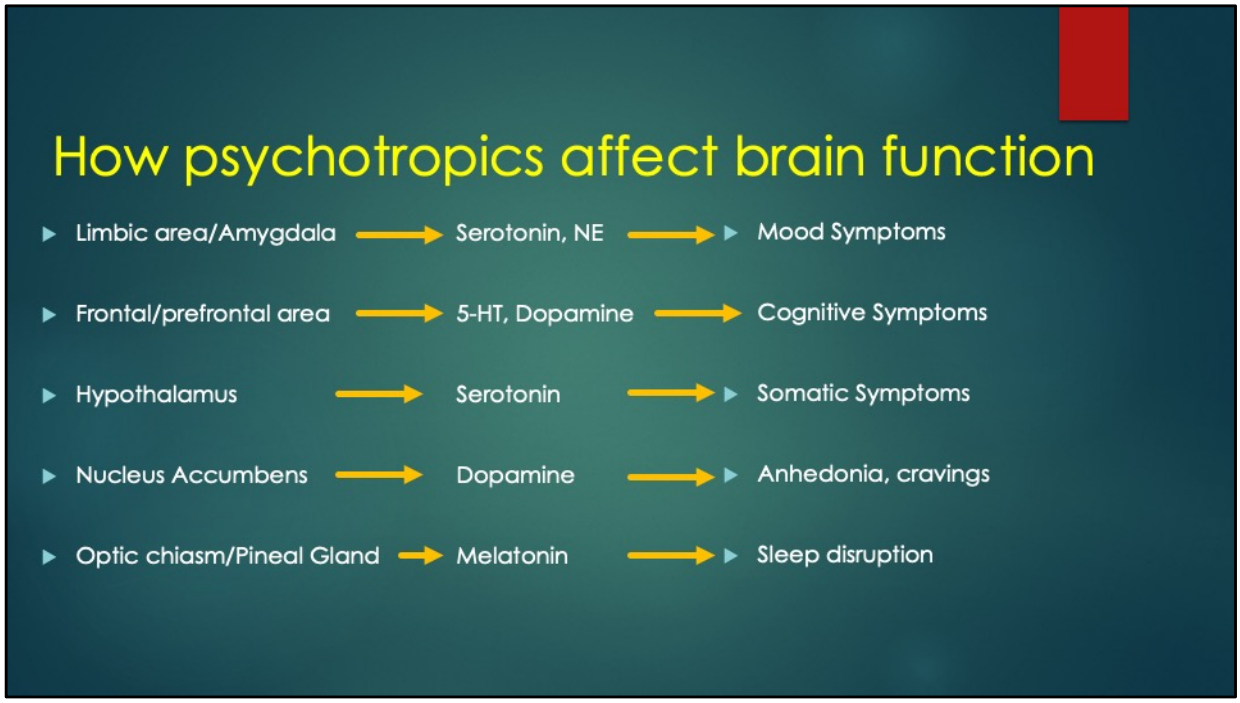
Limbic area/Amygdala	Serotonin, NE
Frontal/prefrontal area	5-HT, Dopamine
Hypothalamus	Serotonin, Oxytocin
Nucleus Accumbens	Dopamine
Optic chiasm/Pineal Gland	Melatonin



From the article "Stress, Neural Plasticity, and Major Depression" in your bibliography, we know, for example, that there's hypo-activity – as measured by rCBF – in parts of the frontal cortex; and there's also anatomical changes including reduced cortical thickness and reduced regional volumes.

In MDD, there is specific loss of volume of the hippocampus, as a result of reduced dendritic length and branching in that organelle. In contrast, we see increased dendritic hypertrophy – an increase in connections and activity – in the brain's alerting and alarm center, the Amygdala.

And or course, other anatomical brain changes, as well. So which neurotransmitters are associated with which brain regions?



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Where we are now:

Depression: antidepressant
Anxiety: same “antidepressant”
Panic disorder: same “antidepressant”
Eating disorder: again, same “antidepressant”
Premenstrual dysphoric disorder: same
PTSD: same
OCD: same
Fibromyalgia pain: same
ADHD: same class of medication
Migraine HA: same

Antipsychotic:
Schizophrenia
Depression in Bipolar disorder
Anxiety & insomnia

Therefore: think no longer in outdated terms such as “antidepressant” or

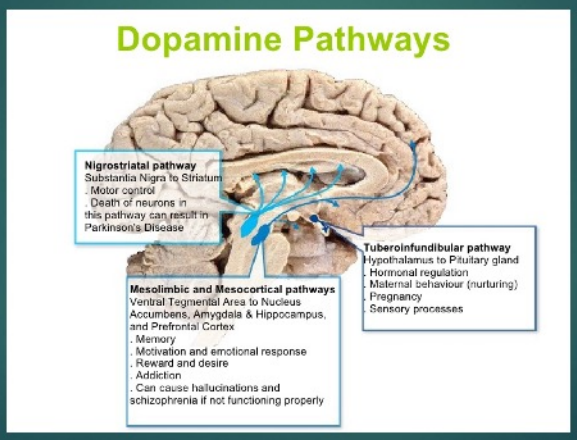
“antipsychotic” or “anti-anxiety” - but rather in terms of the NT type: “Serotonergic” “Dopaminergic” “Anticholinergic” etc.

Principal DA Pathways in the Brain

Tracts in brain…

- The **Mesolimbic Dopamine Pathway :** midbrain ventral tegmental area to the nucleus accumbens ,a part of the limbic system of the brain thought to be involved in many behaviors **such** as pleasurable sensations, the powerful euphoria of drugs of abuse, as well as delusions and hallucinations of psychosis.
- **The Mesocortical Dopamine Pathway** : It also projects from the midbrain ventral tegmental area but sends its axons to areas of the prefrontal cortex, where they may have **a** role in mediating cognitive symptoms (dorsolateral prefrontal cortex) and affective symptoms (ventromedial prefrontal cortex) of schizophrenia.
- **The Nigrostriatal Dopamine Pathway** : which projects from the substantia nigra to the basal ganglia or striatum, is part of the extrapyramidal nervous system and controls motor function **and** movement.
- **Tuberoinfundibular Dopamine Pathway** : projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion.
- **The fifth dopamine pathway arises from multiple sites, including the periaqueductal gray, ventral mesencephalon, hypothalamic nuclei, and lateral parabrachial nucleus, and it projects to the thalamus. Its function is not currently well known.**

Dopamine (DA): 1 Neurotransmitter, many effects

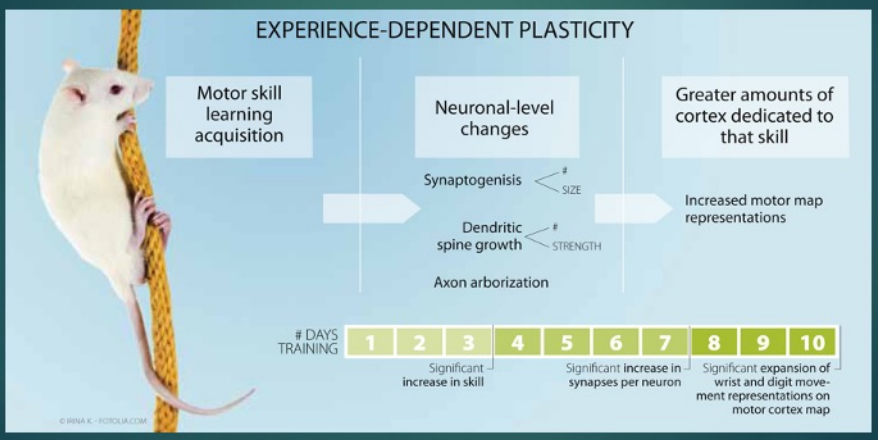


The effect of a psychotropic on the individual depends not only on the characteristics of the drug, and the individual variables in the patient (genetics, presence of essential co-factors in NT synthesis, etc.), but also on which pathways in the brain are affected. For example, if you want to know both the intended effects and the side effects of a DA-blocking drug – a "first generation" antipsychotic – such as Haldol, it helps to know that there are 4 DA pathways in the brain.

And the drug effects correspond to each of the 4 pathways:

1) Mesolimbic: pleasure and reward (limbic: VTA & Nacc)
2) Mesocortical: hallucinations & delusions (PFC & OFC)
3) Nigrostriatal: EPSE and movement disorders (basal ganglia)
4) Tuberoinfundibular (HPA axis) – dopamine > VIP > Prolactin > breast milk & mammary glands

Neuroplasticity, Neurogenesis, Synaptoneogenesis



Probably you've all seen by now that two-minute animated video on "neuroplasticity"; or at the very least are familiar with the dictum "neurons that fire together, wire together."

Psychotropic medicines, as well as some micronutrients and supplements, not only increase utilization of specific neurotransmitter messenger molecules, but actually sculpt and reshape the brain itself, through neurogenesis and synaptoneogenesis.

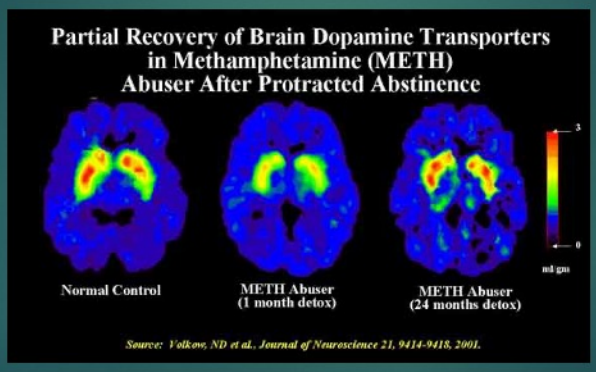
And for extra credit, what was the first "psychological disorder" demonstrated to cause actual, anatomical changes in the size and volume of brain structures?

Ans: PTSD, and "hippocampal atrophy."

Healthy diet = increased hippocampal volume.

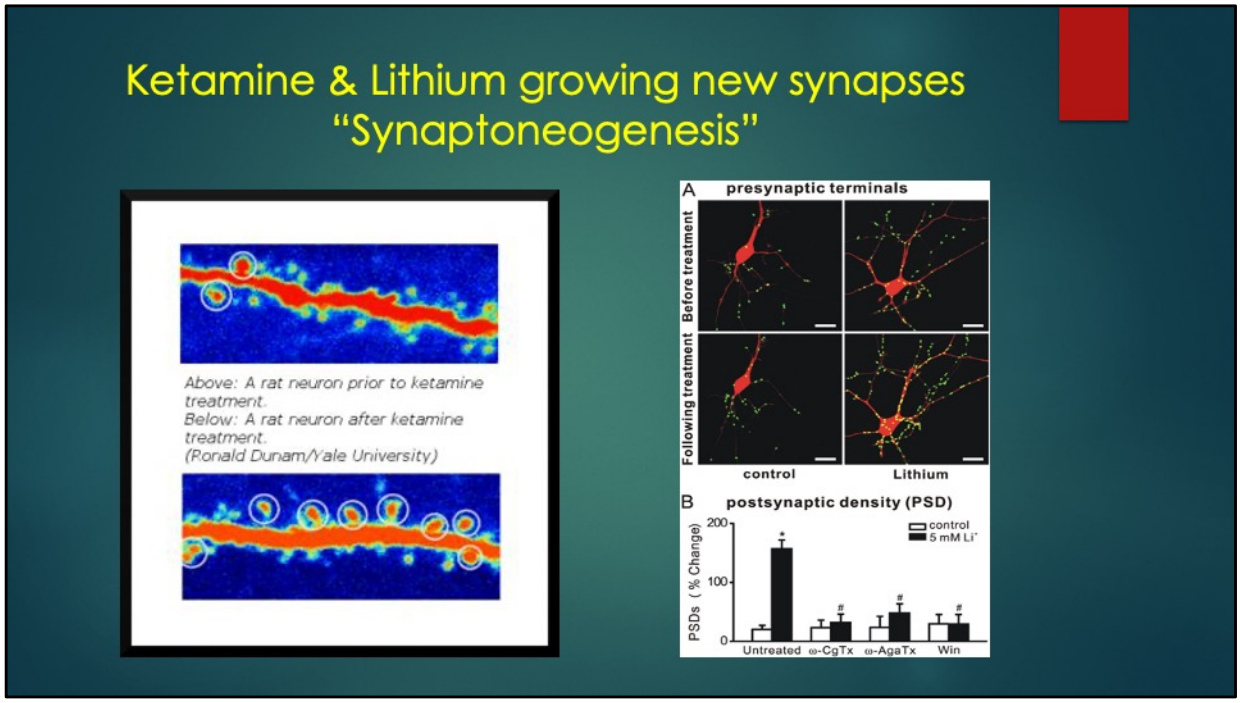
Major depression = reduced hippocampal volume, increase in dendritic spine growth in amygdala.

Methamphetamine: effects on DA in the brain



DA, NT are stimulatory NT's.

Amphetamines & cocaine promote massive DA & NT synthesis (cocaine) & release (amphetamine) & can cause long-term depletion or "burnout" of DA & NE pathways.



Reference: http://www.jbrf.org/2012/06/05/how-ketamine-works-to-treat-depression/, "how ketamine works to treat depression".

Lithium Increases Synapse Formation between Hippocampal Neurons by Depleting Phosphoinositides
Hee Jung Kim and Stanley A. Thayer
Molecular Pharmacology May 2009, 75 (5) 1021-1030; DOI: https://doi.org/10.1124/mol.108.052357

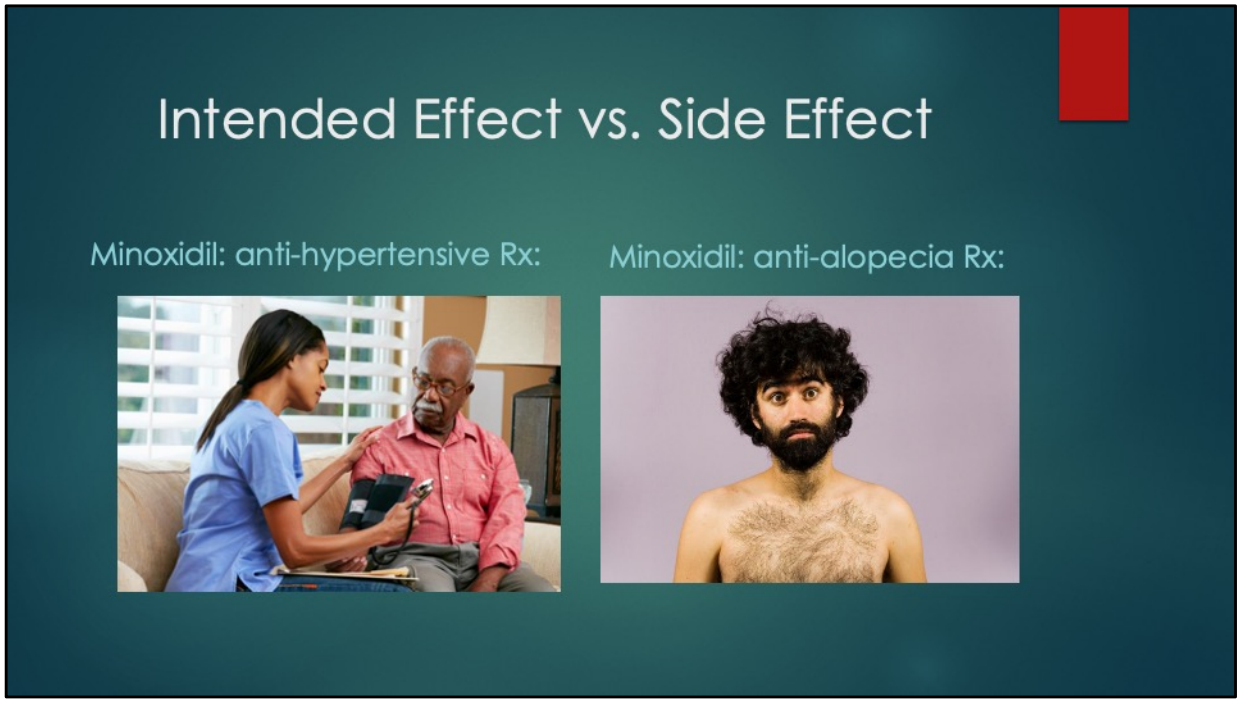
Lithium inhibits GSK3-beta

So, key NT pathways in the brain can be burnt out or depleted by either psychiatric illness or drug abuse, and/or re-grown, via neural plasticity, from recovery or psychotropic medications..

Flower vs. Weed

Dandelions:

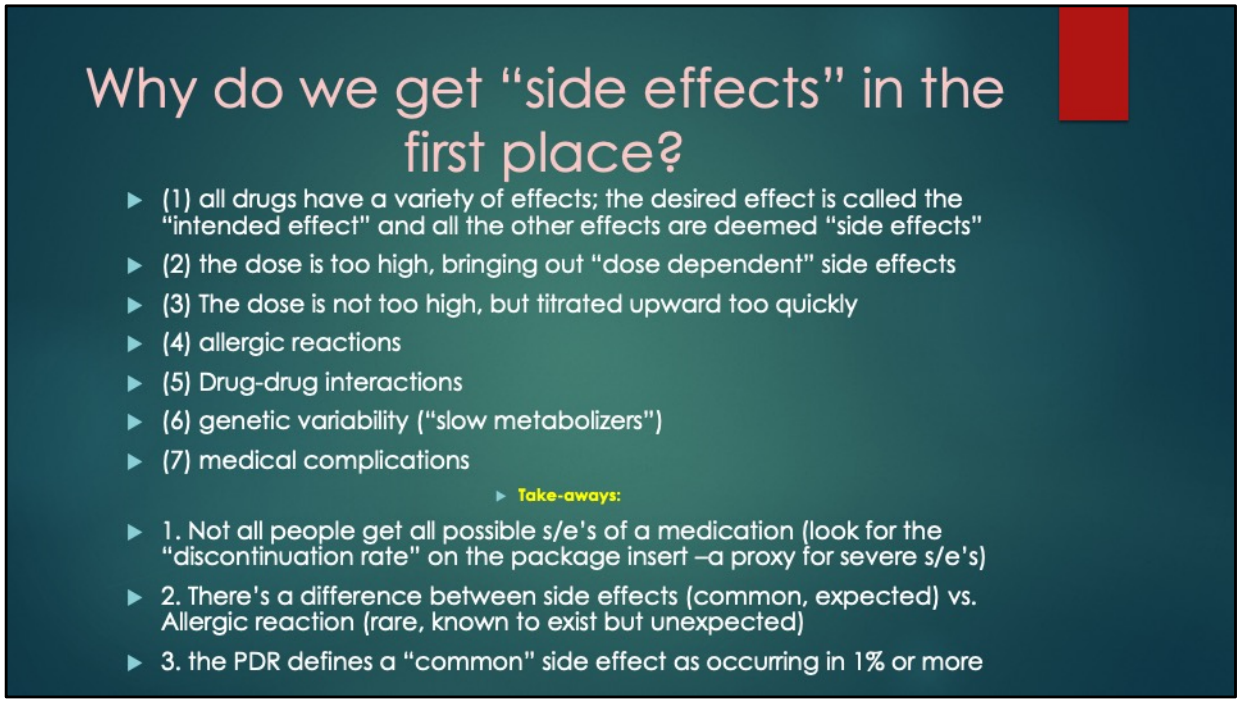
Dandelions:



Sometimes the answer is: using a different drug.

Sometimes the answer is: using the same drug, for a different purpose.

In fact, side effects and intended effects – like the DA that goes to four different pathways in the brain, or like the dandelion flower – are one in the same.



So, if we want to MINIMIZE side effects, we've got to know why our patients get side effects in the first place:

Therefore, it is worth "one slide's worth" of our time and attention to ask the fundamental question, "what exactly are "side effects" and why do we get "side effects" in the first place [pause here and ask the audience for some plausible explanations and discussion];

Bullet #1: indeed, if pharmaceuticals had perfect specificity there would be no side effects; let's reconvene in around 10 years from now and we may find that big pharma has developed drugs that directly target that "third messenger" and turn on or off specific protein synthesis to get a perfectly specific intended effect with no side effects whatsoever.

Until then, the difference between a drug's "intended effect" and its "side effects" is rather like the difference between a flower and a weed: it you like it, it's called a flower, if you don't like it, it's called a weed.

Bullet #2: consider the well-known "anticholinergic profile" of many psychotropic

medications, including notably the FGA's, the TCA's, and some SSRI's.

Bullet #4: e.g., Lamictal & Stevens-Johnson syndrome

Bullet #6: CYP 450 enzyme induction

Bullet #7: e.g., "had gastroenteritis during the study"

Rule # 998: anyone can get any side effect to any medication

IOW: there have been Zillions and Zillions of medication s/e's and therefore even atypical s/e's are sometimes seen.

Key concept: difference between "side effects" (common, expected) vs. "allergic" (rare, unexpected)

Pop quiz

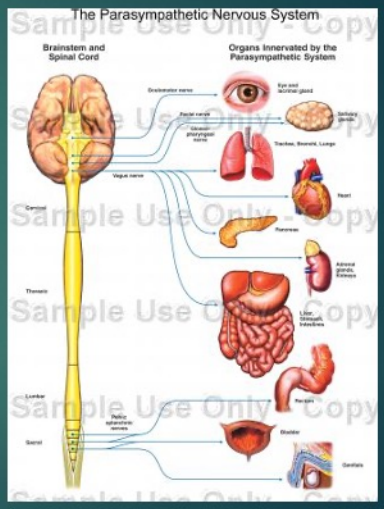
- You've diagnosed your patient with acute mania and immediately placed him on Depakote 1,000 mg TID. Within 48 hours he complains of acute GI upset, diarrhea, and hair falling out. The best explanation for this is:

A. Patient is allergic to Depakote
B. Dose-dependent side effects
C. Psychosomatic reaction in a delusional, manic patient
D. You don't know your psychopharmacology & you prescribed the wrong drug
E. You prescribed the right drug, but you failed to start at low doses & titrate upward

Answer: E

Anticholinergic Side Effect Profile

- Blurry vision
- Dry mouth
- Constipation
- Urinary hesitancy
- Memory loss (elderly)
- Exacerbation of BPH, Glaucoma
- (rarely) hallucinations or delirium
- Mild tachycardia



So that's some fundamentals about side effects in general; one of the most important specific psychotropic side effects to know about is the so-called "anticholinergic side effect profile".

Elderly with less cognitive reserve = "CAS" or Central Anticholinergic Syndrome, severe memory loss and/or delirium

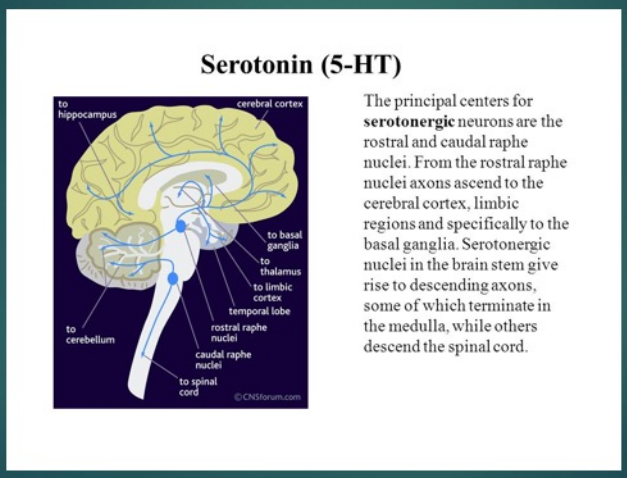
Anticholinergic s/e profile most commonly seen in:

FGA's

TCA's

some SSRI's

Serotonin pathways in the Brain



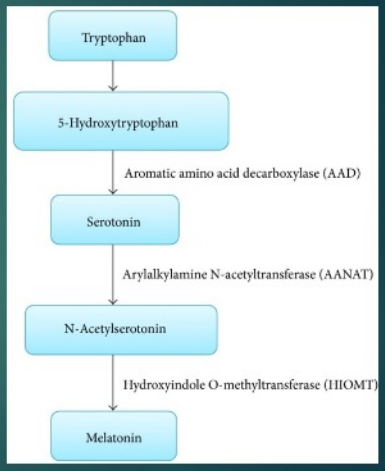
The serotonin pathways in the brain don't so much have discrete names as to the DA tracts, because Serotonin neurons project widely throughout the cerebral cortex and subcortically. 5HT pathways originate in the "dorsal raphe nuclei" deep in the brainstem and medulla and project both rostrally (upward into the brain) and caudally (toward the tailbone – down the spinal cord). Accordingly, serotonin – which is ony transmitted or received by a paltry 1 to 2 % of all neurons – has widespread effects including:

- Mood
- Anxiety
- Blood pressure
- GI function
- Sleep
- Appetite
- Impulsivity
- Obsessive-compulsiveness
- Sexual function
- Social dominance and/or social pain

- 5HT synthesized in brain and gut (80 – 90 % in gut).

The "DOMAINS" of Serotonin

D	Depression	e.g., **Fluoxetine**
O	Obsessions (OCD)	e.g. **Clomipramine**
M	Migraines	e.g., **Sumitriptan**
A	Anxiety	e.g., **Buspirone**
A	Appetite	e.g., **Fenfluramine**
I	Intestines	e.g., **Ondansetron**
N	Nausea	e.g., **Ondansetron**
N	Neuropathic pain	e.g., **Meperidine**
S	Sexual functioning	e.g., **Flibanserin**
S	Sleep	e.g., **Melatonin**



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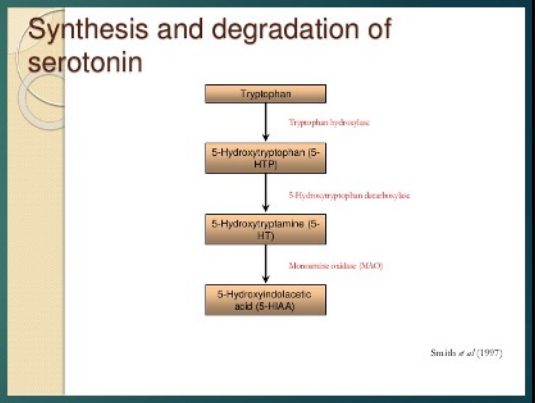
N	Nausea	e.g., **Ondansetron**
N	Neuropathic pain	e.g., **Meperidine**
S	Sexual functioning	e.g., **Cyproheptadine**
S	Sleep	e.g., **Melatonin**

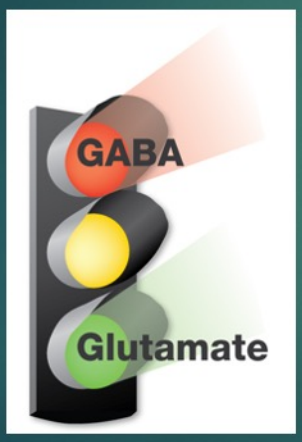


Odansetron = Zofran
- 5HT-3 antagonist
- Anti-emetic

Fenfluramine
- Promotes release of 5HT from pre-synaptic vesicles
- Weight loss drug withdrawn from market b/c of risk of pulmonary hypertension

Meperidine
- Demerol, an opiate analgesic
- Serotonin reuptake blockade
- Libby Zion at NYU hospital – on Phenelzine for depression, maybe serorontin syndrome, got a shot of Meperidine from tired resident physician

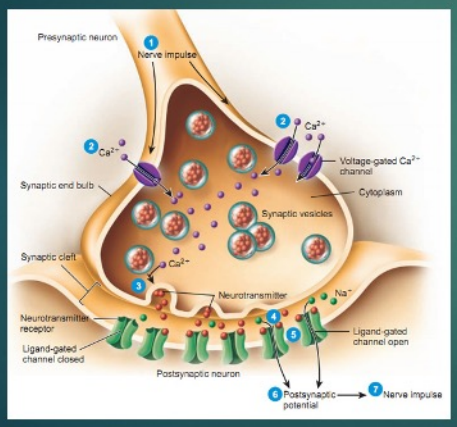
GABA & Glutamate



- **Glutamate and GABA: A System in Balance**
- Glutamate and GABA (gamma-aminobutyric acid) are the brain's most plentiful neurotransmitters. Over half of all brain synapses use glutamate, and 30-40% use GABA.
- Since GABA is inhibitory and glutamate is excitatory, both neurotransmitters work together to control many processes, including the brain's overall level of excitation. Many of the drugs of abuse change the balance of glutamate or GABA, exerting tranquilizing or stimulating effects on the brain. Drugs that increase GABA or decrease glutamate are depressants. Those that decrease GABA or increase glutamate are tranquilizers or stimulants.
- Alcohol decreases glutamate activity.
- PCP, or "angel dust," increases glutamate activity.
- Caffeine increases glutamate activity and inhibits GABA release.
- Alcohol increases GABA activity.
- Tranquilizers increase GABA activity.

Our friend the Synapse

"You are your synapses. They are who you are."
--- Joseph LeDoux, 2002 (in *Synaptic Self*)



- Synthesis of NT's in the neuronal cell body
- The fate of NT's at or near the synapse:
- Transport & Release
- Neurotransmission
- Re-uptake
- Metabolism
- Blockade

Examples of each:

Synthesis: synthesis, or manufacture, of NT's depends on "rate-limiting" steps such as presence of co-factors (folate, methylfolate, MTHFR, etc.) and transcription signals within the neuronal cell nucleus (why consuming more tryptophan-rich foods doesn't cure depression: lack of tryptophan is not usually a "rate-limiting step" in biogenic amine synthesis).

Release: methamphetamine directly promotes release of DA & NT into the synaptic cleft

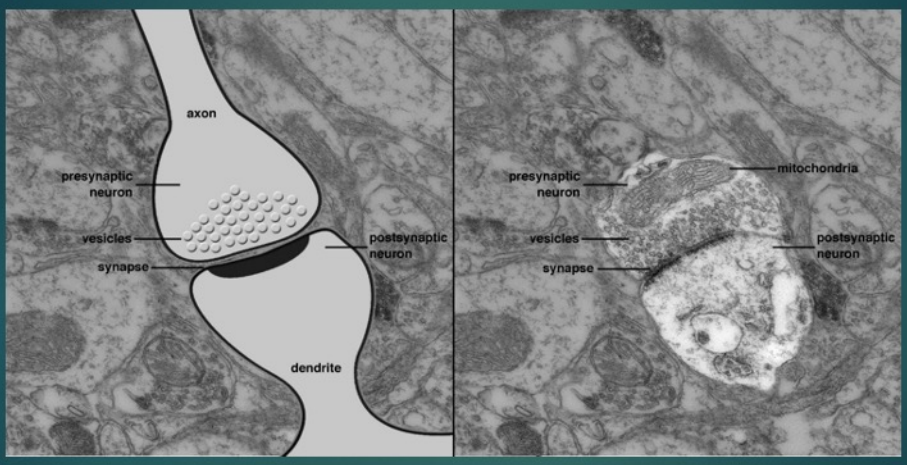
Transmission: successful binding of the NT to the receptor complex protein (results in: ion channel changes, action potential and/or intracellular second messenger release)

Re-uptake: NT resorbed back into pre- or post- synaptic neuron for recycling (note on the acronym "SSRI": SSRI's "inhibit" re-uptake of Serotonin)

Metabolism: NT is "digested" in the synapse by enzymes (predominantly COMT; COMT is blocked by MAO-I's)

Blockade: a competing molecule with greater binding affinity sits on the (pre- or post-synaptic) receptor complex, with either agonistic, antagonistic, or partial agonistic activity (Thorazine = post-synaptic blockade [“competitive antagonism”], [“nerve gas” = non-competitive agonism at post-synaptic, cholinergic receptors], antagonism of an antagonistic receptor (clonidine is an agonist at pre-synaptic [inhibitory] alpha-adrenergic receptors), or partial agonists (Buprenorphene is a “partial agonist”

Synapse: electron microscopy



Second Messenger System

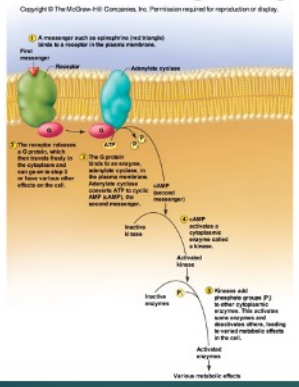


Figure 3.9

3-19

CYCLIC AMP

- cAMP is a second messenger that is synthesized from ATP by the action of the enzyme **adenylyl cyclase**.
- Binding of the hormone to its receptor activates a **G protein** which, in turn, activates adenylyl cyclase.
- Leads to appropriate response in the cell by either (or both):
  - using **Protein Kinase A (PKA)** — a cAMP-dependent protein kinase that phosphorylates target proteins;
  - cAMP binds to a protein called **CREB (cAMP response element binding protein)**, and the resultant complex controls transcription of genes.
- Eg.of cAMP action - adrenaline, glucagon, LH

Explain:

First messengers (neurotransmitters)

Second Messengers (intracellular compounds like ATP/cAMP)

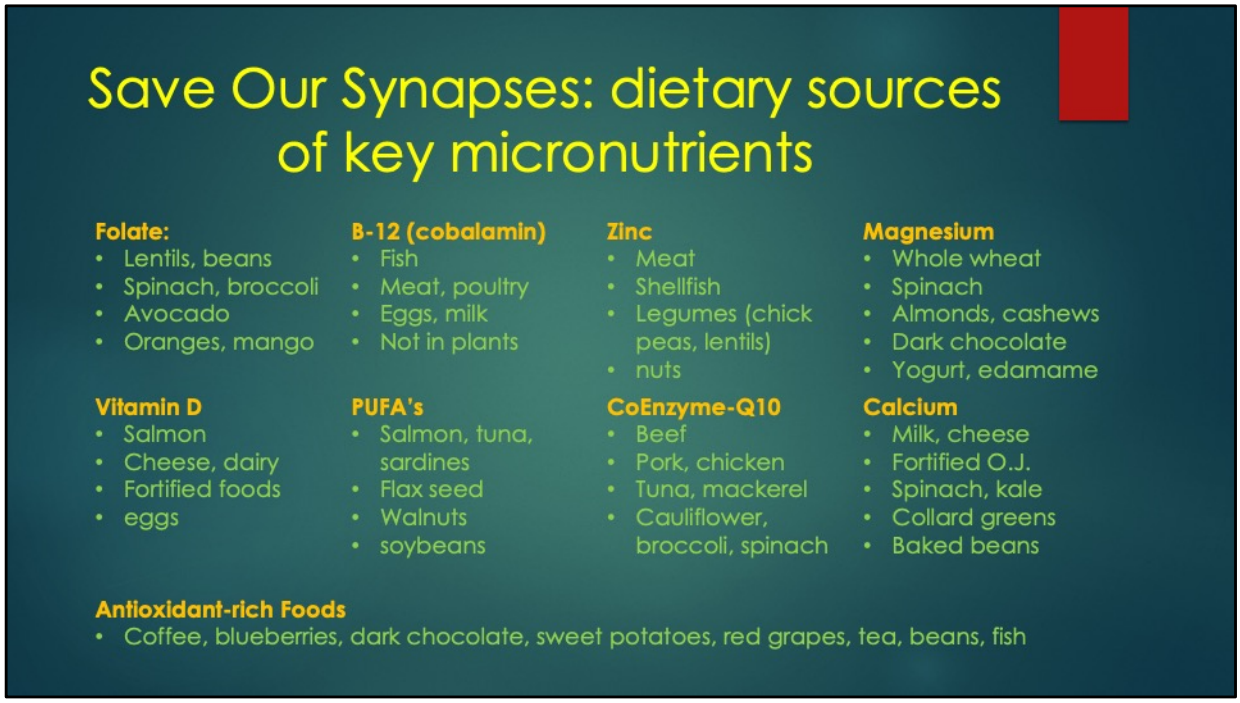
Third messengers

Disorders of the receptor compound:

(1) genetic variants

(2) autoimmune encephalopathies

(3) nutritional deficiencies (hypocholesterolemia)



We've been talking about methyl donors such as folate and B-12, which are essential for biogenic amine synthesis (DA, NE, 5HT), so let's take a moment to remind ourselves of where some of these key nutrients come from in our diet …

Grapes: anthocyanins, polyphenols, selenium

Blueberries:

Coffee, tea: catechins,

Dark chocolate:

Sweet potatoes:

Beans:

Dark leafy vegetables:

Nuts:

Serotonin Syndrome

CAN you diagnosis serotonin syndrome?

C	**COGNITIVE CHANGES**: Agitation, confusion, euphoria, insomnia, hypomania, hallucinations
A	**AUTONOMIC CHANGES**: Tachycardia, HTN, fever, diaphoresis, mydriasis, arrythmias, tachypnea
N	**NEUROMUSCULAR CHANGES**: Tremor, hyperreflexia, clonus, ataxia, incoordination, seizures

Table 1. Drugs That Have the Potential to Cause SS

SSRIs	Miscellaneous
Citalopram	Buspirone
Fluoxetine	Carbamazepine
Fluvoxamine	Cocaine
Olanzapine/fluoxetine	Cyclobenzaprine
Paroxetine	Dextromethorphan
	Ergot alkaloids
SNRIs	Fentanyl
Duloxetine	5-Hydroxytryptophan
Sibutramine	Linezolid
Venlafaxine	Lithium
	L-Tryptophan
Triptans	Meperidine
Almotriptan	Methadone
Eletriptan	Methamphetamine
Frovatriptan	Methylene blue
Naratriptan	Metoclopramide
Rizatriptan	Mirtazapine
Sumatriptan	Ondansetron
Zolmitriptan	Phenelzine
	Selegiline
	St. John's wort
	Tramadol
	Tranylcypromine
	Trazodone
	Tricyclic antidepressants
	Valproic acid

SNRI: serotonin norepinephrine reuptake inhibitor; SS: serotonin syndrome; SSRI: selective serotonin reuptake inhibitor.
Source: References 6-13.

Maybe a more transparent name would simply be “Serotonin Toxicity”, but it’s “Serotonin Syndrome” and we’re stuck with it.

How about the acronym “**CANT**”, where the “T” stands for “taking a serotoninergic medication” as part of the criteria?

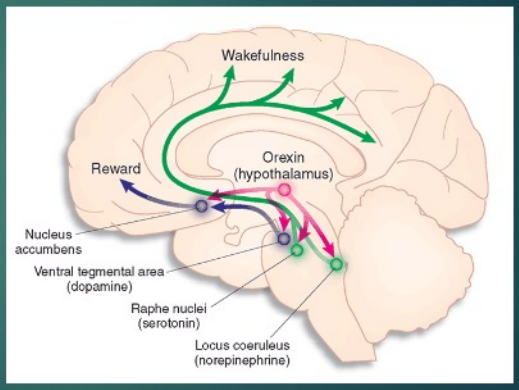
Quite often, the result of taking multiple medications with 5HT-enhancing properties (less common, from one, high-dose medication): e.g., SSRI + migraine medicine (tryptan); SSRI + trazodone or meperidine; SSRI + tricyclic antidepressant (sometimes given as HS sleeping pill), SSRI + another SSRI or SNRI or Lithium; reportedly, SSRI + St. John’s Wort.

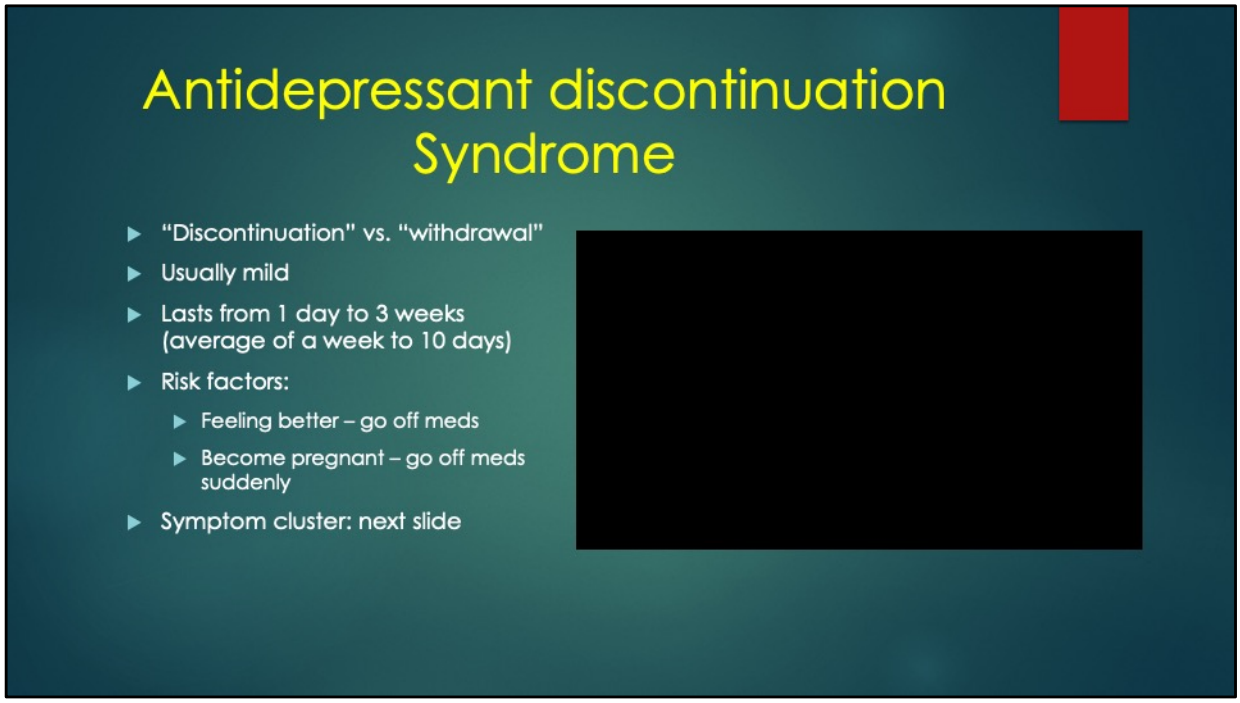
Overall, there’s no specific treatment for serotonin syndrome; stop taking the medicine that’s supplying the serotonin and offer supportive measures to bring down the fever and calm the fevered mind. Remember, pretty much the SSRI’s are wonderfully non-lethal even in massive overdose. The tricyclic antidepressants, that are quite lethal in overdose, kill people by virtue of causing cardiac arrhythmias, not by an overabundance of serotonin in the brain.

Maybe Cyproheptadine (Periactin) 12 mg orally, an antihistamine with 5HT antagonism properties. Cyproheptadine / Periactin has also been used to treat SSRI-induced sexual dysfunction.

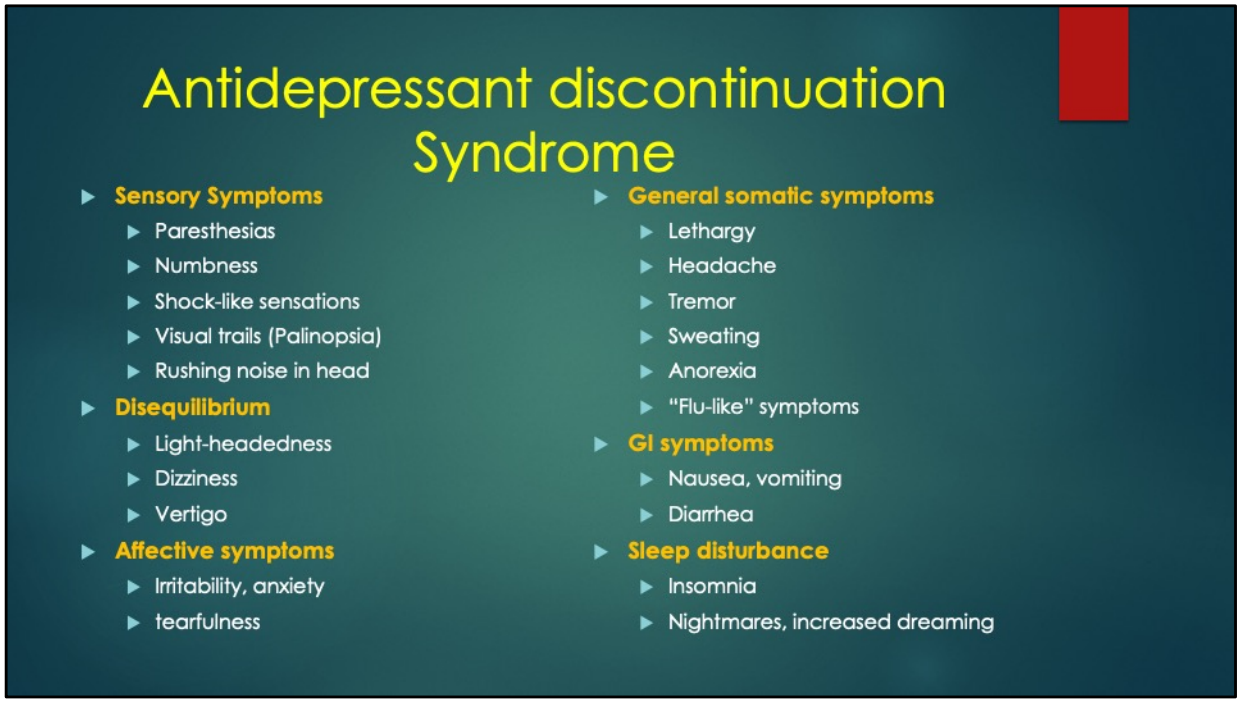
Other NT systems of significance

- GABA
- Glutamate
- Oxytocin
- Acetyl Choline
- Adenosine
- Endocannabinoid
- Orexin





"Discontinuation" vs. "Withdrawal": separates AD's from drugs of abuse (no "cravings", no search for highs, no addictive properties). S. you "withdraw" from heroin, you "discontinue" Paxil.



Six groups of symptoms ….

Some Sx look like depression itself, others are somewhat unique (“shock-like sensations”, “brain zaps”); suspect AD Discontinuation Syndrome by history and timing

Antidepressant discontinuation Syndrome

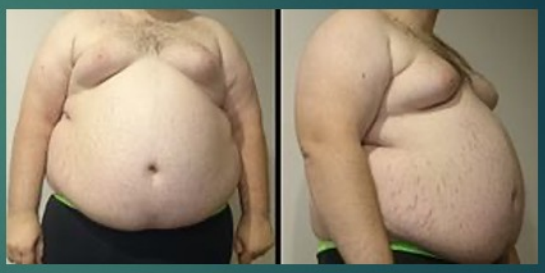
- **DDX:**
  - depressive relapse,
  - Serotonin syndrome
  - flu
- **Tx considerations:**
  - Patient education
  - Fluoxetine: requires no taper
  - Reassurance
  - Restart & change to a slow taper

Antidepressant discontinuation symptoms

- F = flu like symptoms
- I = insomnia
- N = nausea
- I = imbalance
- S = sensory disturbances
- H = hyperarousal (anxiety) (Gelenberg, 1998 cited in Carson, 2000, p. 432)

Metabolic Syndrome

- Includes high blood pressure, high blood sugar, excess visceral body fat (around the waist), & high cholesterol. Increased risk for heart attack and stroke.
- Aside from large waist circumference, criteria for metabolic syndrome have no symptoms.
- Risk Factors include: stress, sedentary lifestyle, pro-inflammatory state (TNF-alpha), diet, sleep deprivation, psychiatric illness, psychotropic meds
- Weight loss, exercise, healthy diet, smoking cessation can help. Medications may also be prescribed.



This is what a BMI of 53 will get you.

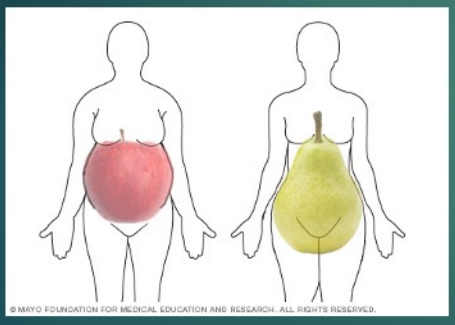
The great bugaboo of 1st generation antipsychotics was Tardive Dyskinesia: irreversible, disfiguring, disabling, virtually untreatable until recently.

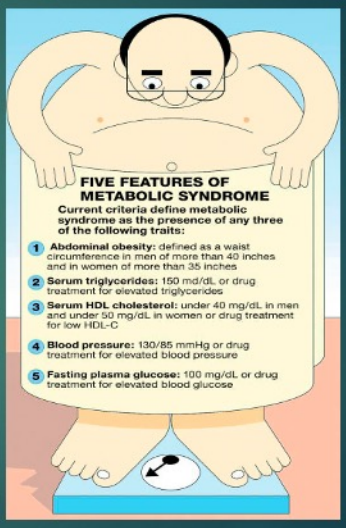
2nd Gen. antipsychotics carry a vastly reduced risk for TD, but there is a new bugaboo: Metabolic Syndrome. Hypertension, hyperglycemia, dyslipidemia, hypercholesterolemia, and truncal obesity. Fats and sugars out of whack. All leading up to a high risk for vascular disease resulting in MI and CVA.

[Read slide]

Interestingly, obesity without metabolic syndrome does not significantly increase risk of heart disease, stroke, or T2D.

Metabolic Syndrome





Metabolic Syndrome

- SGA's most associated:
  - Clozapine (Clozaril),
  - Olanzepine (Zyprexa).
- Middling association with metabolic syndrome:
  - Risperidone (Risperdal)
  - Paliperidone (Invega)
  - Quetiapine (Seroquel)
- Lower risk of metabolic syndrome:
  - Ziprasidone (Geodon)
  - Aripiprazole (Abilify)
  - Lurasidone (Latuda)

Always provide monitoring of metabolic parameters, nutritional recommendations, prescribe exercise and physical activity as part of prescribing antipsychotic medication.

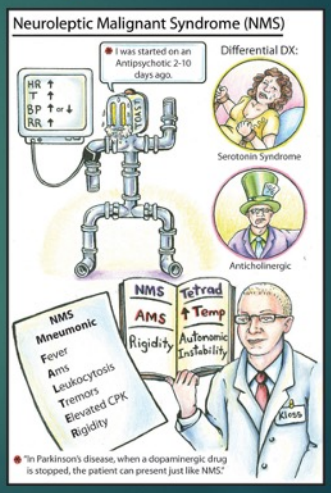
Be willing to switch medications if signs of weight gain or metabolic syndrome appear.

Many psychiatric patients are already taking statins to lower cholesterol and anti-hypertensives for blood pressure; sometimes the SGA can't be lowered due to risk of hospitalization but a statin can be added.

This slide lists SGA's only; all the FGA's (Haldol, Thorazine) have a lower incidence of metabolic syndrome than the SGA's.

Neuroleptic Malignant Syndrome

- Rare but life-threatening complication of Antipsychotic meds
- Largely occurs with 1st or 2nd week of Tx
- Patients will "Shake" –
  - **S**evere muscular rigidity
  - **H**yperthermia
  - **A**utonomic overactivity (BP, diaphoresis)
  - Changes in **K**onsciousness
  - **E**xposed to Neuroleptics recently
- Oral meds: days, IM meds: weeks
- Tx: fluids, bromocriptine or Dantrolene



Severe Muscular rigidity: "lead pipe" rigidity, shuffling gait, trouble swallowing

Changes in consciousness: delirium, confusion, stupor

Lab findings variable but more often than not include elevated CPK (muscle breakdown), Leukocytosis (white blood cells), decreased O2 on oximetry.

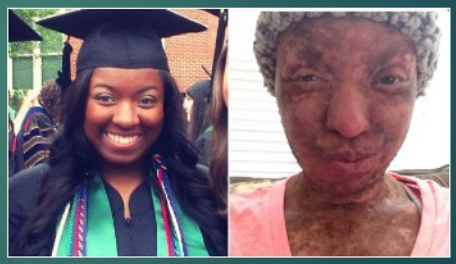
Supportive care includes admit to hospital ICU: fluids, anti-pyretics, O2, benzodiazepines, and DA-agonists for severe cases (Bromocryptine, Dantrilene).

DDx: Serotonin Syndrome, Malignant Hyperthermia, Lethal Catonia, Amphetamine psychosis, aseptic meningitis

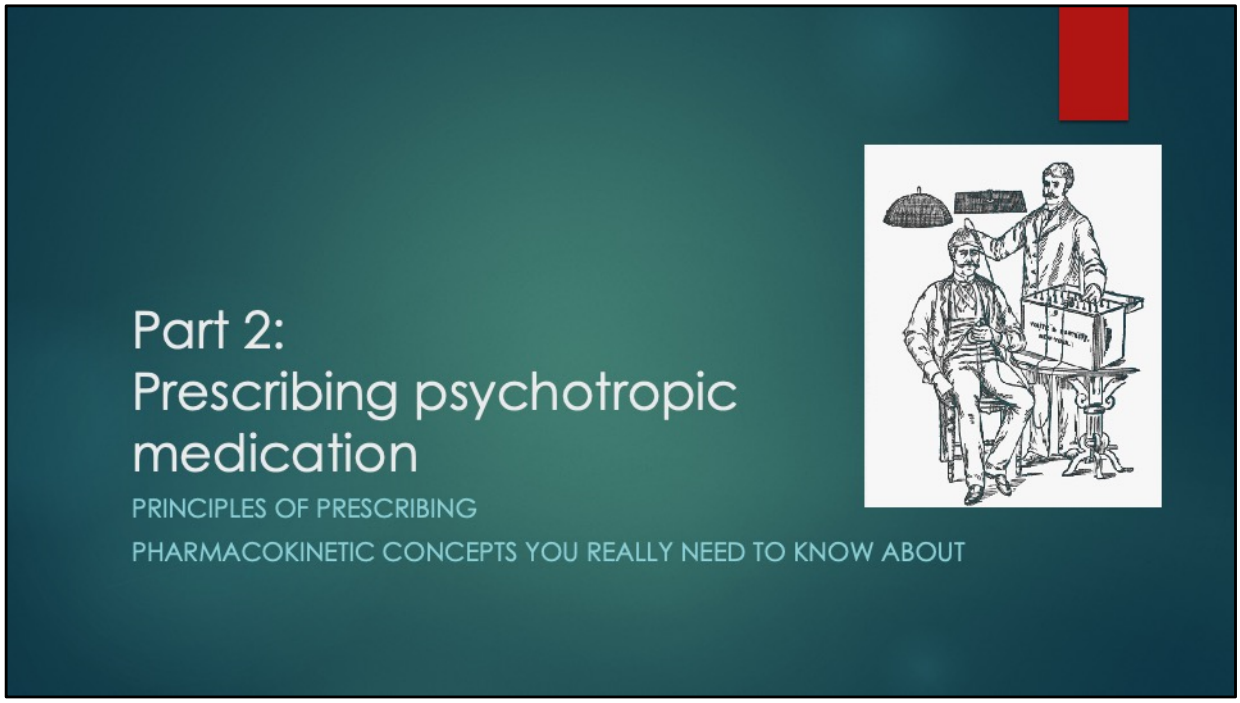
AMS = "Altered Mental Status"

Stevens-Johnson Syndrome

- Severe, potentially fatal exfoliating dermatitis
- Can affect skin, lips, mouth, eyes, genitals
- Often drug-induced including one common psychotropic, Lamotrigine (Lamictal)
- Inform patient of risk, tell them to get to ER, stop taking the medicine at any sign of a deep or extensive or rapidly spreading rash
- Admit to ICU and burn unit



Khaliah Shaw, University of Georgia student



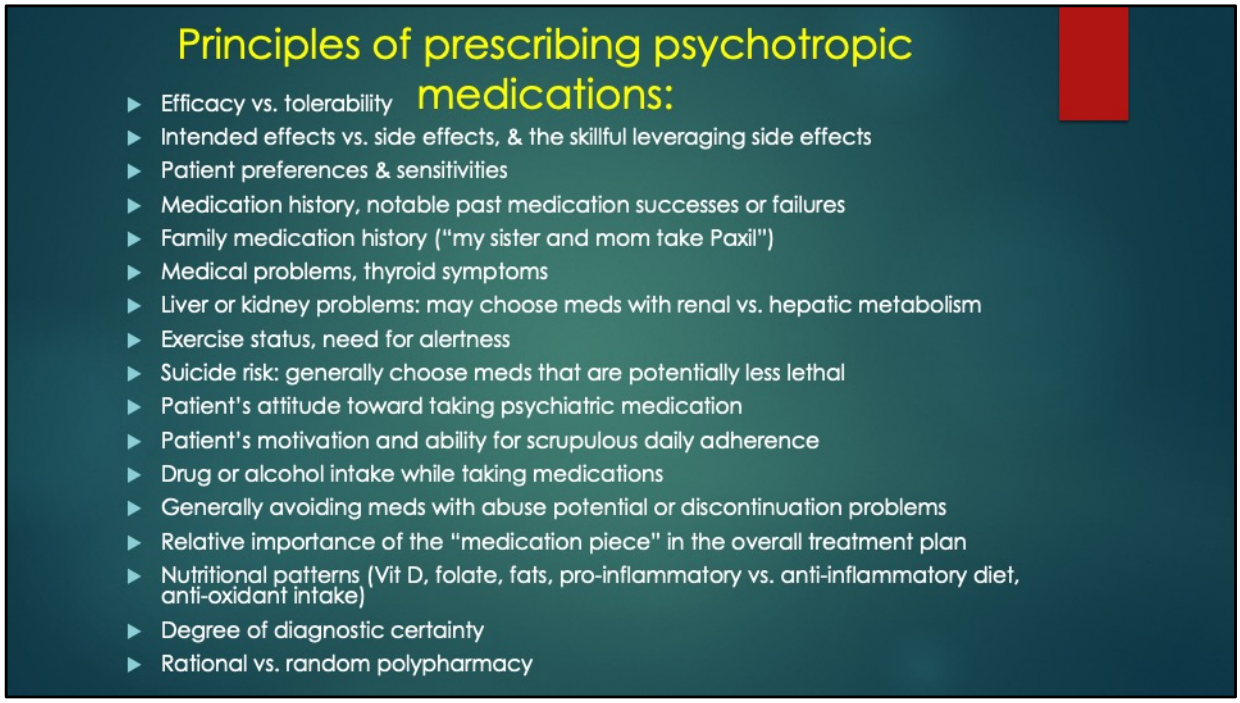
Okay, so in Part 1 we looked at brain regions, brain functions, and the neurotransmitters associated with those regions and functions. We developed an understanding of how "side effects" and "intended effects" are simply different aspects of the overall range of effects of any given drug, subjectively viewed like the difference between a "flower" and a "weed", and considered 4 major syndromes associated with psychotropic prescribing:

AD discontinuation syndrome

Serotonin syndrome

Neuroleptic Malignant syndrome, &

Metabolic syndrome



"patient preferences & sensitivities" e.g., sexual dysfunction may be a very important concern for some patients but not for others; likewise for weight gain, acne, cardiac risks.

As we move along, we'll see examples of specific medications within each class have specific side effects that can be either helpful, neutral, or annoying and harmful for specific patients.

Pop Quiz

Essential Considerations before prescribing a psychotropic include all EXCEPT:

- A. establish the diagnosis by history and examination
- B. identify any comorbidities such substance abuse
- C. gain the allegiance and cooperation of the patient in the proposed treatment plan
- D. have a discussion of target symptoms, precautions, and possible side effects
- E. skillfully leverage likely side effects to therapeutic advantage
- F. be sure to discuss psychotherapy as well as medication treatment
- G. assess for suicide risk
- H. verify insurance coverage

Answer A: the absolute minimum, also gets at the concept of "are we treating symptoms, or are we treating the underlying diagnosis?"

Answer C: important for (a) having realistic expectations, (b) ensuring compliance with taking the medicine every day.

Answer D: ask the patient "of all the symptoms you've mentioned, not sleeping, low motivation, feeling sad all the time, panic attacks, what's most important that we try to take care of first?"

Answer E: i.e., the "kill two birds with one stone" principle: e.g., patient is depressed and sleepless: using an antidepressant that commonly includes sedation as a possible side effect, to be taken at bedtime. Or, E.g., patient has some ADHD symptoms and Wellbutrin or Trintillex makes sense.

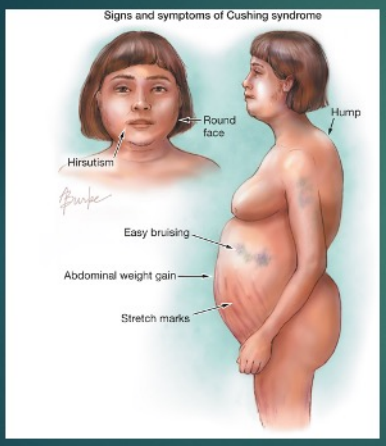
Answer F: gets at the common problems of patients with dysfunctional core beliefs (& maladaptive, reflexive coping mechanisms), who remain "partial non-responders" …

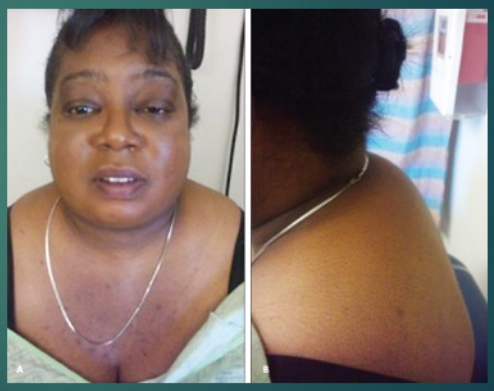
Correct answer: H

Thyroid symptoms: cold/heat intolerance, weakness, oedema, hair loss or trophic changes, amenorrhea, vital signs, constipation or hyperdefecation, lid lag or exophthalmos

Overall, look for (and ask for) ANY unexplained symptom, especially if asymmetrical, visible, or measurable.

Cushing's d.





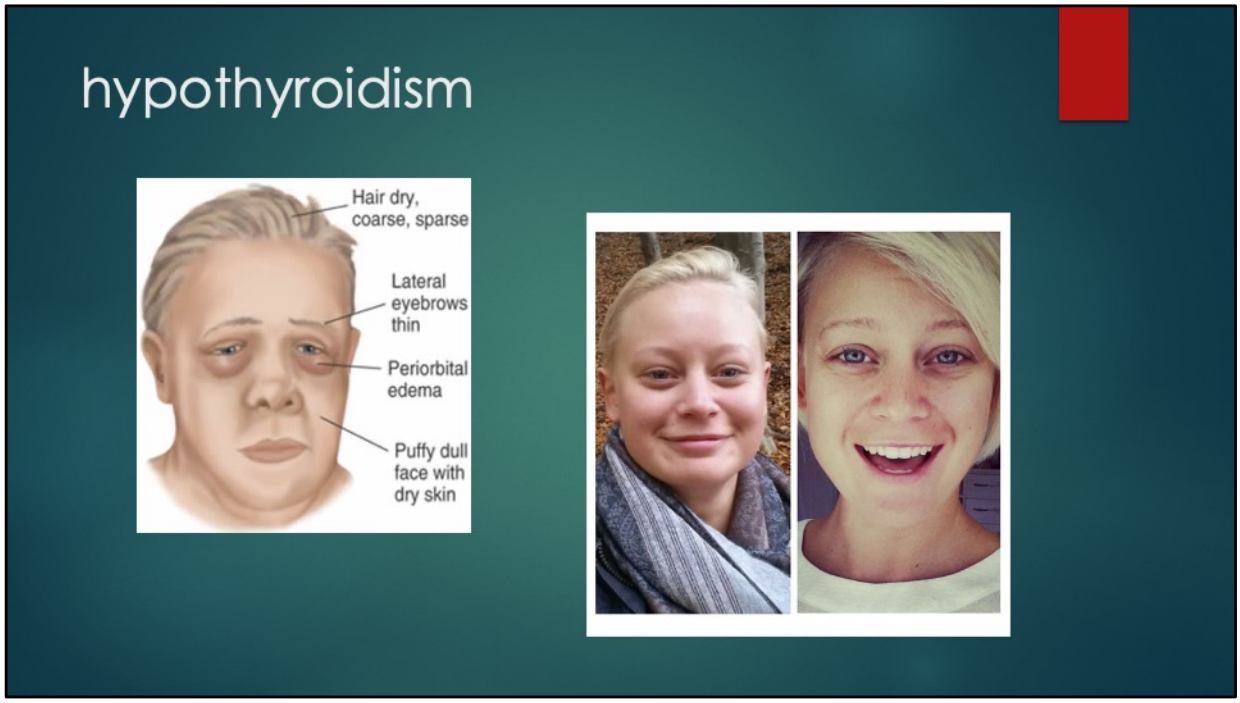
Cushing's syndrome (also called hypercortisolism) – not always easy to diagnose (patient complains of fatigue, depression, weakness, weight gain, and headache)

- Very common: 3 million cases a year in the USA
- Cushings syndrome: too much exogenous steroid
- Cushing's disease: adrenal gland disease, too much cortisol production
- Characteristic signs and symptoms: truncal obesity and extremity wasting ("lemon on toothpicks")
- Pigmented striae (pink or purple stretch marks), thinning and easy brusing of the skin
- Fat pad ("buffalo hump") and rounded face ("moon facies")
- High blood pressure, osteopenia, and hyperglycemia

- Acne, depression, fatigue, muscle weakness, decreased libido

- High dose steroids used for inflammatory conditions such as rheumatoid arthritis, lupus, asthma, transplant immunosuppression, etc.

- Endogenous: pituitary adenoma (with excessive ACTH secretion), exogenous ACTH-secreting tumor, or primary adrenal cortical tumor



Hypothyroidism (underactive thyroid gland, too little thyroid hormone produced)

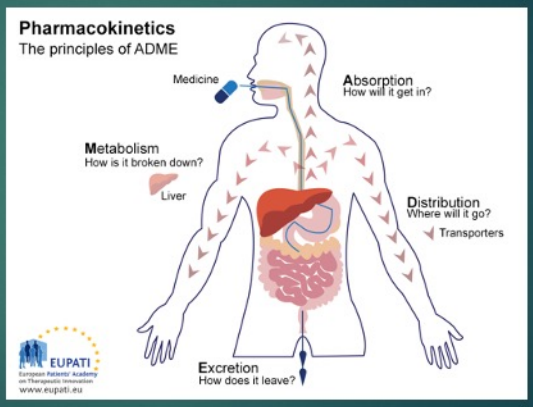
- 10 to 15 million cases per year; contrast to 135,000 new cases of colon cancer per year in US
- More common in women than men
- Fatigue, constipation, edema, weight gain, constipation, amenorrhea
- Characteristic “trophic changes” – hair and skin – , peripheral edema & peripheral neuropathy
- Bradycardia and hypothermia
- Causes: tumor, autoimmune disease, iodine deficiency, medication (lithium), pituitary tumor (low TSH)

Pharmacokinetics (how a drug behaves in the human body)

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

- Just remember the phrase:

- **"AD ME"**



Examples of significant impact:

Absorption: rate of absorption determines whether the patient experiences a rush or "high" from the medicine: e.g., Alprazolam (Xanax) vs. Lorazepam (Ativan).

Distribution:

Absorption

- A tale of two drugs with the same half-life but different rates of absorption

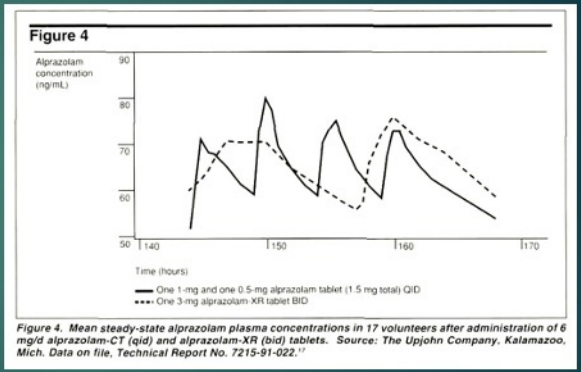
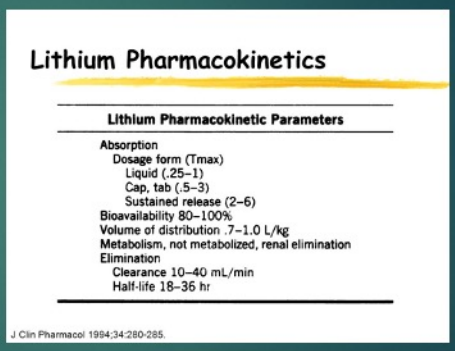


Figure 4. Mean steady-state alprazolam plasma concentrations in 17 volunteers after administration of 6 mg/d alprazolam-CT (qid) and alprazolam-XR (bid) tablets. Source: The Upjohn Company, Kalamazoo, Mich. Data on file, Technical Report No. 7215-91-022.[17]

Distribution

- Lithium distributes in the water compartments of the body
- When dehydrated, lithium level can go up – even to a toxic level
- Propranolol is a lipophilic beta-blocker and can cause CNS side effects such as "beta blocker blues"
- Atenolol is a hydrophilic beta-blocker and doesn't penetrate the BBB
- Zoloft does not distribute to breast milk in lactating mothers
- Paxil, another SSRI drug of the same class as Zoloft, does



Lithium Pharmacokinetics

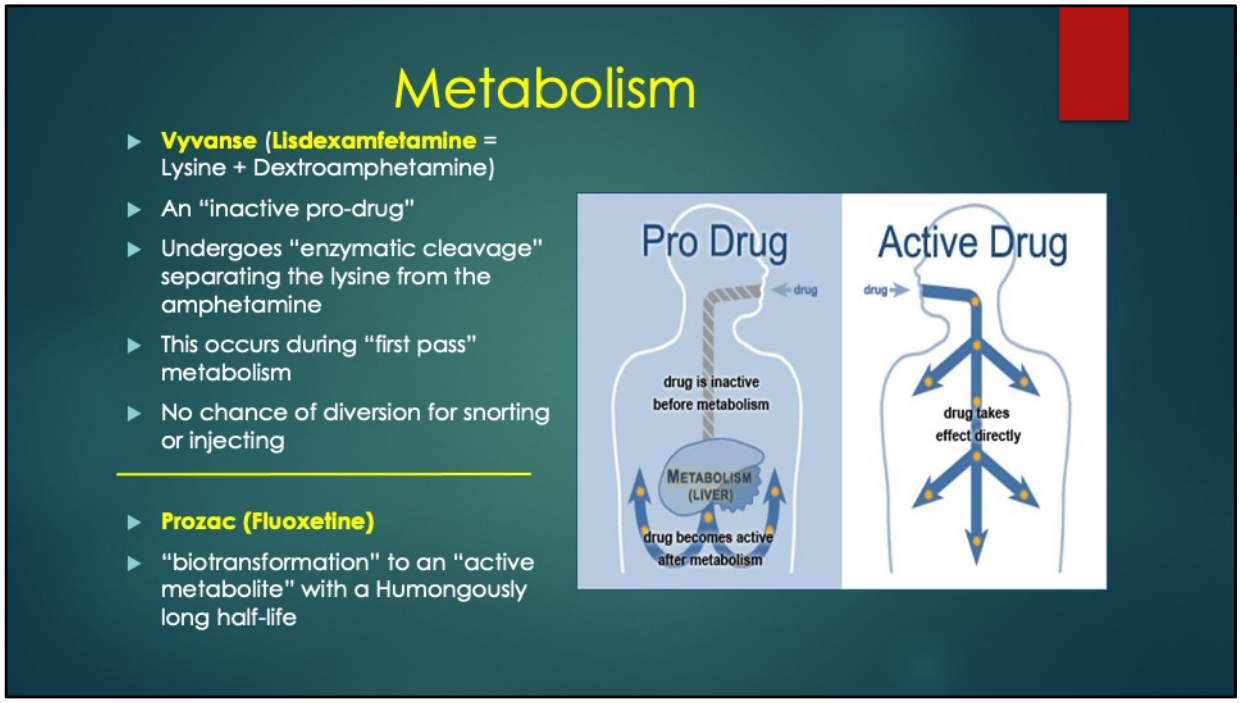
Lithium Pharmacokinetic Parameters
Absorption
Dosage form (Tmax)
Liquid (.25–1)
Cap, tab (.5–3)
Sustained release (2–6)
Bioavailability 80–100%
Volume of distribution .7–1.0 L/kg
Metabolism, not metabolized, renal elimination
Elimination
Clearance 10–40 mL/min
Half-life 18–36 hr

J Clin Pharmacol 1994;34:280-285.

Brand names:

Propranolol = Inderal

Atenolol = Tenormin



The idea of "First Pass" metabolism = the hepatic metabolism that occurs BEFORE your body uses the drug, not afterward …

Fluoxetine T ½ = 2 to 4 days

Norfluoxetine T ½ = 7 to 15 days

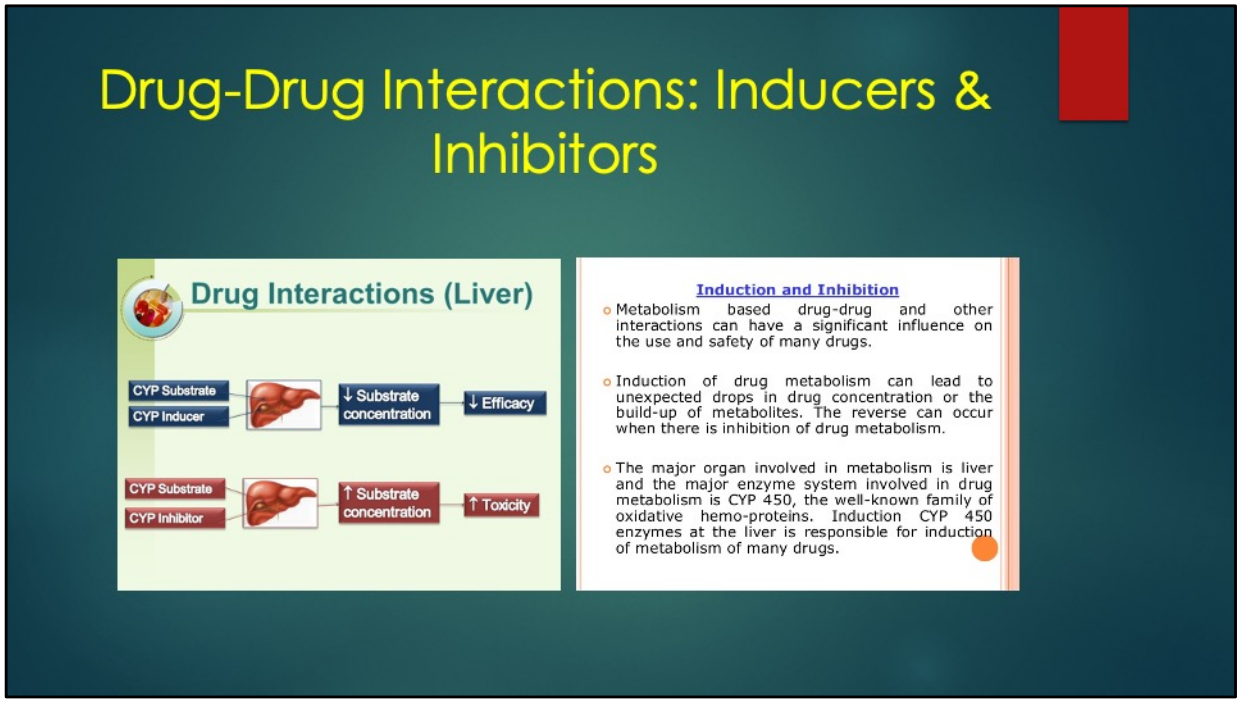
Practical implication: drugs with longer half-lives have to be managed differently:

(1) e.g., when switching antidepressants, can have serotonin syndrome with Prozac

(2) E.g., when switching to an MAO-I, must have longer washout period with Prozac

(3) E.g., "self-taper" lowers risks of AD-discontinuation syndrome, non-compliance

(4) "drug holiday" strategy for Tx of SSRI-induced sexual dysfunction works with Paxil but not Prozac



Hepatic enzyme induction is like when you're at the inveterately slow check-out lines at Giant or CVS, when, miraculously, it's your luck day and the manager opens up another register, increasing the rate at which customers can check out and leave the store; the liver increases the rate of metabolism of a drug by increasing production of the enzymes that metabolize the drug. The result is analogous: fewer customers standing in line at CVS, and a lower serum level of the drug in the bloodstream.

Examples: nicotine = inducer (stop smoking, can get toxic & have seizures w/ Clozapine)

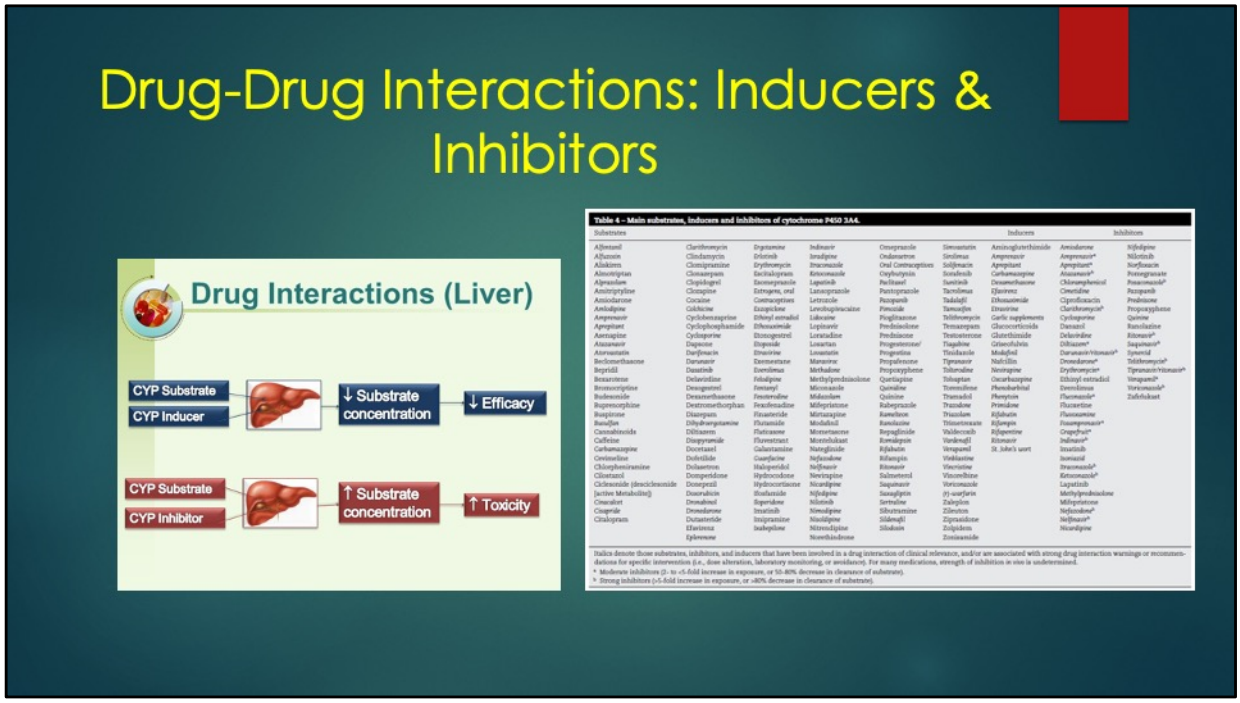
St. John's Wort (hypericum perforatum) = inducer (w/OCP's, can become pregnant)

Carbamezapine (Tegretol) = inhibitor

Grapefruit juice = inhibitor

Induction/inhibition is not the only mechanism for side effects, for example combined,

similar actions of different drugs can result in S/E's: e.g., Celexa for depression + Trazodone for sleep = too much Serotonin & could – in theory – result in Serotonin Syndrome.



Examples: nicotine = inducer (stop smoking, can get toxic & have seizures w/ Clozapine)

St. John's Wort (hypericum perforatum) = inducer (w/OCP's, can become pregnant)

Grapefruit juice = inhibitor, can increase the serum levels of an SSRI and send a patient into Serotonin Syndrome.

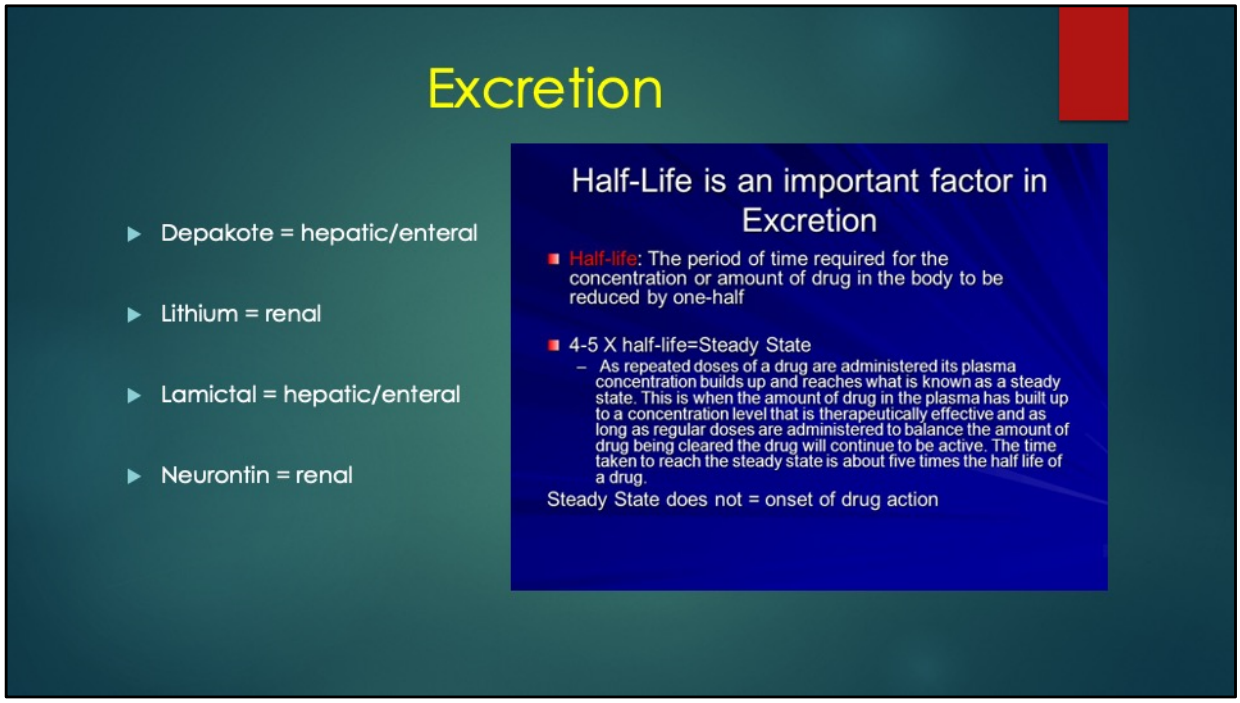
Valproate (Depakote), the mood stabilizer, is a potent CYP450 2C9 Inhibitor; sometimes the doctor wants a patient on a second mood stabilizer like Lamotrigine (Lamictal), and you need to cut the Lamictal dose in half if there is still VPA in the system, or you increase the risk of dose-dependent side effects such as the rare but dreaded "Stevens-Johnson Syndrome" due to P450 enzyme inhibition and the resulting DDI.

The list of inducers, inhibitors, and substrates affected is very long, and too long to be

memorized.

Induction/inhibition is not the only mechanism for side effects, for example combined, similar actions of different drugs can result in S/E's: e.g., Celexa for depression + Trazodone for sleep = too much Serotonin & could – in theory – result in Serotonin Syndrome. Or, Lithium, a salt, is treated a lot like Sodium by the body; drugs like diuretics that lower blood pressure by causing the body to lower fluid volume and lose salt also can increase lithium excretion and lower lithium levels.

Genetic variability also plays a big role, as some individuals are genetic "slow metabolizers" for the P450 system.

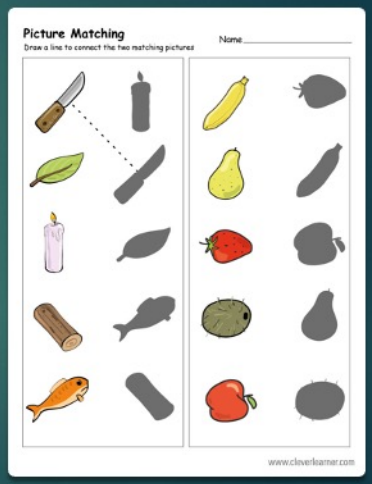


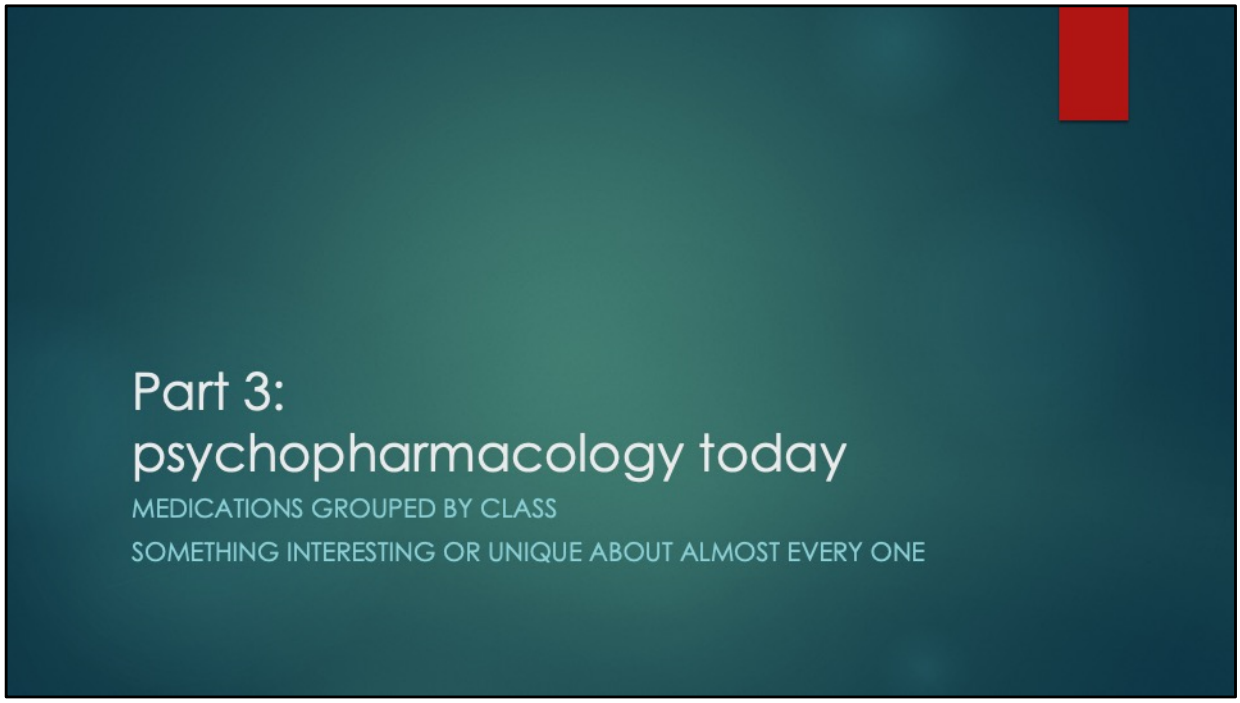
So in treating bipolar disorder, your drug of choice decision may be influenced by the patient's liver or kidney status. If the patient has cirrhosis or another hepatic disease, you might choose drugs handled by the kidneys. Conversely, your patient has renal impairment, you'd be inclined to choose drugs that go the route of hepatic metabolism.

There's the same choice to make in MAT for alcohol abuse: Naltrexone is hepatically metabolized, and conversely Acamprosate (Campral) is renally excreted.

Matching: draw a line to connect the two matching phrases

(1) How long the effect of a drug lasts in a person	(A) Half-life
(2) Precisely what the drug does in the body in order to exert its effect on a person	(B) Mechanism of Action
(3) How long it takes the body to reduce the amount of drug by ½	(C) Therapeutic Index
(4) The ratio between the amount of drug needed to cure and the amount needed to kill a person	(D) Active metabolite
(5) Lipophilicity	(E) Duration of action
(6) A compound not ingested by the person that has a therapeutic effect nonetheless	(F) A proxy for how likely it is that a drug will enter the brain or not

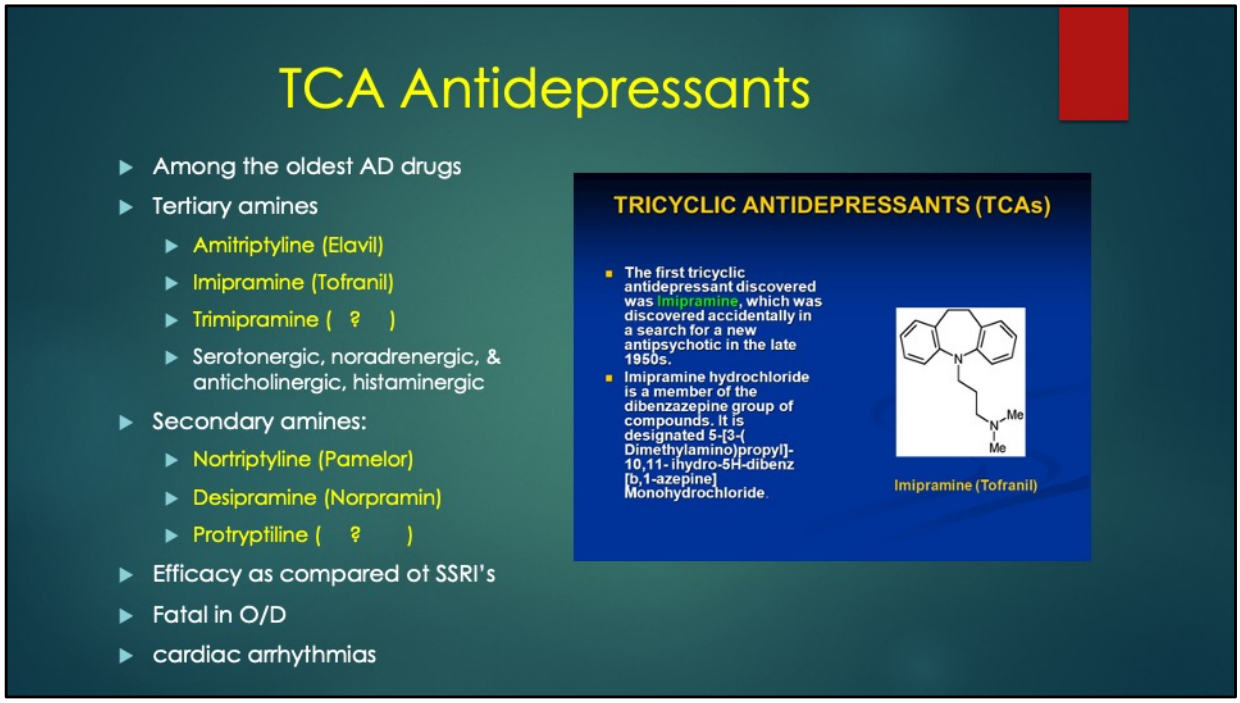




Okay, so in part 2 we looked at the rules and concepts prescribers use when prescribing, we considered some common medical illness that masquerades as psychiatric illness, and we got introduced to the very important field of pharmacokinetics, specifically how knowledge of absorption, distribution, metabolism, and excretion, or “AD ME” informs skillful psychotropic prescribing.

The classes of psychotropics:

- Antidepressants
- Anti-anxiety agents
- Antipsychotics
- Mood stabilizers
- Sleeping agents
- Dementia medicines
- Medication treatments for addictions
- ADHD medications



AMI is metabolized to NT

IMI is metabolized to DES

An interesting fact is that AMI is one of the most anticholinergic (think: lots of side effects) antidepressants, while NT is one of the LEAST anticholinergic antidepressants.

There are also related compounds known as “tetracyclic” antidepressants (maprotiline, amoxapine) just for the record, but we don’t need to go into those for today’s purposes. OR: amoxapine was thought to act as BOTH an AD and anti-psychotic …..Amoxapine wonderful brand name: Asendin.

Some Danish studies suggested that TCA’s are more effective than SSRI’s, and if you’re hospitalized for severe depression non-responsive to SSRI’s, you’re likely to get Rx’ed TCA’s.

Trimipramine = Surmontil; Protryptiline = Vivactil.

TCA's

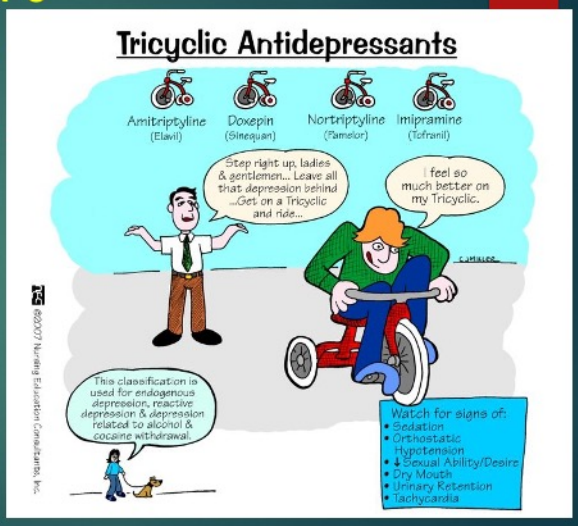
Tricyclic Antidepressants: Adverse Effects

- Commonly reported AEs (generally anticholinergic):
  - blurred vision
  - cognitive changes
  - constipation
  - dry mouth
  - orthostatic hypotension
  - sedation
  - sexual dysfunction
  - tachycardia
  - urinary retention

Fewest AEs

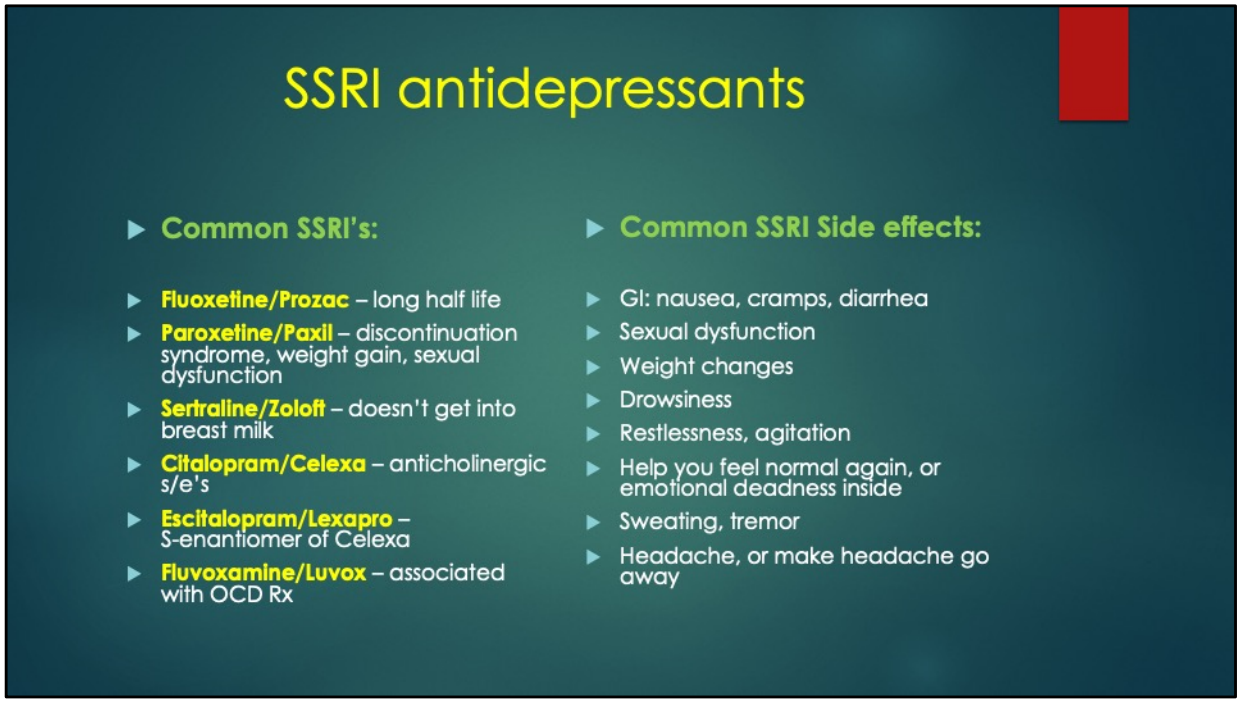
- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

Most AEs



TCA's effective in depression, anxiety & panic attacks, OCD.

Another TCA: Chlorimipramine (Anafranil);



Well, the TCA's brought millions of people out of depression but there was a heavy price to be paid. Patients weren't happy with weight gain, sedation, "cotton mouth", blurred vision, orthostatic hypotension (fainting from low blood pressure when you stood up too quickly), and other TCA side effects, and doctors weren't happy being constantly distracted from their golf games by nagging thoughts that their depressed patients might at that very moment be taking a fatal overdose of their TCA medication, or developing serious cardiac arrhythmias. So, when the first of a new class of drugs, Fluoxetine or Prozac, came out as an "SSRI", essentially the modern era of psychopharmacology was ushered in. SSRI's are non-fatal in overdose. Prozac didn't yet exist when I was first prescribing antidepressants and I still remember being taught not to prescribe more than a total of "2 grams" of a TCA to a new patient. Because an average daily dose was up to 100 mg, and the TI put a potentially fatal overdose at 30 to 50 times the daily dose, "2 grams of Elavil" (or equivalent in Pamelor or Norpramin) was roughly 20 days' supply, but still well short of a potentially fatal concoction if the patient were to go suicidal and swallow their entire bottle of pills at once.

Nearly impossible to overdose on SSRI's – in stark contrast to TCA's. That made everyone happy: the doctors could make it to the 18th hole without worrying about a call from the ICU or their malpractice attorney, and the patients could take an

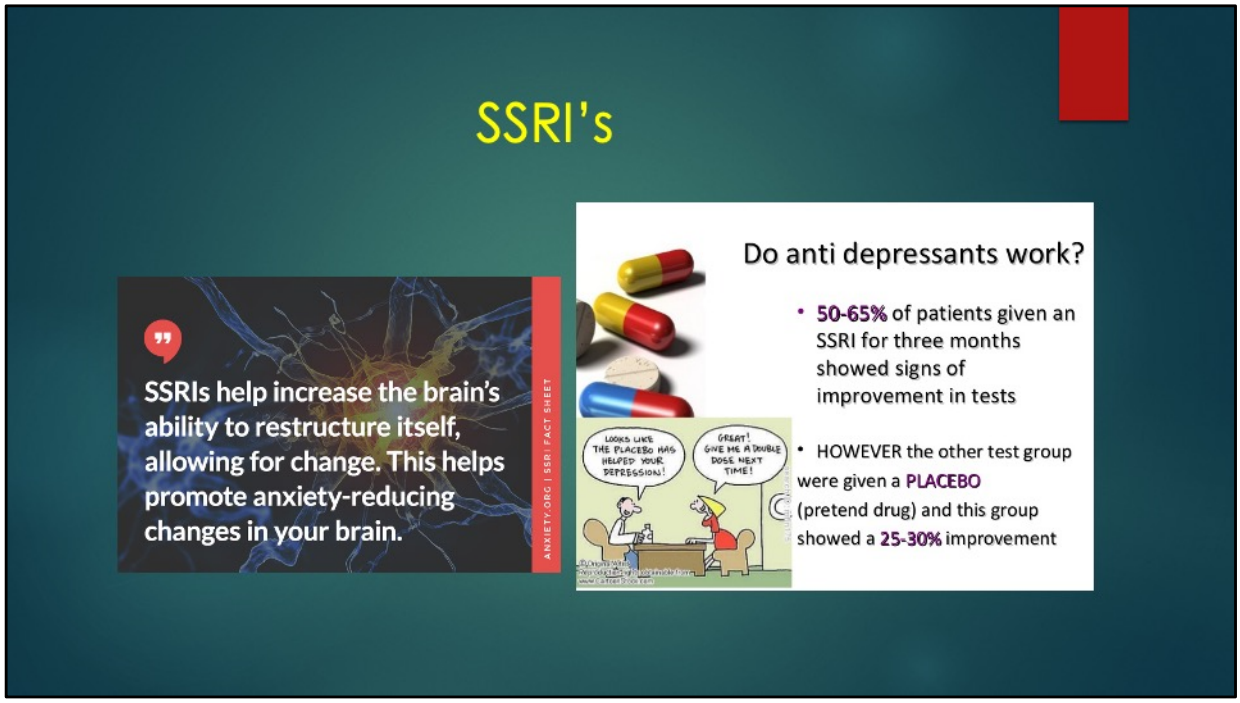
attention-getting overdose of their SSRI and not have to worry about a fatal miscalculation. As a result, Prozac and the other "me too" SSRI's that quickly followed soon became more popular than a bitcoin offering at a NASDAQ convention. Patients rushed to their doctors crying "get me some Prozac". Doctors rushed to their stock brokers crying "get me some Eli Lilly." Everyone was happy. It was a good time to be alive.

SSRI's are most commonly Rx'ed class of AD's, but not really because they are more effective than the old-fashioned TCA's, but – remembering the rule about considering both efficacy and tolerability – they were both safer and more tolerable than the TCA's. Mostly, the SSRI's have very little cardiovascular impact and that has made everyone more comfortable. I can recall occasional reports about sudden cardiac death in children prescribed TCA's and we haven't had to worry about that problem any more.

Prozac = longest half-life. Implications: good for patient who might miss a dose here or there; self-tapers therefore no discontinuation syndrome; bad if switching to another SSRI because it lingers in the system.

Citalopram vs. Escitalopram = Citalopram risk of QTc prolongation at 60 mg/day; therefore upper limit recommended at 40 mg daily; dose of Escitalopram half that of Citalopram.

The list of s/e's is kind of crazy and sometimes I feel embarrassed to tell a patient "you may sleepy or you may get insomnia" … "you may feel less depressed or you may feel suicidal" …. "Your sex drive may return or your sex drive may go down" ….. so I say "**serotonin is a balance and either too much or too little can cause a problem"**



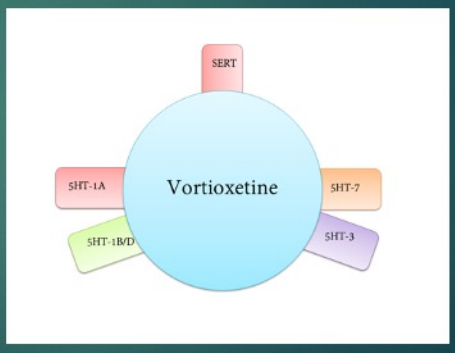
The safety profile of SSRI's became such that the threshold for writing a prescription went down. Previously, a patient had to be considered very seriously depressed before being put on a course of (TCA) antidepressants. A lot of time was spent trying to tease out whether the depression was "biological" or "psychological" before deciding to prescribe an antidepressant. After Prozac and the SSRI's, however, anyone who reported feeling depressed or perhaps, at times, even just a little "bummed out" was issued a prescription for Prozac. Peter Kramer wrote a book with the absolutely worst pun in the entire history of biological psychiatry called "Listening to Prozac" suggesting the drug was so potent that it could potentially remold personality which had been subtly misshaped by undiagnosed depression, and again the masses stampeded to their doctor's offices. The demand was so great that treating depression was no longer the domain of the psychiatrist but family practitioners, internists, and OB-GYN began doing the majority of antidepressant prescribing. Oh, by the way, Dr. Kramer's pun? He was smitten with the idea that "Prozac" sounded a lot like "Muzak" and thought the title would make everyone think of the phrase "Listening to Muzak". Nonetheless, patients began comparing their antidepressants over water cooler talk at the office and I can recall many patients saying, "my boss said he's on Paxil and I wonder if that would be better for me than my Zoloft, doc". The trend has not let up and nowadays 13% of the US population over the age of 12 – more than one

of every eight adults – is taking an antidepressant medication.

"Daily use of SSRIs for more than a week or two eventually results in changes in the structure of neurons. This is neuroplasticity, the brain's ability to reorganize its neural connections, in action. As neurons adapt to new levels of serotonin, they make adjustments in the number of receptors, grow new dendrites, or even promote the development of new connections or circuits.[1] In other words, new, higher levels of serotonin may somehow stimulate the neurons to remodel themselves and their circuits in a variety of ways, a process called neurogenesis."

SNRI & other antidepressants

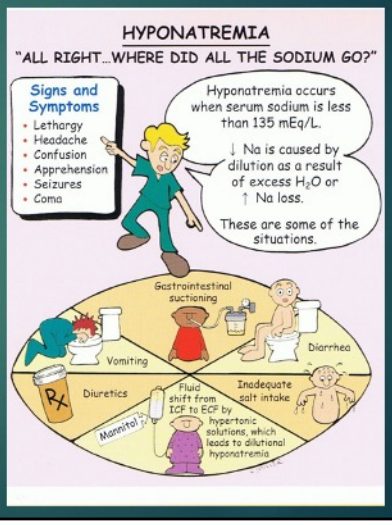
- **Venlafaxine (Effexor)**
  - Both 5HT and NE agonist
  - Less serotonin excess
- **Desvenlafaxine (Pristiq)**
- **Mirtazapine (Remeron)**
  - Add Bupropion for "California Rocket Fuel"
- **Duloxetine (Cymbalta)**
  - Short half-life
  - Approved for neuropathic pain
- **Vortioxetine (Trintillex)**
  - Aids cognition?
  - Low side effect profile?



Discuss prescribing an SNRI, vs. prescribing two separate meds, e.g., Zoloft + Wellbutrin (advantage of the former, is using one med vs. two; advantage of the latter is that you can start with the SSRI and if there's a partial response but side effects are creeping in, then you add the Wellbutrin rather than increase the SSRI and increase the dose-dependent side effects).

Antidepressant-induced hyponatremia

- About 1 in every 200 people
- Symptoms are non-specific so need a high index of suspicion
- Elderly are more at risk
- Can be fatal in up to 25% of elderly
- Often have other risk factors for hyponatremia
- Can be asymptomatic
- Among US athletes,
  - No deaths from dehydration
  - 15% rate of hyponatremia from excessive H20 drinking
  - MD Alerts suggests deaths in marathoners assoc w/ low Na+



Drug-induced hyponatremia is also common and should not be overlooked. "Natrium" is Sodium, or "table salt." (Sodium Chloride, or NaCl).

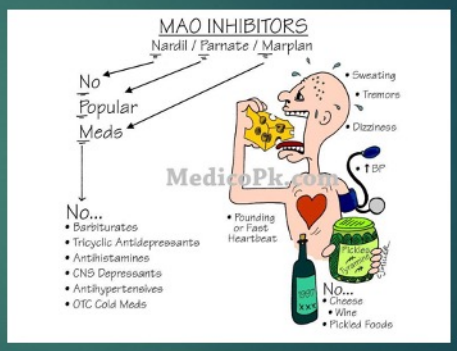
Hyponatremia is defined as having a serum sodium level of less than 134mmol/L. Most patients with mild hyponatremia are asymptomatic. However when the serum sodium level drop below 120mmol/L, the patient may start to experience headache, lethargy and nausea. In severe cases of hyponatremia, neurologic and gastrointestinal symptoms can occur with the risk of seizure and coma to increase rapidly as the sodium level continues to drop.

Every Year, More Athletes Are Injured By Hyponatremia than Dehydration
By John Henry Dreyfuss, MDalert.com staff.
April 14, 2015 EndocrinologySports Medicine

MAO Inhibitors

MAO-I Antidepressants

- Monoamine Oxidase (MAO)
- Metabolizes, or breaks down, the monoamines (DA, NE, 5-HT) at the synapse
- MAO inhibitors block the action of MAO
- The result of this "enzyme inhibition" is less NT breakdown
- Therefore, more NT activity at the synapse
- Nardil, Parnate, Marplan, Eldepryl
- Also used in Parkinson's D to increase available Dopamine



MAO-I side effects are most commonly:

- Hypotension
- Weight gain
- Sedation

Less common but worrisome:

- Acute hypertensive crisis
- Tyramine/tyrosine build-up
- Avoid aged, pickled, fermented foods
- Includes cheeses and wine, some beer
- Chicken or tuna salad leftover in fridge, pizza, etc.

Rarely prescribed nowadays due to (1) common side effects, (2) risk of hypertensive crisis, (3) superior alternatives available, and (4) less commonly see "hysteroid dysphoria".

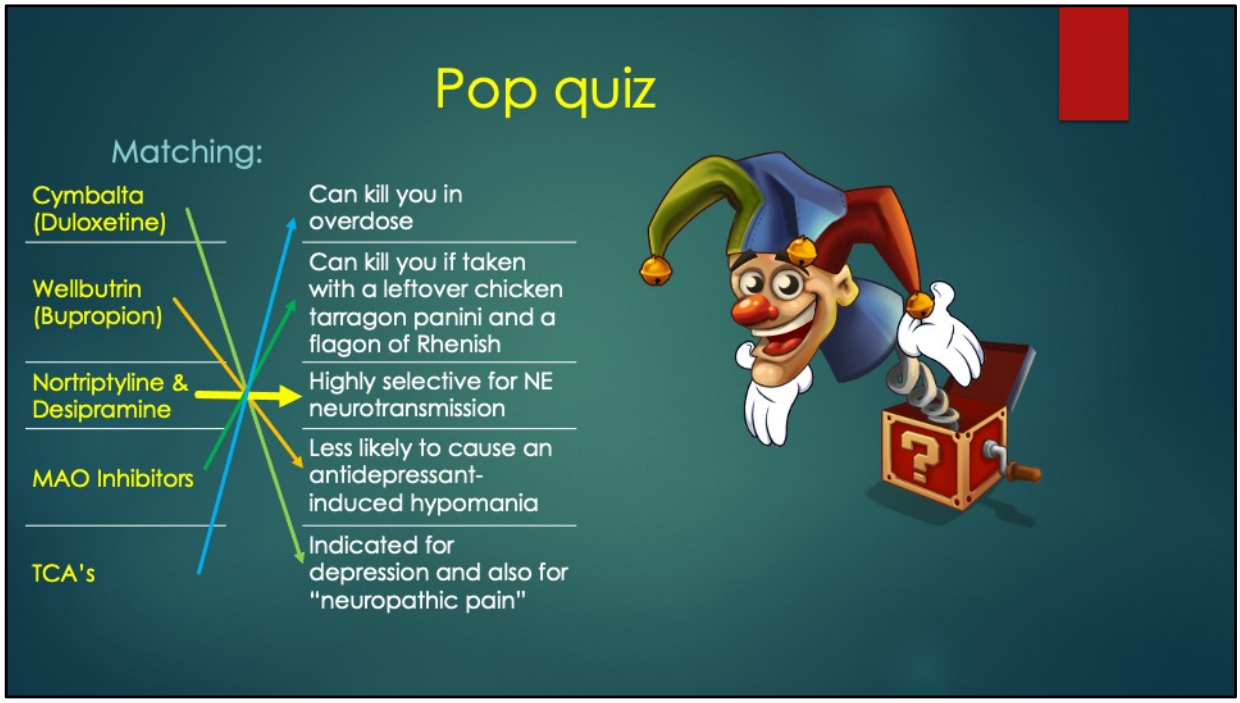
- Generic names: phenelzine, tranylcypromine, isocarboxycid, selegine

Remeron: complex pharmacological mechanism of action, "NaSSA" – "NE and specific serotonin antidepressant" b/c hits a few specific 5HT sub-types.

Wellbutrin: think of Wellbutrin when

(1) non-response to multiple SSRI's
(2) Want to avoid SSRI-induced sexual dysfunction
(3) Want to avoid weight gain or sedation as a side effect
(4) Maybe some ADHD and you can kill two birds with one stone ("rational monotherapy" vs. "rational polypharmacy")
(5) Want to minimize risk of medication-induced hypomania
(6) For a "poor-man's contrive"
(7) Have partial response to SSRI but getting limited by dose-dependent side effects

Trazodone: Ubiquitous, for sleep these days



Duloxetine: NE and 5HT blockade; indication for neuropathic pain thought to be due to Sodium ion channel blockade in the spinal cord

If you see a patient on duloxetine, suspect a medical condition such as diabetic neuropathy or fibromyalgia.

SJW: pretty yellow flower that blooms every year around St. John's Day. Probably the most well-studied of all the CAM therapies for depression. Evidence suggests it's about as effective for mild to moderate, but not severe, depression as TCA's or SSRI's at a dose of around 500 mg BID. Personally, I don't believe it b/c I've never seen anyone for whom it's worked, but then again, if it was working, they would need to visit a psychiatrist office, would they? Not without side effects, particularly constipation and photosensitivity reaction, with a lot of redness and peeling of the exposed skin. Can induce mania in bipolar patients.

Dozens of trials of **SAMe** vs. Rx antidepressants, generally mild side effects including loss of appetite, dry mouth; also possible to induce mania in bipolar patients. Some studies suggest efficacy in depression. Pricey, however. May be combined with standard antidepressants.

OFA's: At least one impressive study found DHA levels inversely correlated with risk of suicide. ALA from flax seed also very healthy but less psychoactive.

Other non-Rx & natural remedies:
Rhodiola Rosea – a plant that grows in Russia and Eurasia, more widely known there.

May have adaptogen & anti-oxidant properties, and some MAO-I properties. Taken from 100 to 600 mg daiy, few side effects, used for depression, anxiety, fatigue, stress, and sexual dysfunction.
5 Hydroxytryptophan: short half-life necessitates TID or QID dosing (t ½ = 4 hours); usually 100 mg TID or QID, Gi side effects are possible (nausea, vomiting, diarrhea).

Valerian Root: used for over 1,000 yrs; carried in WWI medic bag; may have GABA-ergic properties; "natural substitute for benzo's?"; 450 to 600 mg at HS; powerful smell prevents RCT b/c no placebo has a similar smell; overall, probably good for sleep but so-so for depression.

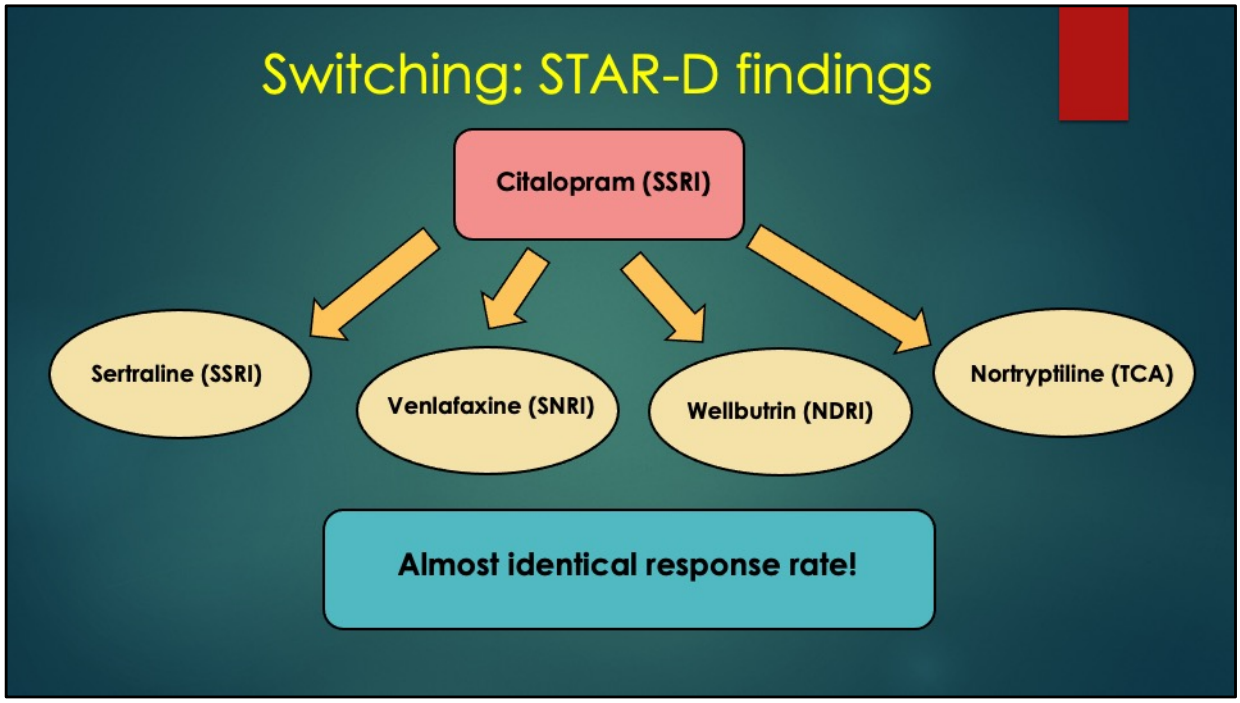
Melatonin: resets Circadian rhythm; a sleep-inducing hormone. Rx 1 to 5 mg at HS. Few side effects include confusion, sedation, nightmares; rarely infertility, lowered body temperature, and immunosuppression.

Gingko Biloba: cognitive enhancer for dementia, also being used for reversing SSRI-induced sexual dysfunction; functions to stabilize neuronal cell membrane and a free radical scavenger; some efficacy in slowing dementia and a lot of speculation as to whether taking it early can help prevent dementia. Can be combined with Cholinesterase Inhibitors (Aricept) for increased efficacy; possible side effect of worsening bleeding disorders so should not take if taking an anticoagulant.

Who prescribes psychotropics

Medication class	Psychiatrists (%)	Non-psychiatric MD's (%)
Antipsychotics	40	60
Antidepressants	15	85
Antianxiety	10	90
Hypnotics	11	89
Lithium	62	38

Pomerantz et. al. 2004. J Clin Psychiatry



With respect to "switching", from the well-known STAR-D trials, intuitively you would imagine that if the patient has failed one SSRI, the last thing you'd want to do would be to switch to a second SSRI.

Well, switching to a second SSRI after a failed 1st SSRI was compared to switching to an SNRI, an "NDRI" (no serotonin augmentation), or an old, frumpy, antiquated TCA.

The result – counterintuitive: all were helpful, no differences in efficacy.

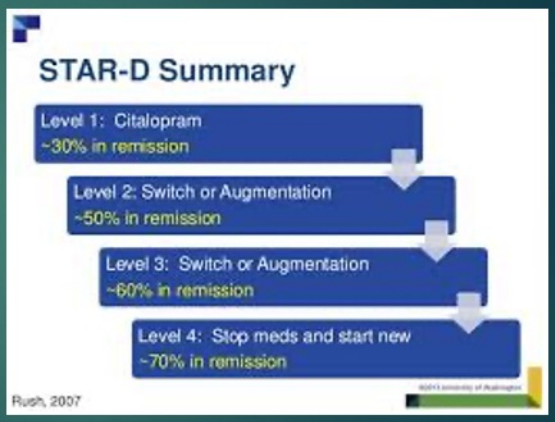
That goes for "what to switch to"; as for "how to make the switch" – i.e., an overlap? An underlap? A sudden switch? The answer lies in: pharmacokinetics! For almost all AD's, you can just do a sudden, "all at once" switch.

But for Prozac, with Norfluoxetine and its Humongously long half-life, wait a week – otherwise you're at risk from side effects of too much serotonin, or even Serotonin Syndrome.

The trouble with algorithms: every patient is an individual in terms of symptoms, severity, length of illness, comorbidities, & vulnerabilities.

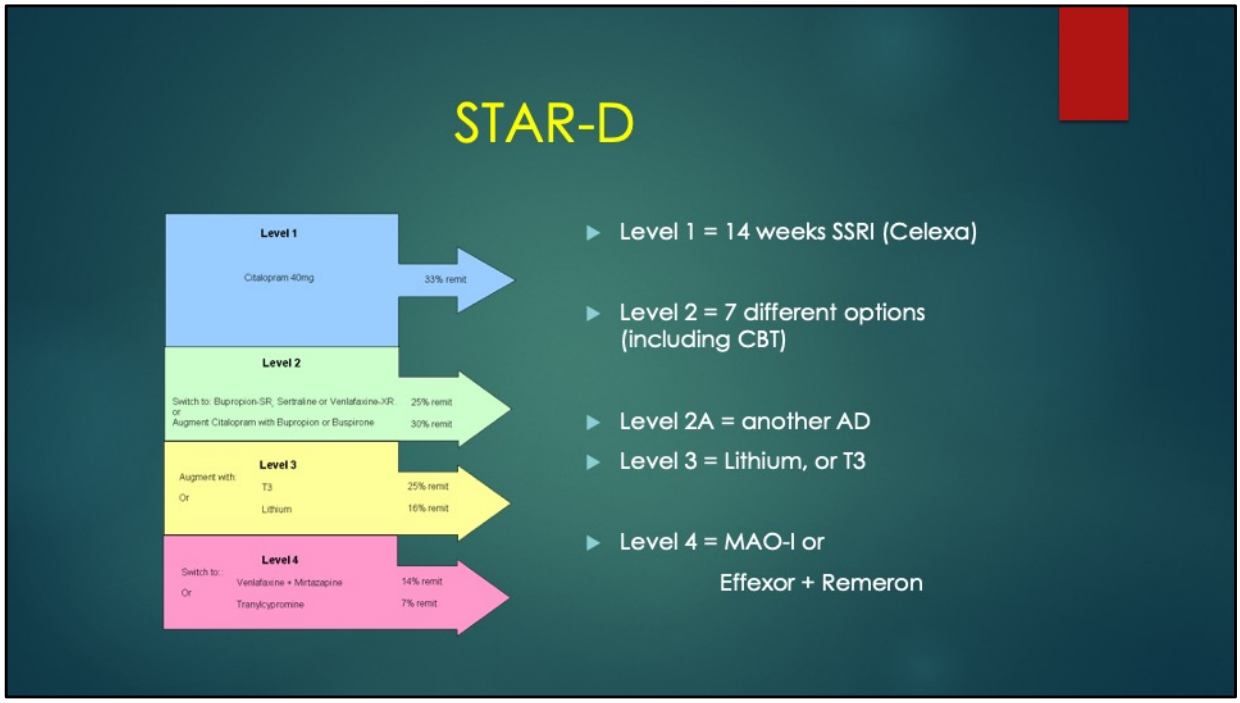
STAR-D

- Large patient population (n = 4,000), year is 2006
- From both psychiatry and primary care clinic populations
- Minimal exclusionary criteria
  - (intended to capture "real world" patient populations)
- Treatment not blinded
- Patient preferences taken into account
- 4 "treatment levels"
- Move to next level if < 50% toward remission



For "extra credit": What does STAR-D stand for?

"Sequential Treatment Alternatives to Relieve Depression"

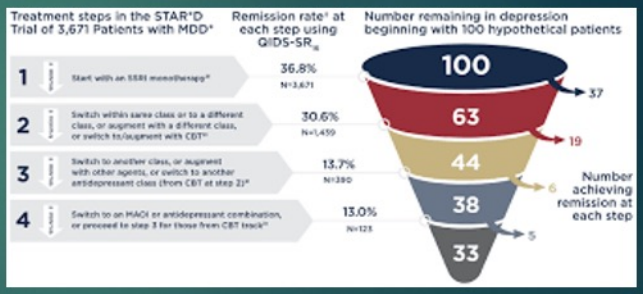


Level 2 = 3 combo's + 4 switches for a total of 7 different options

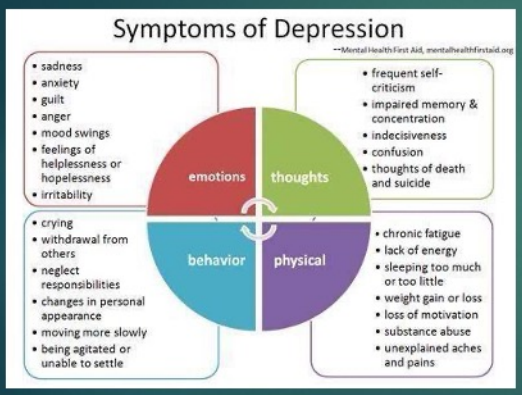
"Non-remitters" go to level 3, or Level 2A

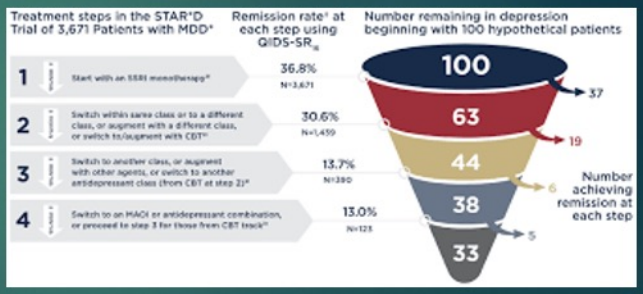
STAR-D

- Level 1: 47% response, 37% remission
- Level 2: No Significant differences between antidepressant choices
- Level 3 remission rates:
  - Remeron = 12%
  - Nortryptiline = 19%
  - Added Lithium = 16%
  - Added T3 = 25%
- Level 4: 13% remission rate for either option



STAR-D

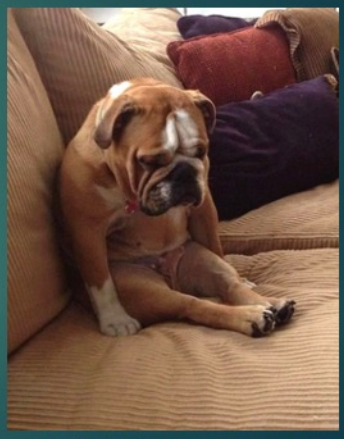




So the beauty of STAR-D is the naturalistic conception of depression that minimizes exclusionary criteria and therefore maximizes the similarity to real-world patient populations. But as you can see, there's tremendous flexibility built into this algorithm with lots of choices within each of the four levels.

Some groups likely to non-respond or get worse on antidepressants

- **Bipolar patients**
  - More likely to see mixed Sx appear rather than AD-induced hypomania
- **MDD with mixed features**
  - Recommend: SGA's rather than AD's
- **Borderline PD**
  - Recommend: anti-convulsants or SGA's
  - Meds get wrapped into SIB dynamics
- **Younger age**
  - Less efficacy
  - Higher para-suicidality
- **Genetic variants**
  - Short-Short 5HT transporter gene
  - Slow-metabolizers have higher blood levels and see side effects before therapeutic effects



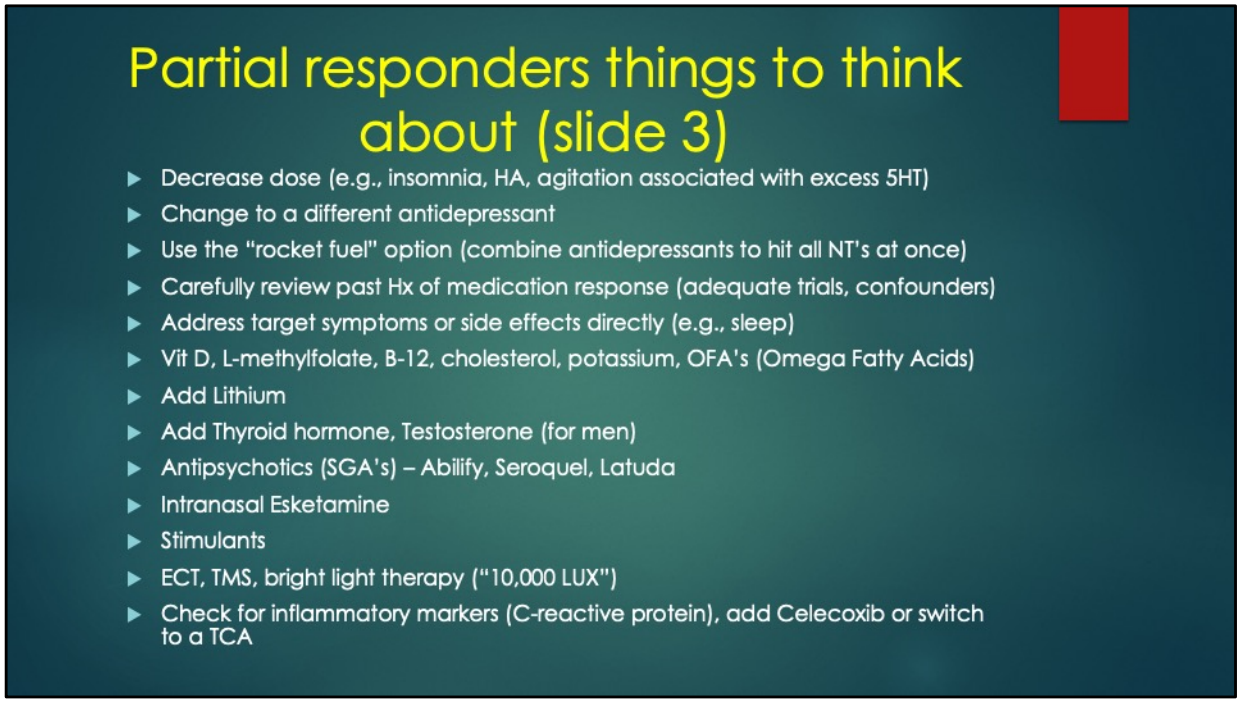
Portrait of a non-responder

Examples:
Rethink diagnosis: evidence seems to show that bipolar depression responds to different meds vs. unipolar depression; also, 'are there psychotic features present'
Re-assess your end points: What level of remission can you realistically expect? "Remission" for you or me might be different from your chronic, persistently seriously ill patient; does every child have to get into Harvard, of will you be happy if they get into Vanderbilt? But, lowering expectations shouldn't really be your first strategy with TRD, even though it's listed up here near the top.
Evaluate medical problems: common examples include: anemia, avitaminosis D, thyroid problems, pancreatic cancer, pituitary adenoma,
Review all medications: eg, "beta blocker blues" and other depressogenic or anxiogenic meds; chronic benzodiazepine usage
Life stressors: divorce, marriage, etc.
Blood levels: lithium, VPA, "window" for nortryptiline
Generic vs. brand name: rarely, these days, but still worth thinking about. Used to be a notable difference between Depakote and generic valproic acid; still see that occasionally. Another one you might is generic Bupropion vs. brand-name Wellbutrin
Current dosage: E.G., MOST AD's are Rx'ed by non-psychiatrists, yet non-psychiatrists are still often reluctant to increase dose to a therapeutic level

Medication compliance: non-compliance or partial compliance is the rule rather than the exception
Substance abuse: appallingly common in US society
GI issues: microbial dysbiosis associated with anxiety, depression, OCD symptoms; “gut brain axis”: gut microbiome influences absorption of nutrients, vagus nerve signals, overall serotonin regulation
.

Partial responders things to think about (slide 2)

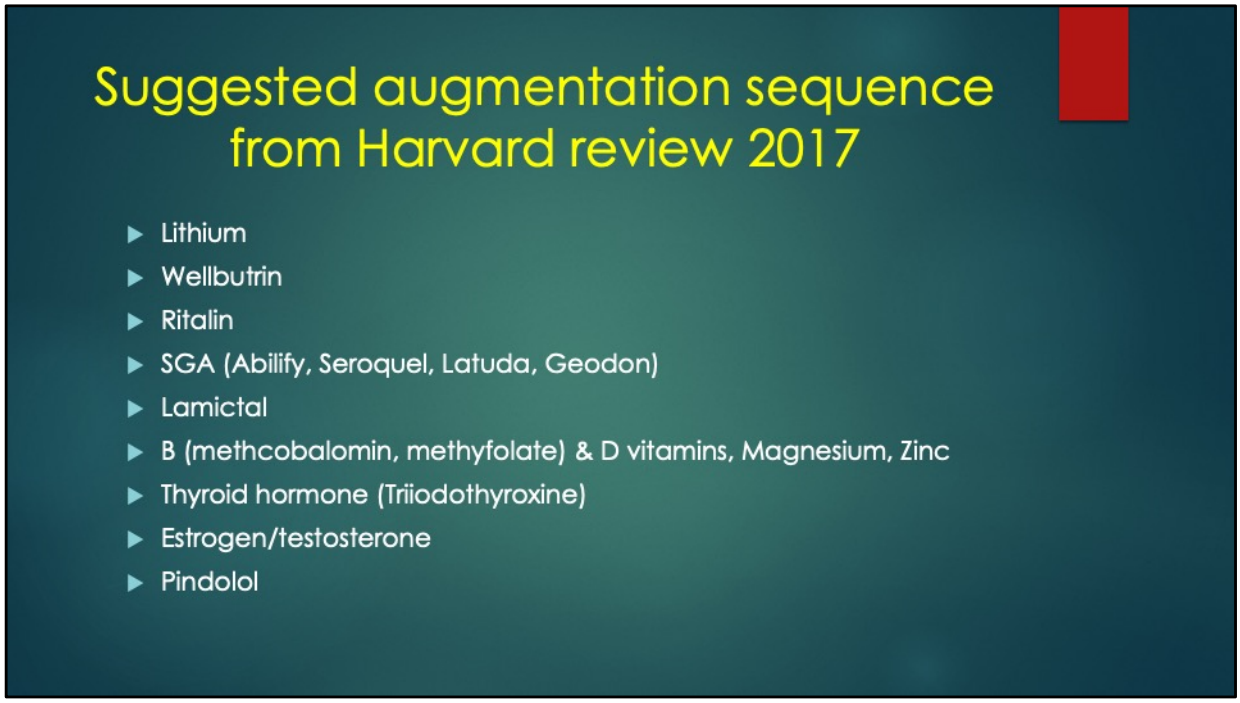
- Identify drug & alcohol use
- Add exercise
- Address "sleep hygiene"
- Keep a "one positive thing" journal or a "SAGE" journal
- Increase "dose" of psychotherapy
- Pastor's Potent Micronutrient Potion: Supplement with Vit D, folate, Magnesium, B12, Zinc, PUFA's, Co-Q-10
- Bright light/dark night therapy
- Negative ions
- Music & art, aromatherapy
- Logotherapy (re-connecting with purpose in life)



What is an "augmentation strategy": use of a drug or modality that is not generally considered an efficacious treatment for depression in and of itself, but acts synergistically for additive effect when added to an existing depression treatment.

All these maneuvers fall into the hand acronym of: "S.C.A.R.I.E.R." –

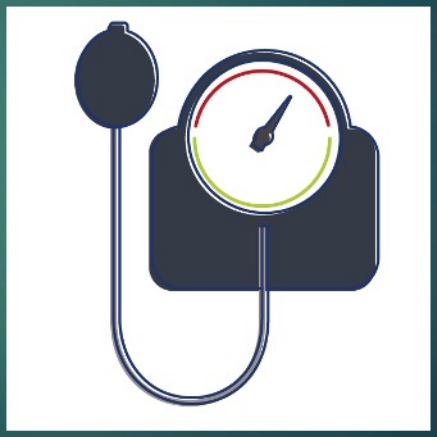
- Switching
- Combining
- Augmenting
- Referring (to a specialist)
- Inquiring (as to compliance, substance use)
- Empathizing (counseling, therapy, dealing with ongoing crises or trauma)
- Rediagnosing (consider both medical & psychiatric diasnoses)



Pindolol (Visken) = non-selective beta-blocker with “ISA” (Intrinsic Sympathomimetic Activity), therefore has “partial agonist” activity

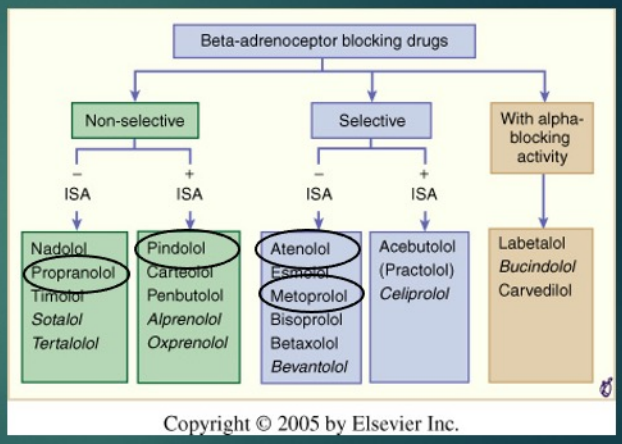
Pindolol

- Beta-blocker drug
- Anti-adrenergic
- Non-selective
- More Lipophilic than not
- Anti-hypertensive
- Has "ISA"
- **Intrinsic Sympathomimetic Activity**
- Potentiates the SSRI response for some patients
- Helps SSRI's work faster?



Pindolol & Beta-Adrenergic Blockade

- Non-selective includes Beta-1 and Beta-2 activity
  - Negative inotrope
  - Negative chronotrope
  - Bronchiolar broncho-constriction
- Selective includes Beta-1 only (cardiac)
  - Propranolol is contra-indicated with patients with bronchial asthma
- Beta-blockers further classified by hydrophilic vs. lipophilic
  - Atenolol is most hydrophilic
  - Propranolol is most lipophilic

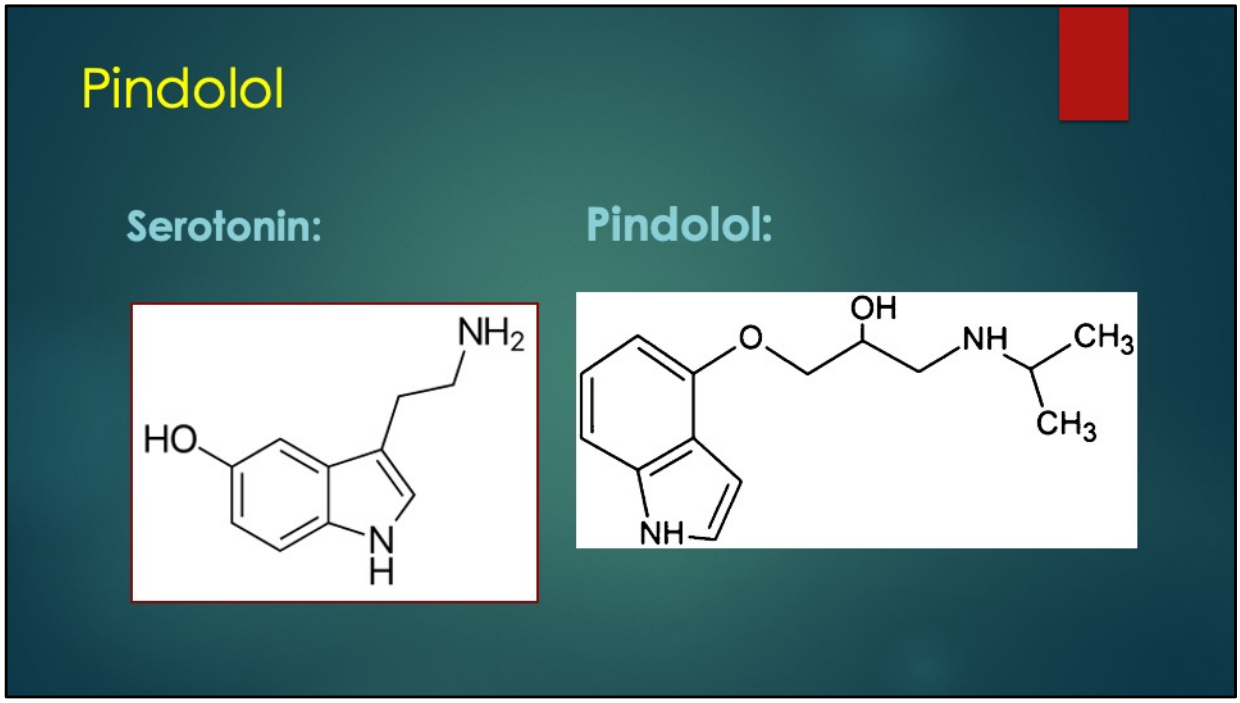


Three features of every Beta-blocker:

(1) Selective vs. non-selective
(2) With ISA or without ISA
(3) Hydrophilic (won't cross BBB) or hydrophobic (will cross BBB)

Atenolol: an outstanding example of pharmacokinetics at work: Atenolol, being most hydrophilic, is least likely to cross the blood brain barrier, and studies find it has the lowest incidence of CNS side effects (lethargy, low-level depression euphoniously known as the "beta blocker blues").

So if you want to treat blood pressure alone and avoid potential CNS complications, your best bet is Atenolol.



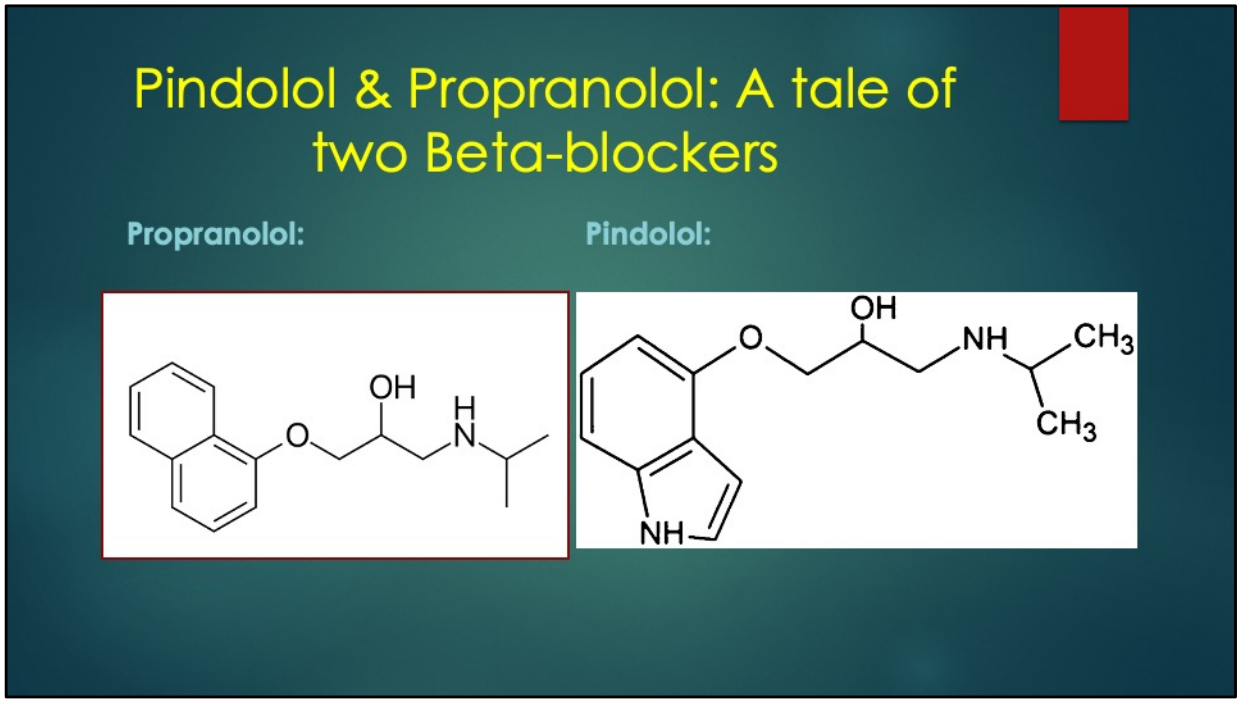
It defies logic at first: why should a drug (Pindolol) that in essence antagonizes sympathetic-adrenergic activity **also** have effects that increase catecholeminergic activity?

The answer, like that annoying-ly ubiquitous Ed Sheeran song, lies in "the shape of you" – well, the shape of the molecule, actually.

The shape of the molecule determines whether it fits into a particular neuro-receptor protein or not – in a lock and key fashion; we can all see this with our own eyes, even if we never took a chemistry class.

[observe the two rings in comparing Pindolol and Serotonin – ignore the "moieties" that are attached]

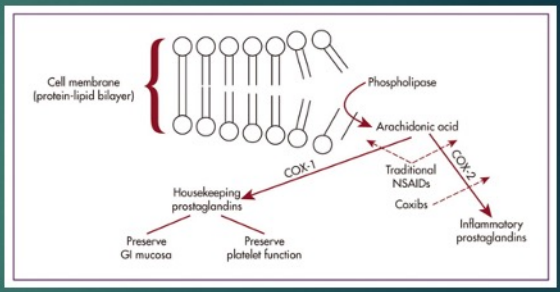
[Go to next slide]



I think the study in your bibliography finds that only “high dose” Pindolol is effective, i.e., 7.5 mg/day vs. 5 mg.

Inflammatory markers in TRD

- A majority of patients with depression who are treatment-resistant have positive markers for systemic inflammation
  - C-reactive protein
  - Interleukin-6
  - Tumor Necrosis Factor-alpha
- Non-depressed people, given Interferon (IF), experience depression
- For depressed patients with CRP > 2 mg/L, Nortriptyline (a TCA) works and SSRI's don't
- When CRP is < 2, SSRI's are superior to TCA's
- TNF-alpha blocker is superior to placebo
- Check inflammatory markers and Rx adjunctive Celecoxib (Celebrex) if elevated



TRD = Treatment Resistant Depression

We are referring to “chronic and systemic” inflammatory states, as opposed to temporary and localized inflammatory states (like a paper cut or a toe stub). An endocrine, immune system, and CNS response to some sort of stress or irritation. The body mobilizes its resources to fight off the potential threat but doesn’t shut down the inflammatory response over time – kind of like what we’re more familiar with, when the stress response persists over time (reference Sapolsky’s book “Why don’t Zebras get ulcers”).

Chronic systemic inflammatory disease may affect the GI, cardiovascular, or CNS systems. Turns out more than half of TRD patients have positive markers – called cytokines - for systemic inflammation: CRP, IL-6, TNF-alpha.

Slide shows just one small part of a very complex cascade or chain reaction in the body; inflammation can lead to blood clotting, vasoconstriction, decomposition of the mucosal lining of the GI tract, arthralgia, fatigue, and – we put a little “question mark” here – depression.

TNF-alpha blocker is: Infliximab. “Interferons” are proteins produced by the body in response to viral infections and function to “interfere” with the replication viral pathogens, ergo the name “Interferon”. IF’s are members of the cytokine family and generally pro-inflammatory.

Reference: Trends in Immunology, Volume 33, Issue 11, p571–577, November 2012
Review: **Interleukin-6: from an inflammatory marker to a target for inflammatory diseases**
Mercedes Rincon
Department of Medicine/Immunobiology, University of Vermont, Burlington, VT 05405, USA
DOI: http://dx.doi.org/10.1016/j.it.2012.07.003

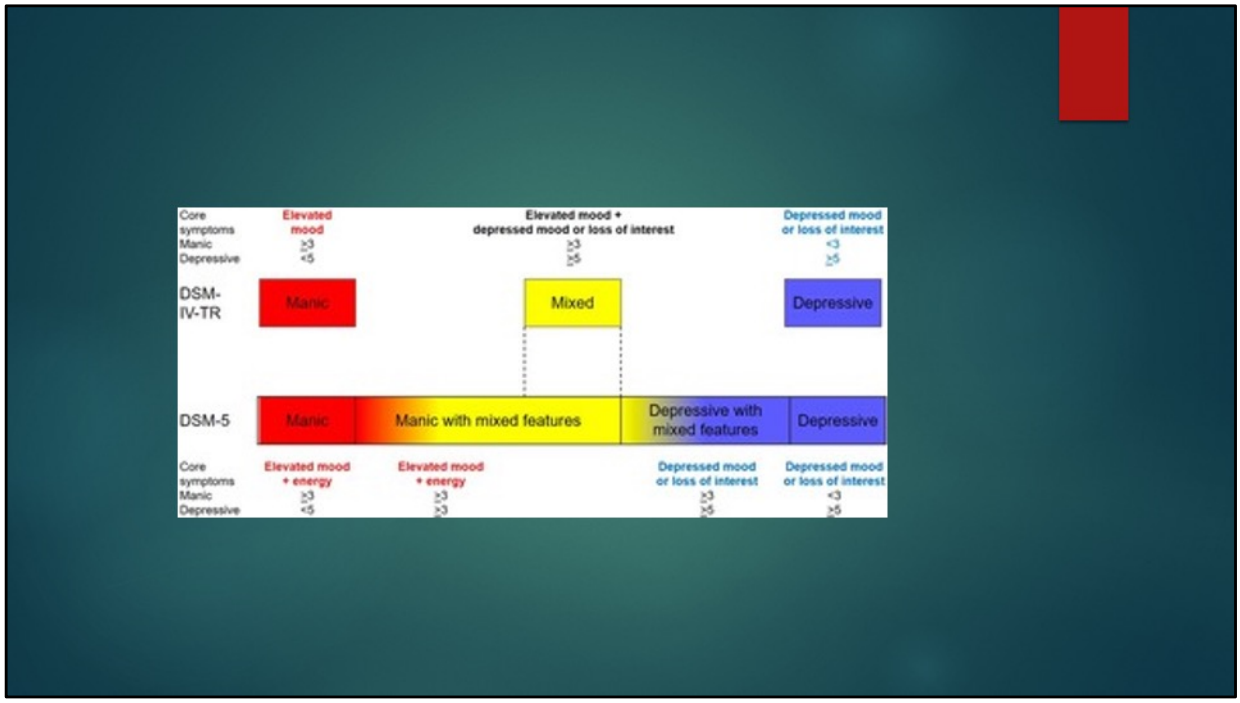
Up to one-third of patients diagnosed with MDD are found to eventually merit a diagnosis of Bipolar Disorder (J Clin Psychiatry 78.8 Sept.Oct 2017). For one thing, patients tend to under-report hypomanic symptoms such as hypomanic symptoms such as elevated mood, reckless behavior, or increased activity. We can think of a continuum from unipolar depression ("MDD"), to MDD with mixed features, to Bipolar type II, to classic Bipolar disorder with manic as well as depressive episodes. Understanding this continuum is extremely important when treating depression because it now appears that patients with bipolar or mixed features respond to different medications than patient with unipolar depression.

These findings are entirely counter-intuitive to me, for two reasons. One, SSRI's are so widely effective that it seems that everyone with depression deserves a trial of SSRI therapy before moving on to more complex or uncommon treatments. Two, I feel why treat symptoms or diagnoses that haven't yet – and may never – reveal themselves? If a patient is depressed, we'll treat the depression, and THEN if other symptoms appear, we'll address those if and when they arise. However, evidence if accumulating that antidepressants including TCA's and SSRI's are less effective than the SGA's for treating depression with mixed features. The SGA often needs augmentation and the algorithm-recommended augmenting medicine is not an SSRI but rather a mood-

stabilizer such as Lamictal, Depakote, or Tegretol. Lithium, too. Overall best evidenced-based response rates for depression in BPD = OFC, Lithium, Seroquel, Lamictal, followed by VPA and then Abilify.

So we've got to know what mixed features are, how to look for them, and keep our noses to the ground and our index of suspicion for mixed features and bipolarity high.

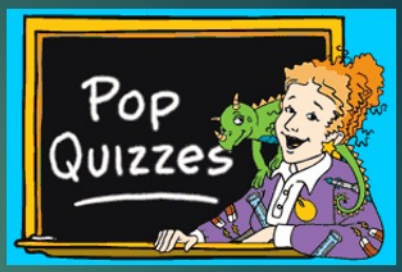
It is wise to remember that the spectrum of mood disorders is dynamic and evolving and a single office-visit, cross-sectional evaluation can be misleading. Obtain a detailed personal history, including family psychiatric history, and longitudinal follow-up.



From: Hu, et al, Mixed specifier for bipolar mania and depression: highlights of DSM-5 changes and implications for diagnosis and treatment in primary care, Primary Care Companion CNS Disorders 2014; 16(2): doi: 10.4088/PCC.12r01599.

You've correctly diagnosed your patient as MDD with "mixed features". According to expert guidelines, the best choice of medication is:

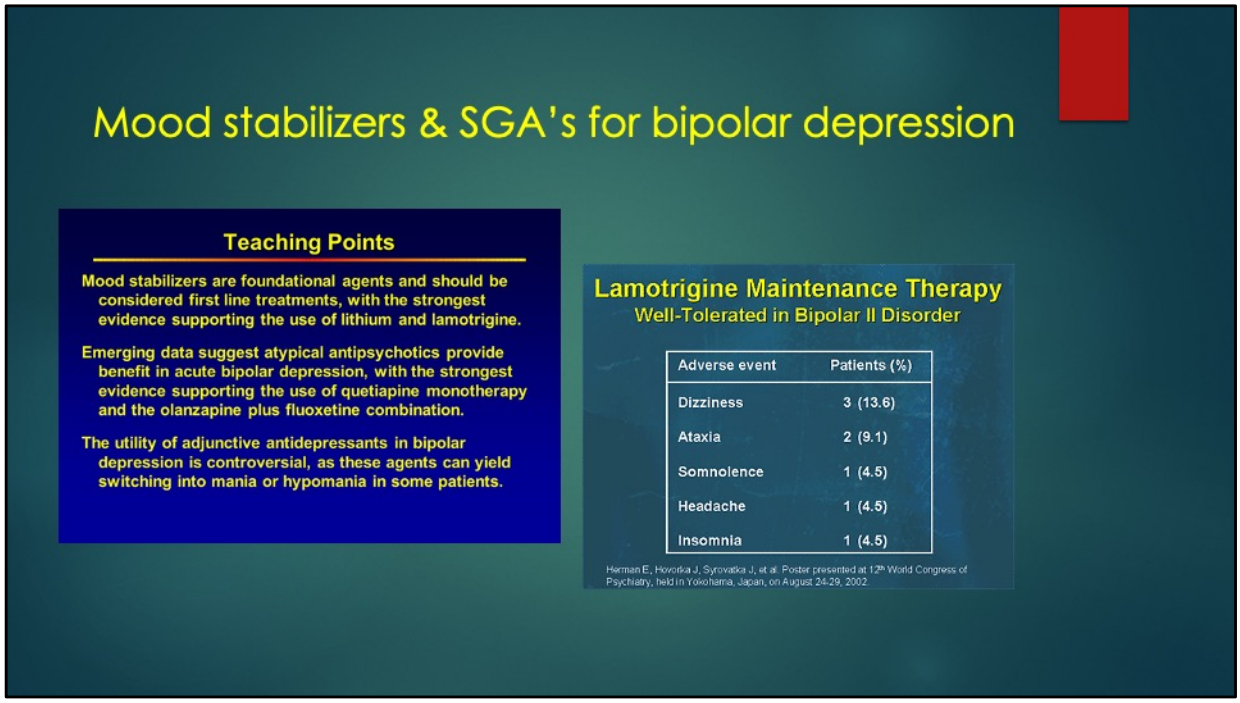
- (A) an Antidepressant with mixed Serotonin and Norepinephrine activity
- (B) a Psychostimulant with mixed amphetamine salts
- (C) a Benzodiazepine initially, followed after 1 to 2 weeks by mixing in an antidepressant
- (D) a second generation antipsychotic such as Latuda, Seroquel, or Abilify



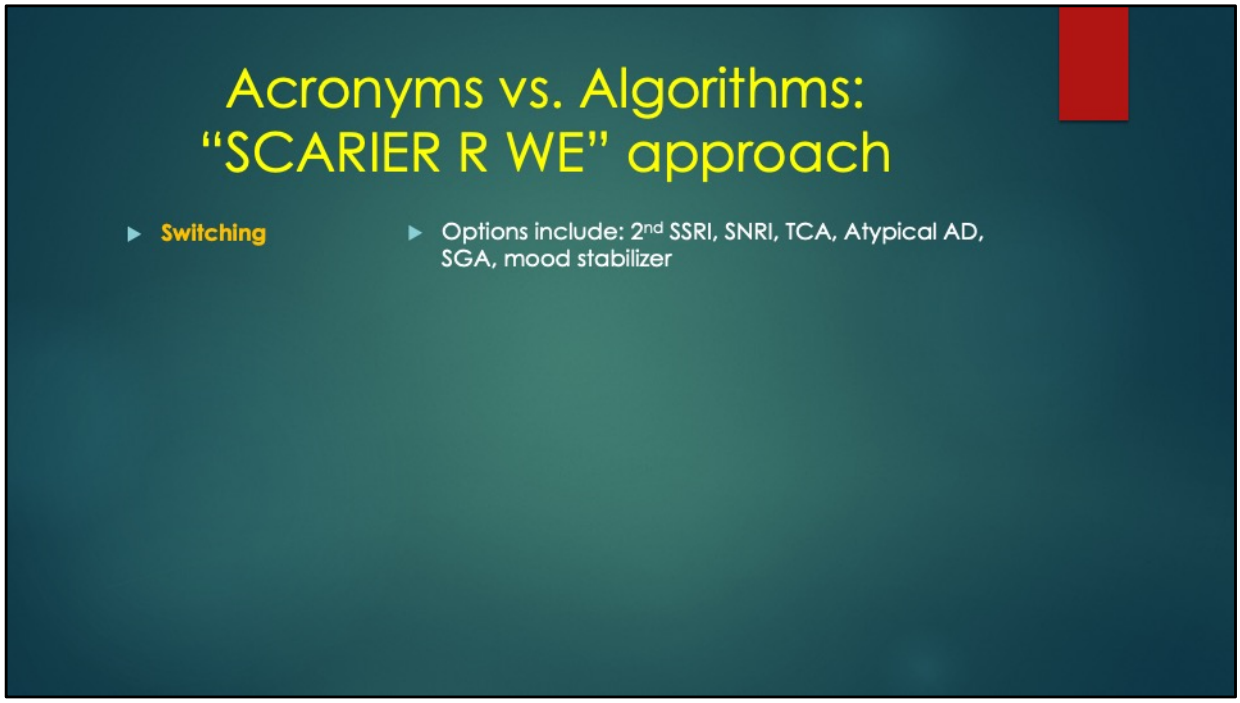
Answer: D

"Joel, an outwardly successful professional, has had recurrent depression since the autumn that he began high school. He's now 28 years old and has failed three courses of antidepressants. Current symptoms include intense anxiety and sleep disturbance. There's a history of frequent suicidal thoughts, and recently he's begun to wonder if the government is spying on hm." His father was diagnosed with bipolar disorder last year.

To me, it still seems like "everyone" – or every depressed patient – deserves a trial of an SSRI before we get into more complicated or risky medication strategies. But again, RCT's and algorithms find better evidence for initial treatment with an SGA with proven efficacy for MDD with mixed features and/or depression in the context of bipolar disorder.



Indeed, the use of antidepressants may not only induce switching, but evidence suggests they are also linked to an increased likelihood of rapid cycling.



A clash of paradigms: Acronyms or Algorithms for Tx of antidepressant non-responders?

SCARIER R WE =

Switching = options include: (1) second SSRI, (2) SNRI, (3) TCA, (4) atypical AD, (5) SGA, (6) mood stabilizer

Combining = options include: pretty much all of the above, generally an AD from a different class and MOA

Augmenting = generally with agents that are not AD's in themselves, e.g. (1) T3, (2) Pindolol, (3) lithium, (4) OFA's, (5) stimulants (methylphenidate, modafinil)

Referring = call your friendly neighborhood psychiatrist

Investigating = i.e., asking about compliance (lower when PCP is the prescriber vs. psychiatric prescriber), asking about drug and alcohol use

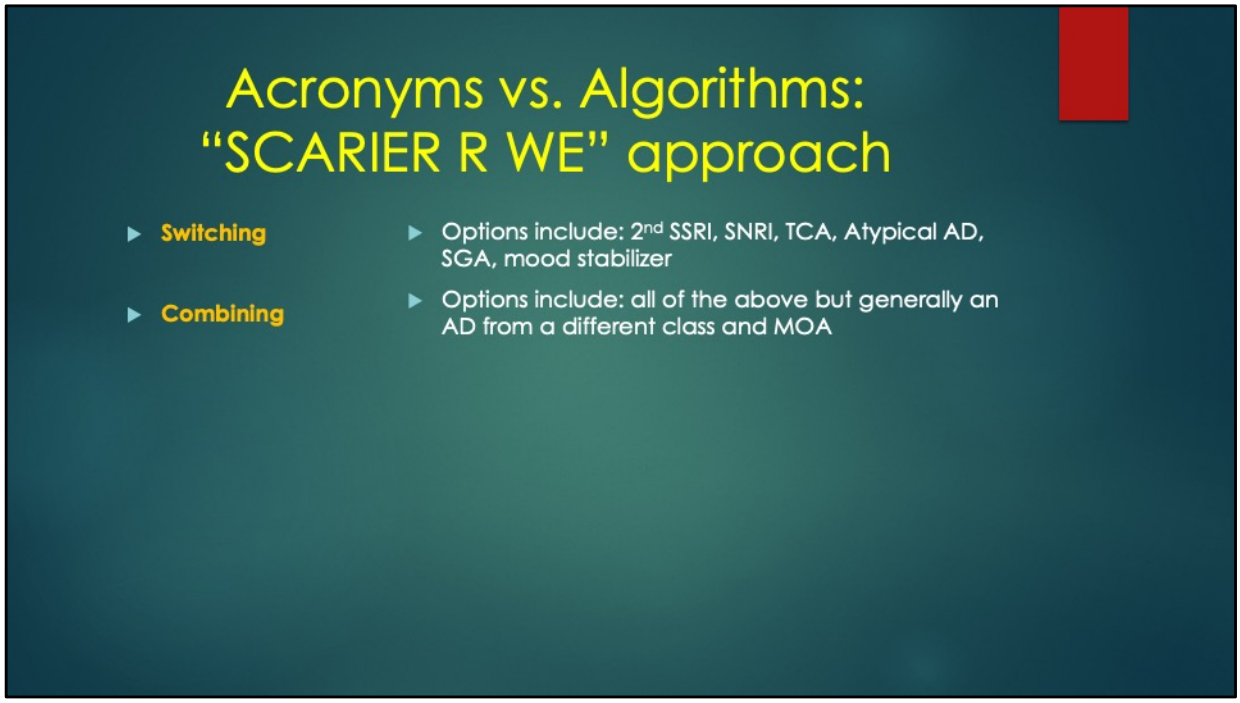
Empathizing = a tortured way of mentioning that psychotherapy should be a part of nearly every treatment plan for depression

Re-diagnosing = consider both medical diagnoses, deficiency syndromes, and differential psychiatric diagnoses

Receptor supersensitivity = consider effects of both antidepressant withdrawal and re-starting; serotonin supersensitivity can look like anxiety, dysphoria, insomnia – i.e., depression

Waiting = not evaluated in STAR-D, after 10 weeks of non-response, waiting another 6 weeks was as effective as any switching tactic attempted

Escalating the dose = related to "waiting", increase dose if tolerated by side effect and safety considerations



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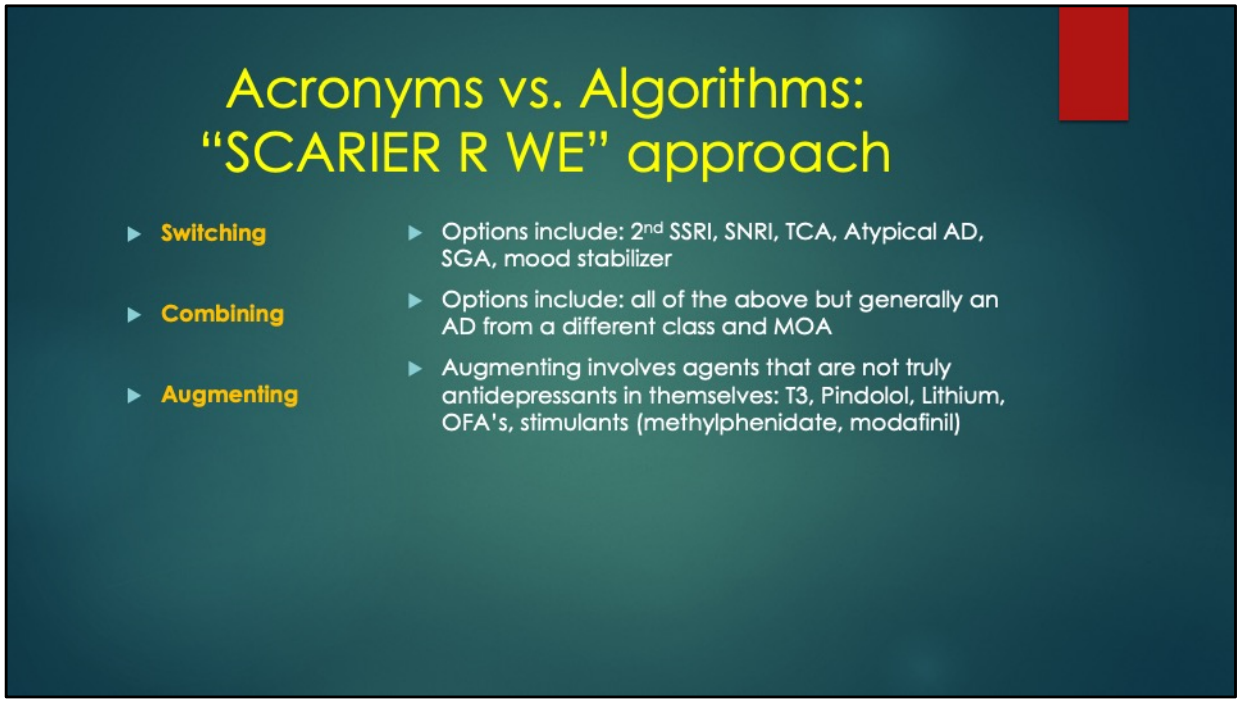

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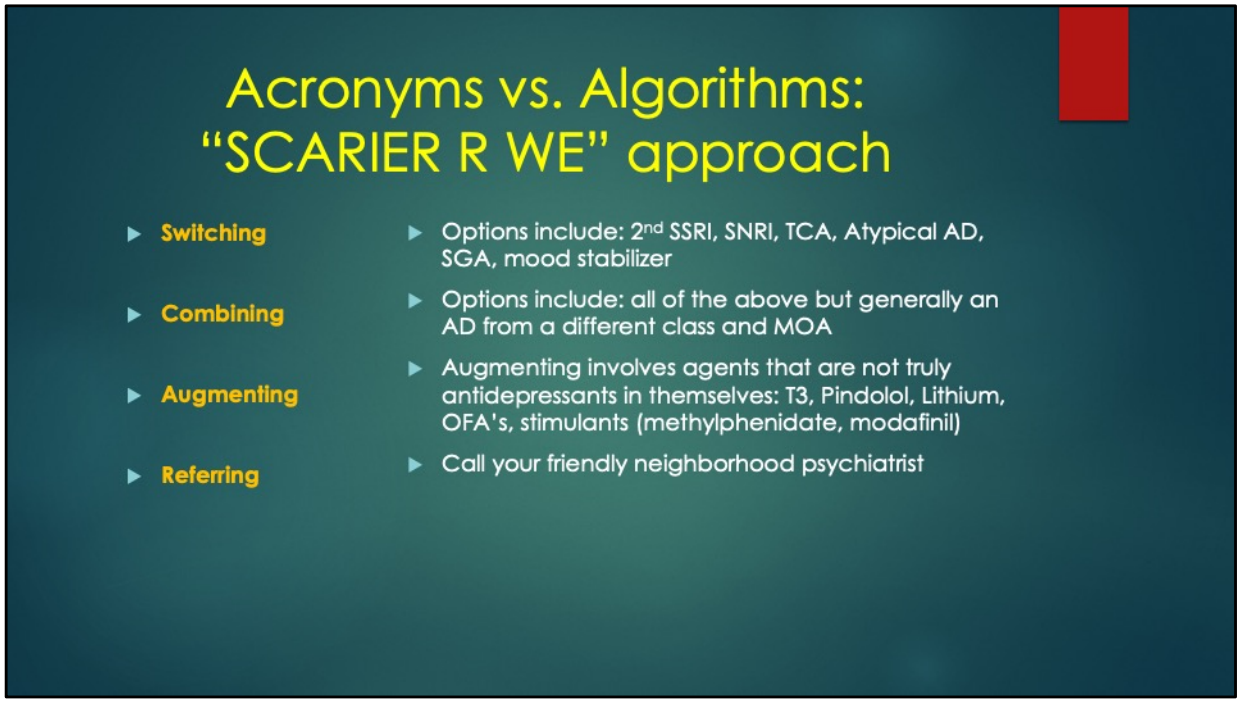

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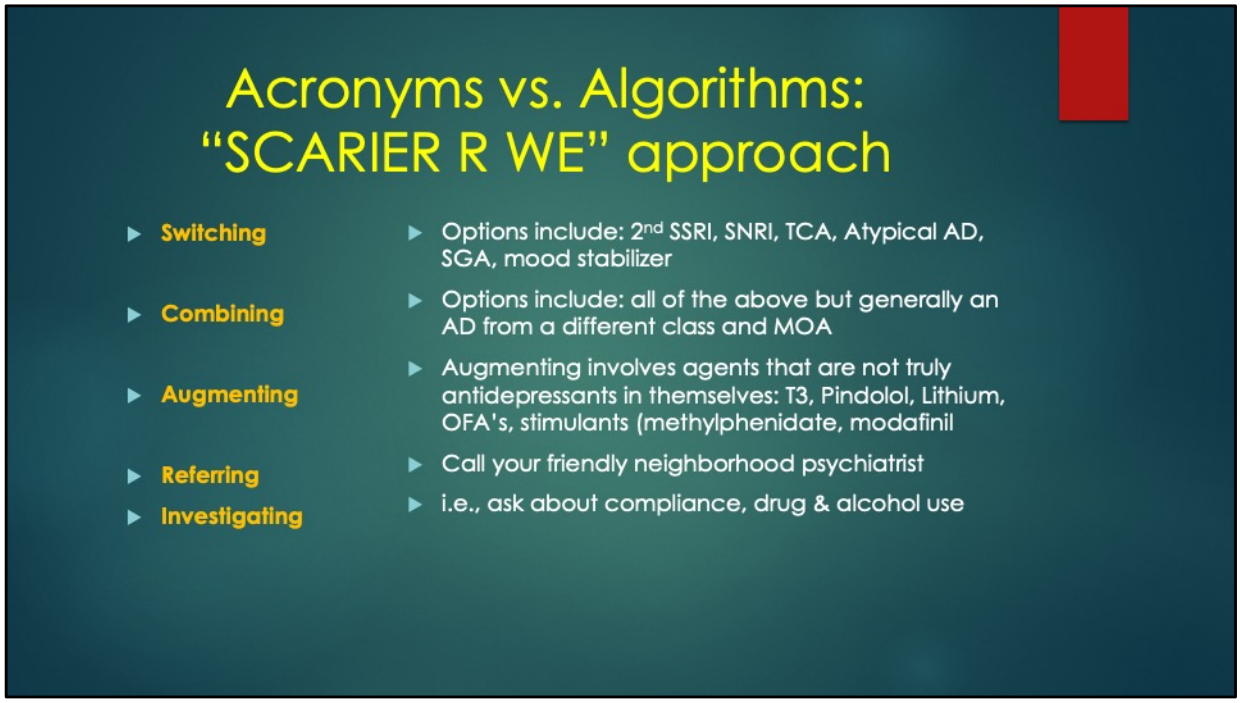

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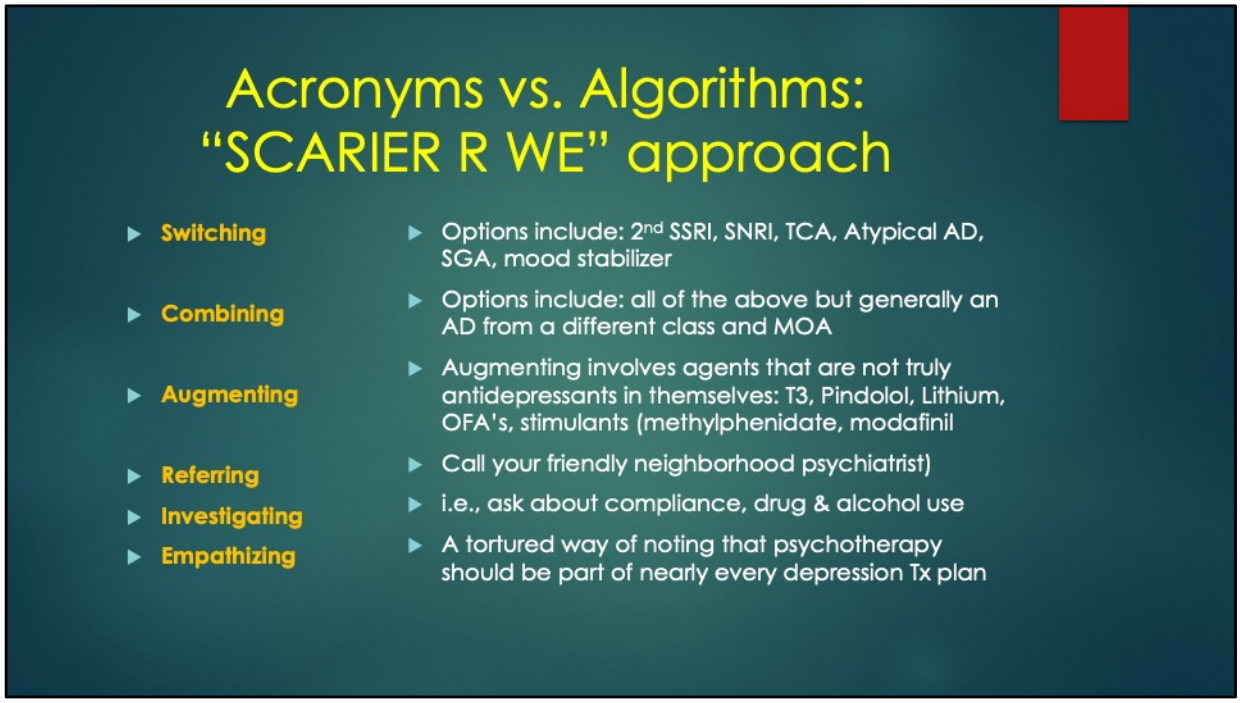

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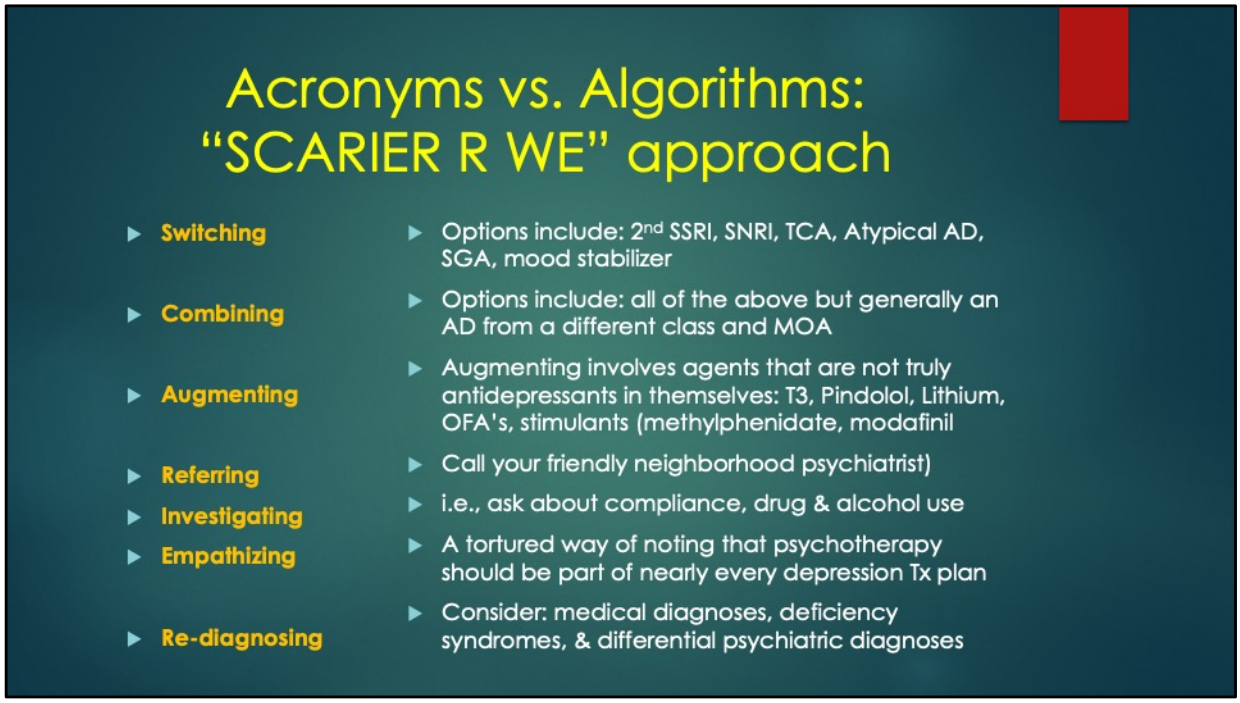

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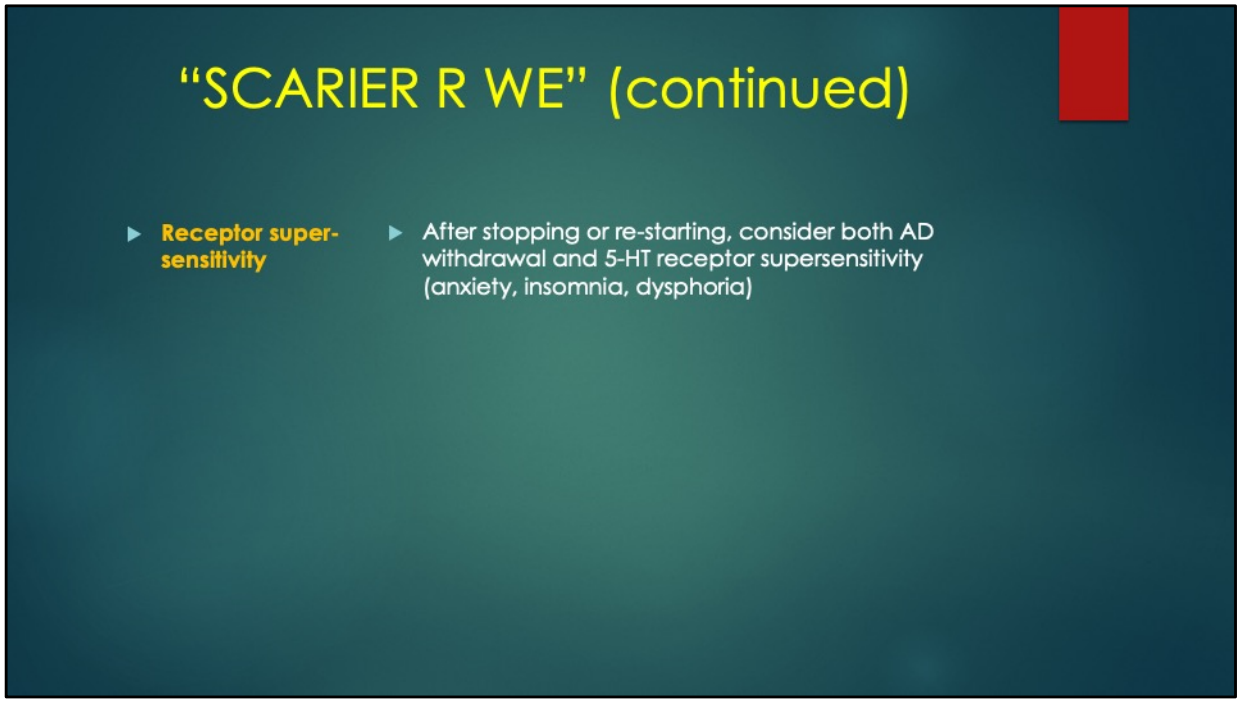

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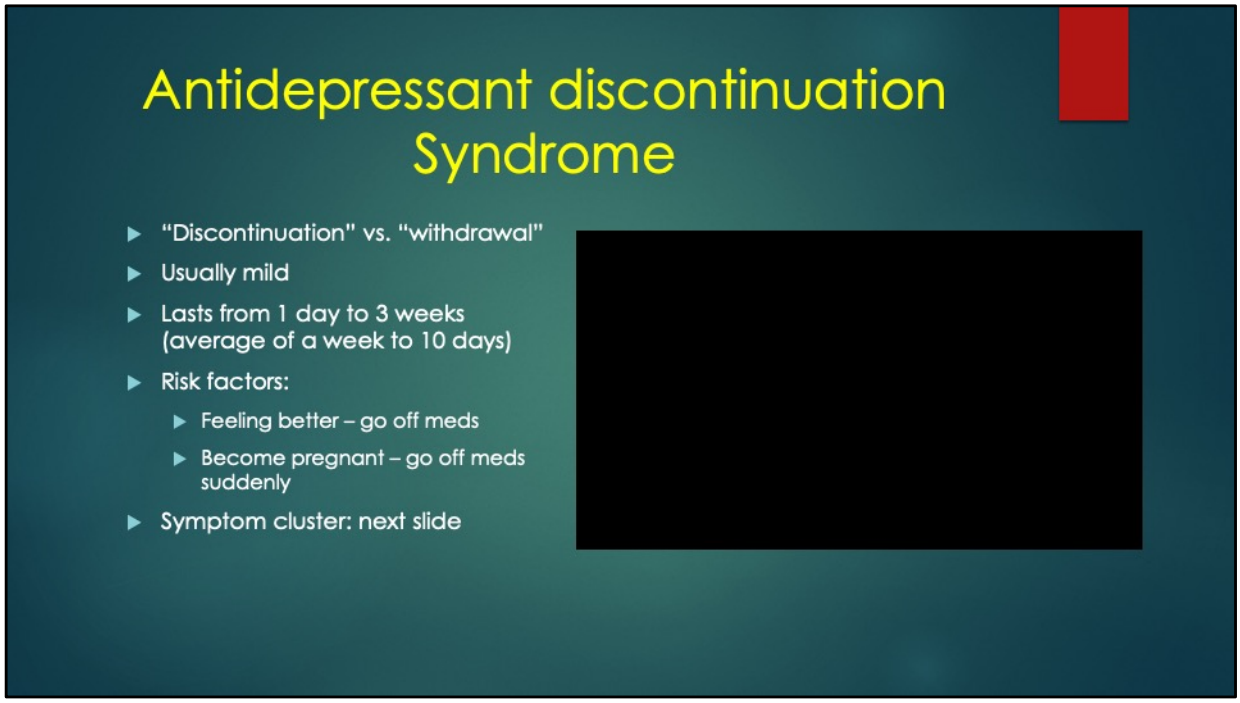
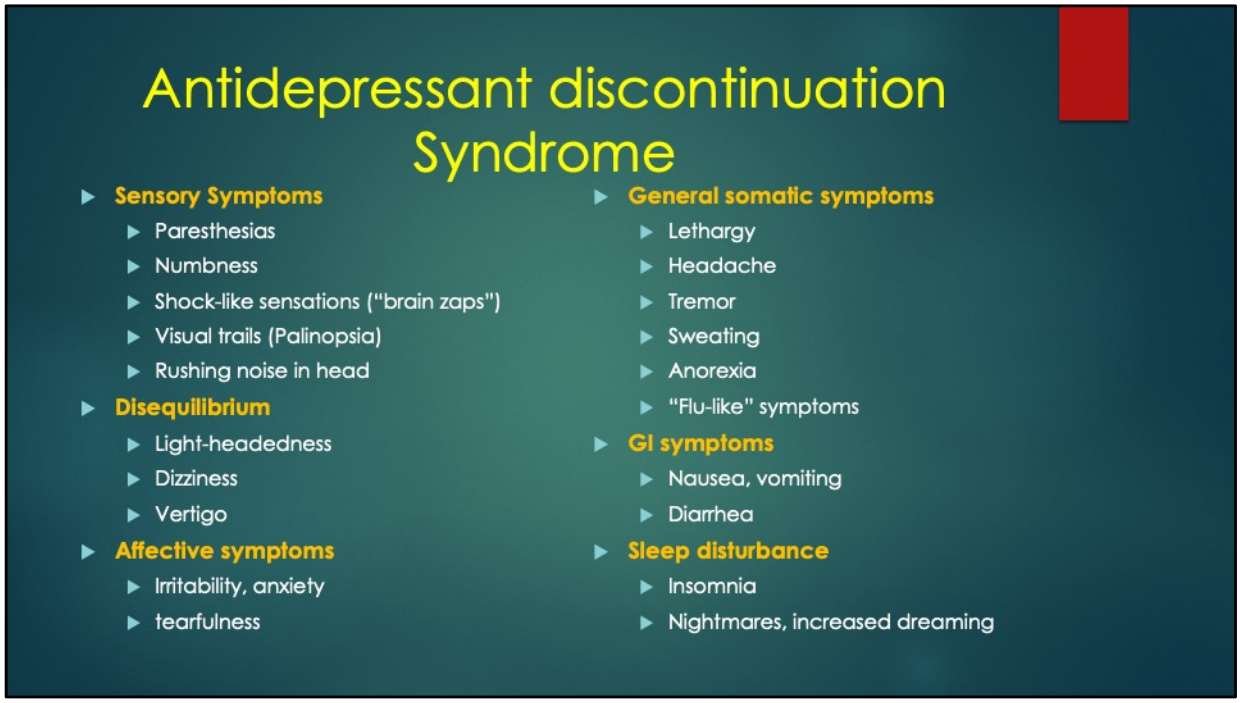


"Discontinuation" vs. "Withdrawal": separates AD's from drugs of abuse (no "cravings", no search for highs, no addictive properties). S. you "withdraw" from heroin, you "discontinue" Paxil.



Six groups of symptoms ….

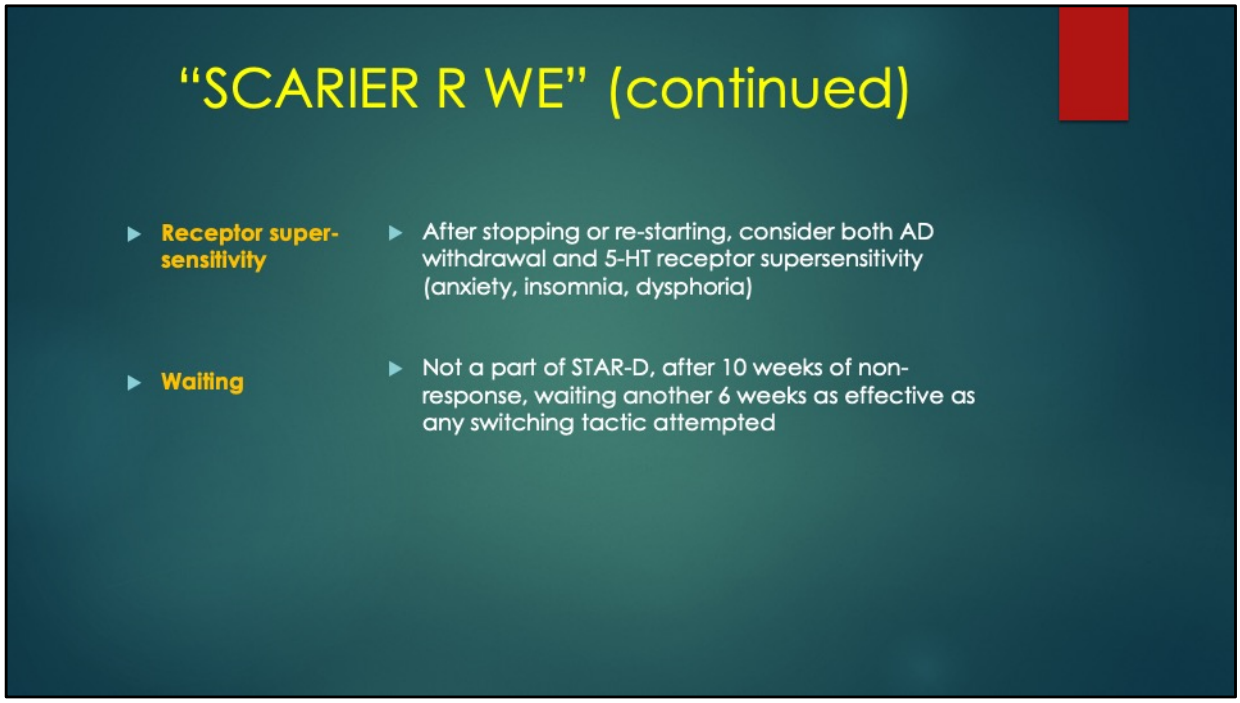
Some Sx look like depression itself, others are somewhat unique (“shock-like sensations”, “brain zaps”); suspect AD Discontinuation Syndrome by history and timing

Antidepressant discontinuation Syndrome

- **DDX:**
  - depressive relapse,
  - Serotonin syndrome
- **Tx considerations:**
  - Patient education
  - Fluoxetine: requires no taper
  - Reassurance
  - Restart & change to a slow taper

Antidepressant discontinuation symptoms

- F = flu like symptoms
- I = insomnia
- N = nausea
- I = imbalance
- S = sensory disturbances
- H = hyperarousal (anxiety) (Gelenberg, 1998 cited in Carson, 2000, p. 432)



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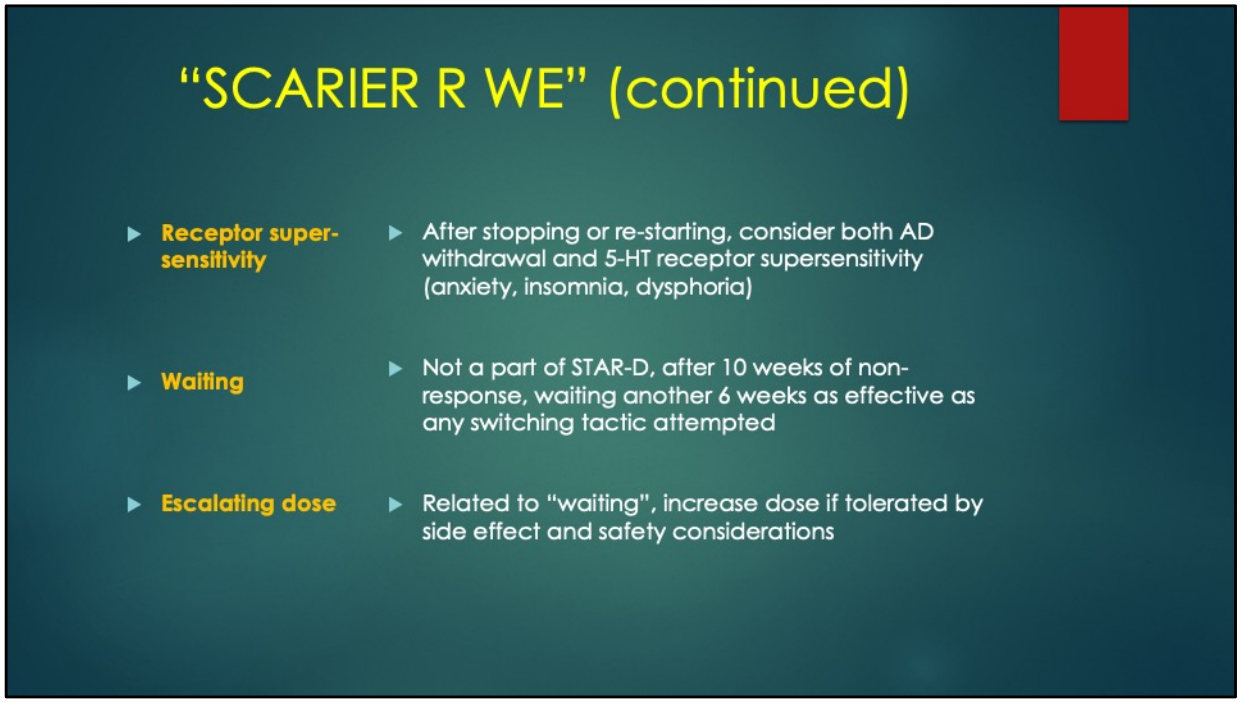
Waiting = not evaluated in STAR-D, after 10 weeks of non-response, waiting another 6 weeks was as effective as any switching tactic attempted; "Waiting" is derived from the axiom in medicine, "Don't just do something, stand there."

Escalating the dose = related to "waiting", increase dose if tolerated by side effect and safety considerations



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Antipsychotics

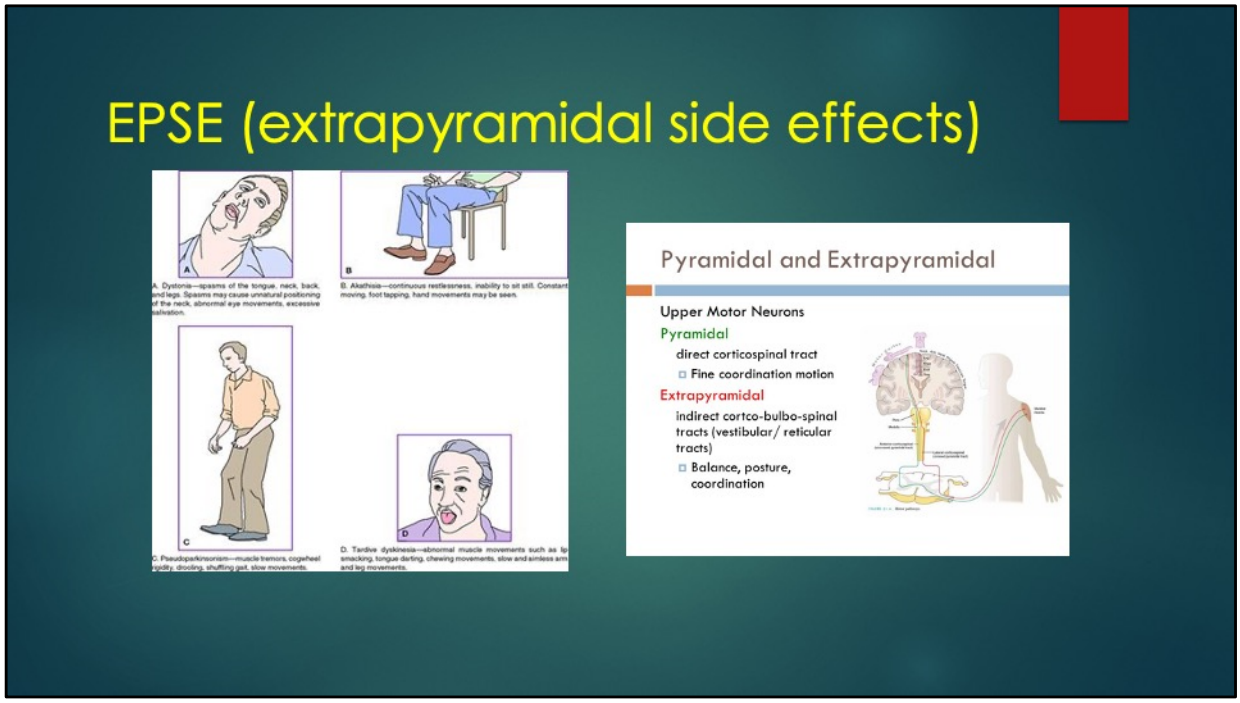
The 1st Antipsychotic: Thorazine

- First-generation antipsychotics (FGA)
- Side effects include:
- Movement disorders
- Endocrine
- Sedation
- Anticholinergic

Dopamine blockade provides treatment for hallucinations, delusions, agitation, cognitive disorganization associated with psychosis.

FGA's and SGA's equally efficacious for positive symptoms, SGA's may be somewhat more efficacious for negative symptoms. Otherwise, equally efficacious.

SGA's have 5-HT activity as well as DA activity; some have indications for Tx of depression.



Describe the four types of EPSE.

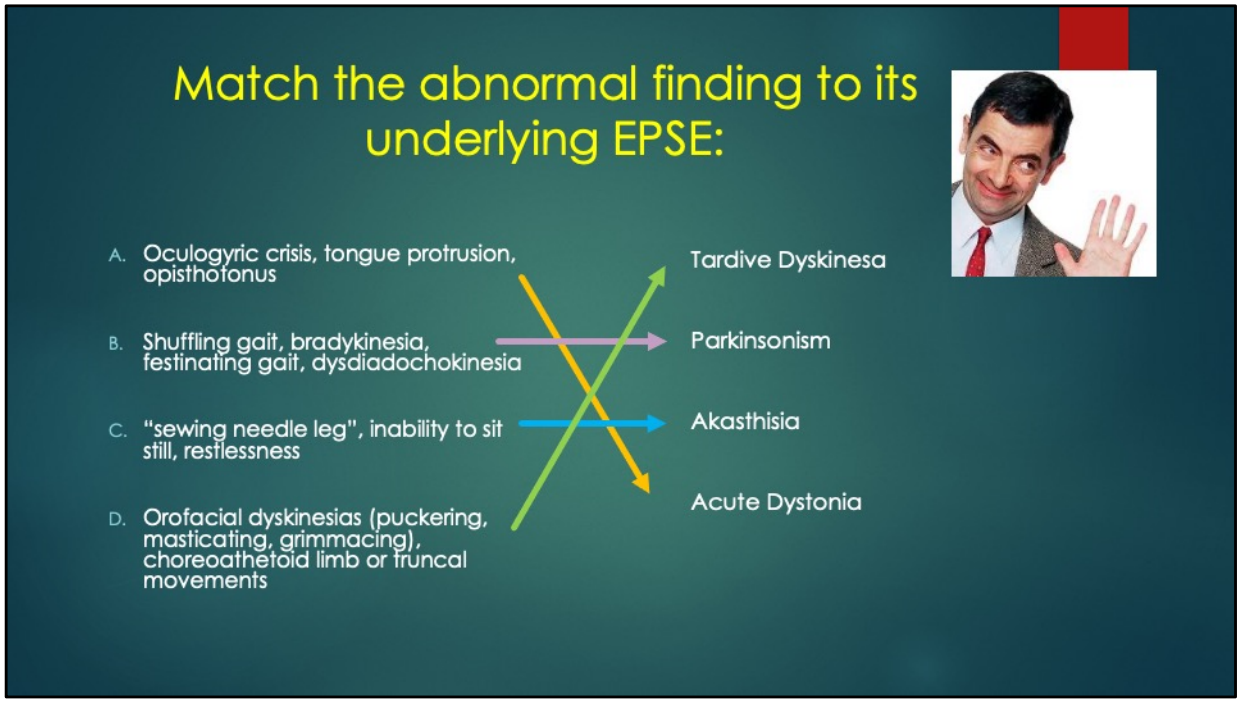
Acute dystonia: eye rolling back in head, tongue protrusion, paraspinal or neck muscle contractions

Akasthisia: restlessness, foot-tapping, can't sit still, "inner" restlessness

Parkinsonism: shuffling gait, loss of postural adjustment, stiffness, mask-like faces, slowness, resting tremor

Tardive Dyskinesia: puckering, chewing, grimmacing; abnormal limb or truncal movements

Mention where the term "extrapyramidal" comes from.

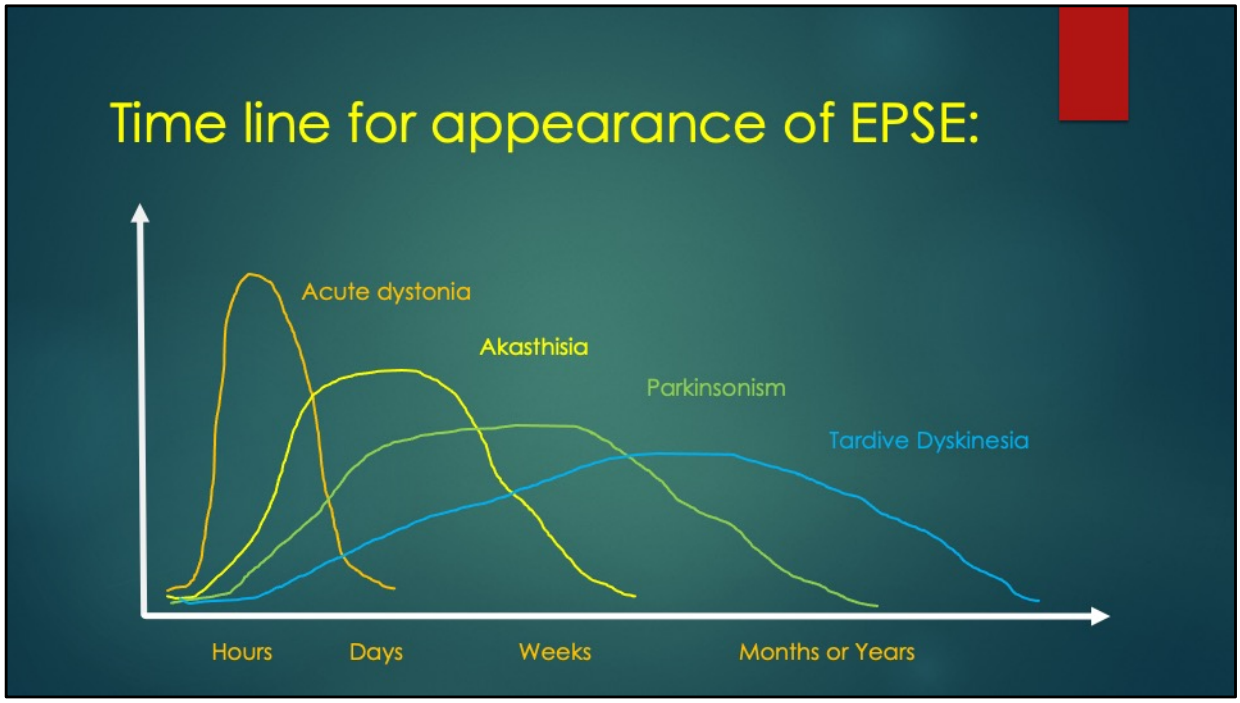


Festinating gait: a stiff, forward-leaning gait, often on tiptoes, with short, accelerating steps, and difficulty stopping; due to the loss of postural reflexes in Parkinson's disease or drug-induced Parkinsonism.

Dysdiadochokinesia = impaired rapid alternating movements

Overall incidence of TD is up to 25% of schizophrenics Tx'ed with long-term neuroleptics; however, incidence is approximately 15% in treatment-naïve schizophrenics. Elderly and edentulous are more at risk.

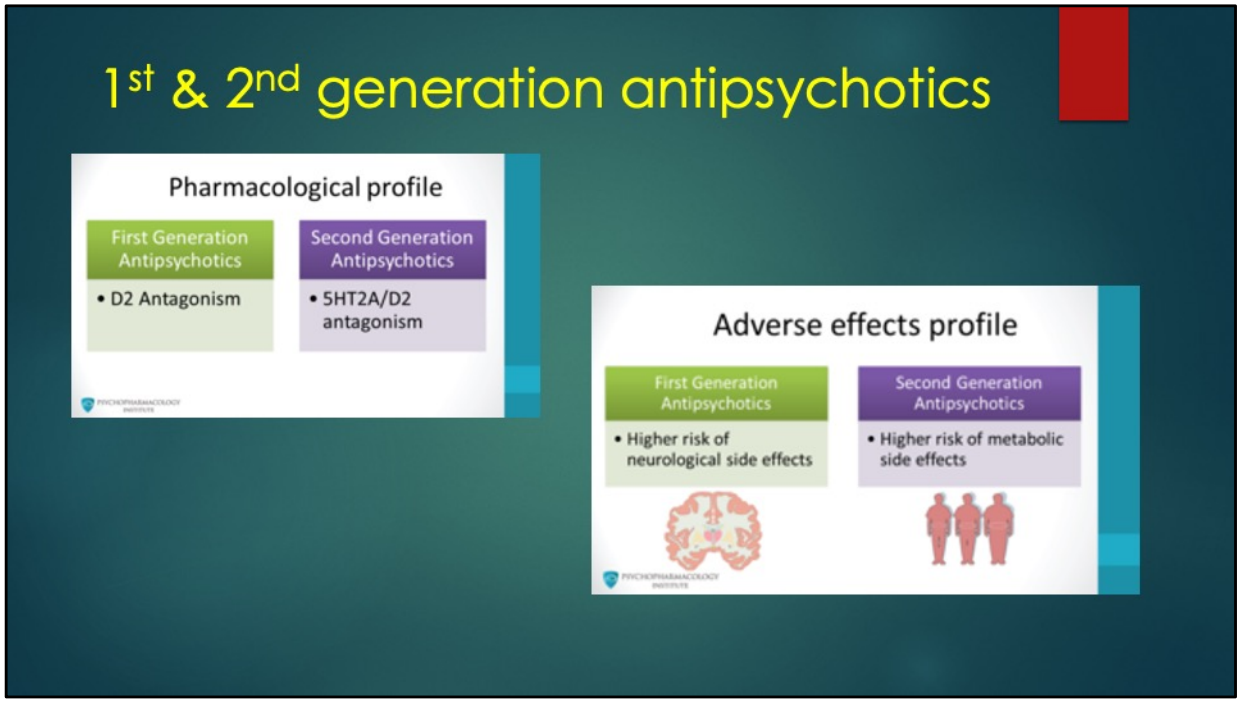
TD can be induced by chronic phenothiazine Rx for nausea.



A Take-away: not all neuroleptic-induced movement disorder is T.D.

Another take-away: avoid saying "this could be tardive dyskinesia" if the patient's only been on a neuroleptic for a few days or weeks.

Another take-away: EPSE and fear of T.D. is a major reason why the SGA's are Rx'ed today more commonly than the FGA's – it's an extremely bad advertisement for you as a physician to have a patient walking (or shuffling) around with severe T.D. and everyone is point at the patient saying, "Oh, that fellow, that's one of Dr. Pastor's patients ….."



The key difference between 1GA and 2GA antipsychotics:

DA blockage only vs. DA + 5HT activity

This difference is reflected in the key S/E profile

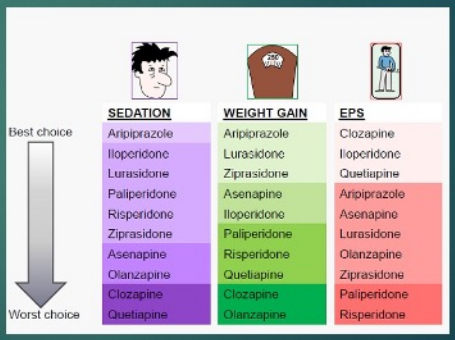
2GA purportedly improves negative symptoms and cognitive dysfunction of psychosis.

Second-generation antipsychotics ("atypicals")

Table 2. Select Antipsychotic Agents

Traditional (First Generation) Antipsychotics
Chlorpromazine (Thorazine)
Fluphenazine (Prolixin, Permitil), fluphenazine decanoate
Haloperidol (Haldol), haloperidol decanoate
Loxapine (Loxitane)
Mesoridazine besylate (Serentil)
Molindone (Moban)
Perphenazine (Trilafon)
Thioridazine (Mellaril)
Thiothixene (Navane)
Trifluoperazine (Stelazine)
Atypical (Second Generation) Antipsychotics
Aripiprazole (Abilify, Abilify Discmelt)
Clozapine (Clozaril, FazaClo)
Iloperidone (Fanapt, Fanapt Titration Pack)
Olanzapine (Zyprexa)
Paliperidone (Invega), paliperidone palmitate (Invega Sustenna)
Quetiapine (Seroquel, Seroquel XR)
Risperidone (Risperdal, Risperdal Consta, Risperdal M-TAB)
Ziprasidone (Geodon)

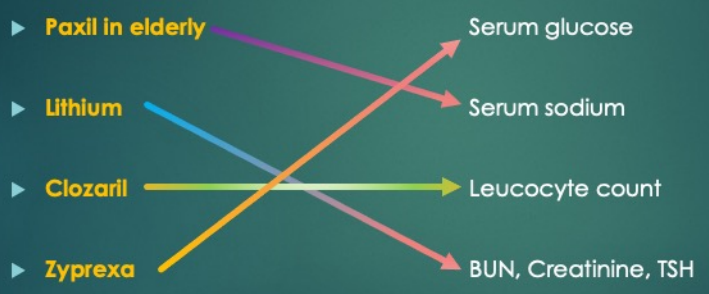
Source: References 2,15.

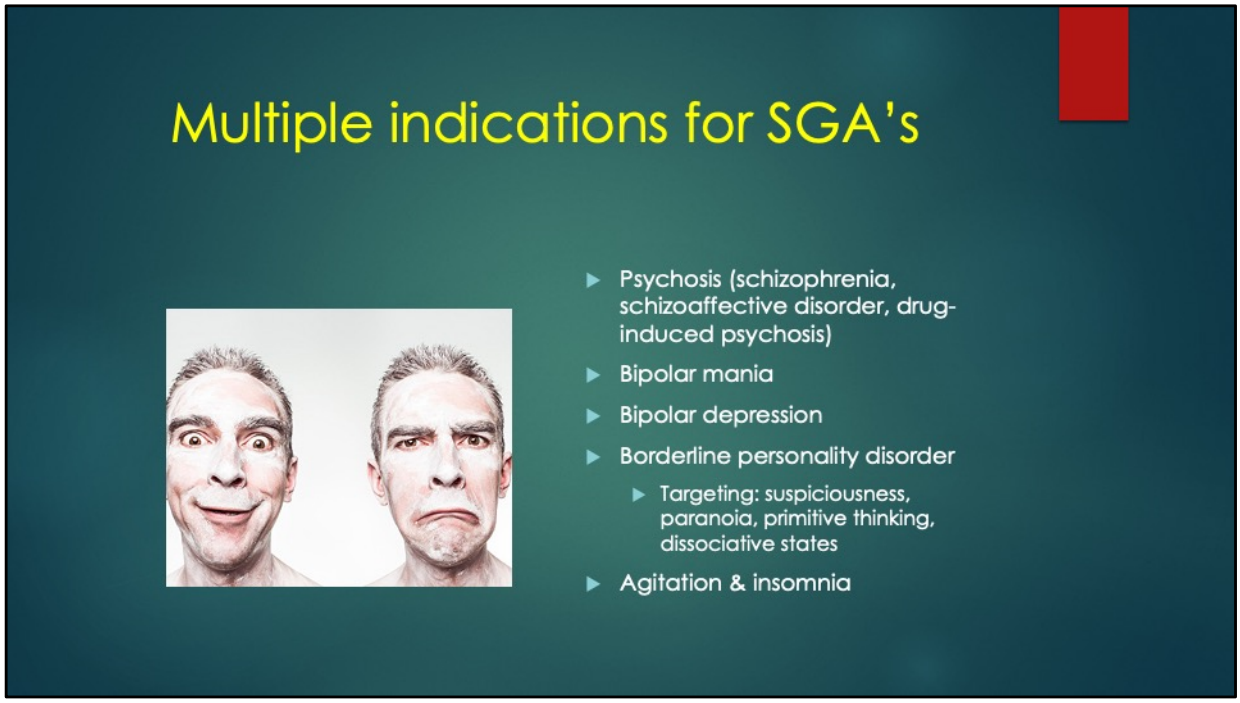


SGA's

- Zyprexa (Olanzapine)
  - Very sedating
  - Instantly dissolving preparation called "Zydis"
  - Weight gain & sedation
  - Good for highly agitated patients
- Seroquel (Quetiapine)
  - Very wide dose range provides flexibility (25 to 800 mg daily)
  - Will put anyone to sleep
  - Proven efficacy for depression
- Risperdal (Risperidone)
  - Low risk of metabolic syndrome but
  - Higher risk of EPSE & hyperprolactinemia-induced gynecomastia
- Abilify (Aripiprazole)
  - Not very sedating
  - Not associated with weight gain
  - Proven efficacy for depression
- Lurasidone (Latuda)
  - No weight gain
  - Proven efficacy for depression
  - 1st line for BPD (with Lamictal)
- Clozaril (Clozapine)
  - Treatment-resistant Schizophrenia
  - Needs blood monitoring for agranulocytosis
  - Weight gain, S-T prolongation

Pop Quiz: match the medicine with its relevant lab test



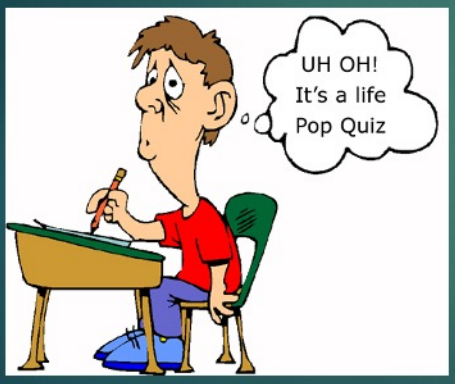


Lurasidone (Latuda) should be added to "Table 1"

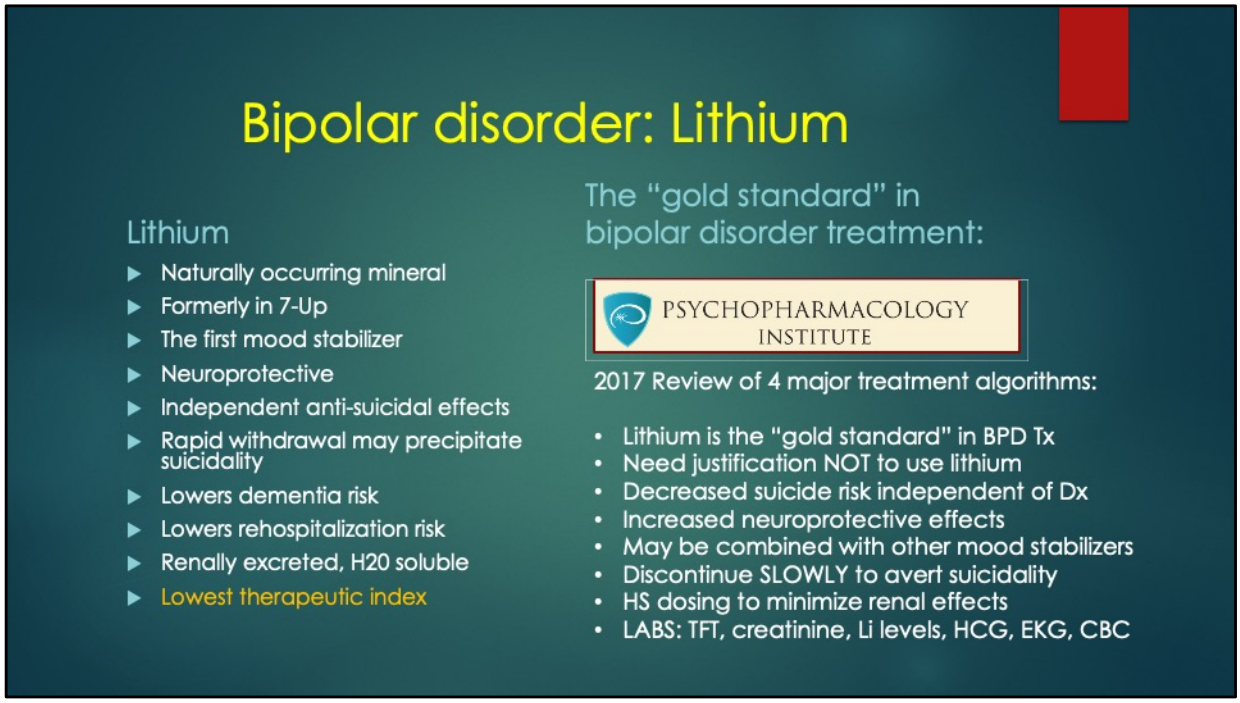
Additional uses of SGA's:

- Psychosis (schizophrenia, schizoaffective disorder, drug-induced psychosis)
- Bipolar mania
- Bipolar depression
- Borderline personality disorder (target Sx = suspiciousness, paranoia, all-or-none primitive thinking, dissociative states)
- Agitation & insomnia

Pop quiz



- Which medication is **incorrectly** paired with its notable side effect?
  A. **Zyprexa** – weight gain
  B. **Haldol** – acute dystonia
  C. **Seroquel** – sedation
  D. **Clozaril** – agranulocytosis
  E. **Lithium** – tardive dyskinesia
- Correct answer: E



Many Lithium enthusiasts would like to see Lithium classified by the USDA as an "essential trace element" like other metals such as Zinc, copper, selenium, and Magnesium.

Zurich cohort: lowers dementia risk.

Clin Psy News: 50% reduction in hospitalization of depressed patients

Lithium has a potential side effect of elevating white blood cell count (has been used for that purpose in patients with chemotherapy-induced leukocytopenia)

Lithium has been used for cluster headache, may be used in CTE

Titrate to blood levels .4 to .8 for maintenance. .8 to 1.2 for acute Tx; toxicity at 1.5 or higher

Dose-dependent side effects include nausea, sedation, weight gain, tremor, acne, polyuria, polydipsia, xerostomia

Bipolar disorder: the mood stabilizers

- **Lamotrigine (Lamictal)**
- more efficacious for depression than mania
- slow titration lessens risk of Stevens-Johnson syndrome
- Second line Tx after Lithium in Psychopharmacology Institute review
- used for affective instability in borderline personality disorder

Pop quiz

- All of the following are true **except**:

A. **Depakote** (valproate) – better for rapid-cycling mania

B. **Lithium** – perilously low "Therapeutic Index"

C. **Lamictal** (Lamotrigine) – rare but serious rash reaction

D. **Topamax** (Topiramate) – risk of weight gain

E. **Latuda** (Lurasidone) – good for bipolar depression

- Answer: D

PTSD

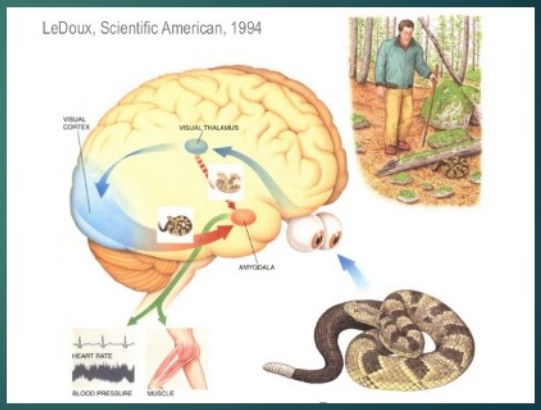
PTSD paradigms

- Neurobiological
  - Limbic hyperarousal
- Behavioral psychology
  - Classical conditioning
- Existential/experiential
  - Shattered assumptive world

PTSD

Neurobiological aspects:

- **Neuro-anatomical**
  - Amygdala, hippocampus, anterior cingulate gyrus
- **Neuro-endocrine**
  - Cortisol, HPA axis; NPY is protective
- **Neuro-transmitters**
  - Catecholamines (NE), 5HT projections, Glutamine



In terms of the neurobiology of PTSD, it's somewhat complex and I won't try to review it here, but rather to note there are three aspects. The neuroanatomy involves the crucial role of the Amygdala, in charge of "fear signaling" in the brain, which is considered overactive in PTSD; the hippocampus, which involves memory and learning. There was a finding of hippocampal atrophy early on in brain imaging of PTSD and researchers speculated that PTSD shrunk the hippocampus, preventing new learning and leaving the patient "stuck" in a repetition of the paralyzing fear of the original trauma. However, subsequent studies, including twin studies of one twin with PTSD and the other without combat exposure, suggested that reduced hippocampal volume was pre-existing. In other words, a risk factor for PTSD and not a consequence of PTSD. A small hippocampus is associated with low intelligence, which is also a risk factor for PTSD. The hippocampus is involved in "the contextualization of trauma" – putting upsetting events into an understandable context that the mind can assimilate into the fabric of everyday experience and move on with life, and a smaller hippocampus correlates with impaired contextualization of trauma. The anterior cingulate gyrus is up in the cortex and serves to put the brakes on the amygdala and tone down the fight or flight response.

The neuroendocrine aspect of PTSD is significant, including increased production of

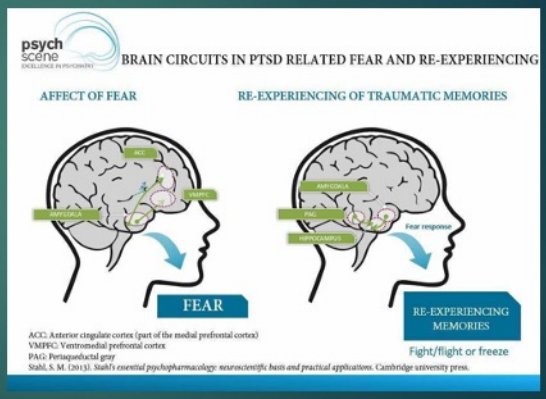
CRH, which goes to many areas in the CNS and triggers catecholaminergic excess, as well as disrupting the usual hypothalamic-pituitary-adrenal axis feedback loop. As a result, there is an initial surge of cortisol, causing excito-toxicity of the ACG, disrupting the normal inhibition of the amygdaloid fear signaling. In terms of the neuro-endocrinology of PTSD, there's also a role for endogenous opioids. In fact it has been shown the combat casualties who received larger doses of morphine on the battlefield are subsequently less likely to develop PTSD

With all these brain regions and systems activated in threat detection and threat management activities, you can easily see how a number of now-familiar neurotransmitters are involved in PTSD, leaving a potential therapeutic role for serotonergic, norepinephrinergic, and other psychotropics. By the way, we should note that GABA receptors are located diffusely throughout the cortex. Therefore the benzodiazepines, which potentiate GABA, are sedating the very parts of the brain that we need to activate, in order to balance and tone down the amygdaloid and limbic overactivity. This correlates with clinical experience that shows that benzodiazepines are not an effective treatment for PTSD.

PTSD

Treatment principles:

1) Control of nightmares and sleep disturbance
   - Prazosin (minipress) and Trazodone
   - Doxazosin, another alpha-blocker
   - Remeron clinically useful
2) 5HT projections to amygdala and Hippocampus
   - Rx: Paxil, Zoloft
3) Mood stabilizers may play a role in Tx but VPA ineffective in studies
4) Why not lithium for neuro-protective effects?



This graphic is interesting in that, if you can follow it, it shows that the initial emotion of fear – that which is experienced during the initial traumatizing event, involves cortical or conscious systems including the ACC and VMPFC. But the re-experiencing of the trauma can involve limbic and other subcortical structures only – the PAG, amygdala, and hippocampus. Thus symptomatic episodes can involve the emotion of fear that has been triggered by some stimulus, without any conscious perception of what the fear is all about.

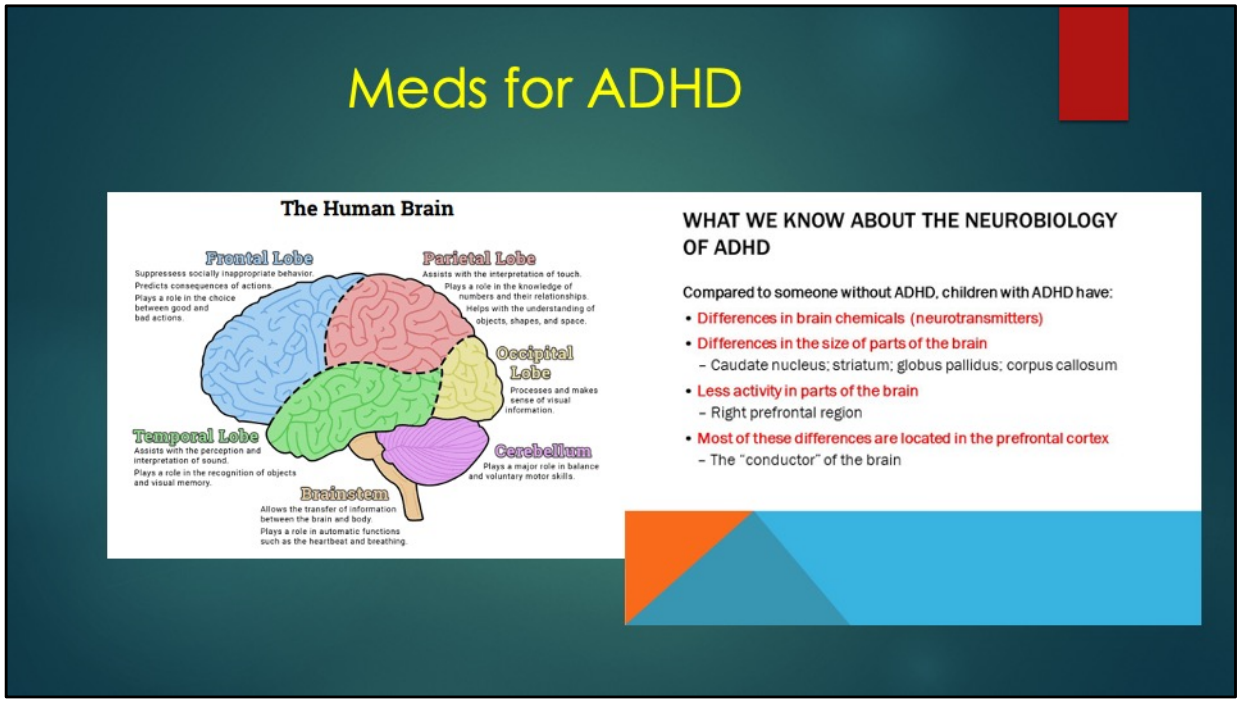
A hallmark of PTSD is sleep disturbance and nightmares. Without sleep disturbance and / or nightmares, whatever post-traumatic symptoms experienced are far less debilitating. Therefore the psychopharmacology of PTSD begins with normalizing sleep and reducing nightmares. Prazosin, an "alpha-blocker" (remember the familiar term "beta-blocker"), is an NE antagonist. It was originally developed for control of high blood pressure but it turned out it wasn't very good as after a few days the arteries compensating for the anti-adrenergic vasodilation and BP returned to previous levels. However, some PTSD folks reported improved quality of sleep and fewer nightmares, and once again, a new field of psychotherapeutics was born. A second-line treatment for sleep in PTSD is trazodone.

Doxazosin has less penetration of the BBB but the advantage of a longer half-life with easier once a day dosing and may be an alternative. Doxazosin was originally developed for treating urinary hesitancy associated with BPH.

The next big treatment step in PTSD is the addition of an SSRI, owing to serotinergic innervation of the hippocampus and amygdala. Probably any SSRI will do, but Paroxetine and Sertraline have been the most studied.

There is some evidence that the TCA's, Seroquel, and as mentioned the Benzodiazepines may worsen PTSD symptoms, because we don't' want to oversedate the part of the brain – the cortex – that is needed to be thoughtful and active and counterbalance an overactive limbic system.

The SGA's should generally be reserved when dissociative or thought disorder (paranoid) or transient hallucinatory ("hearing the screams of wounded soldiers") symptoms are present.



Neurobiology of ADHD: not completely understood;

80% of variability in ADHD determined by genetics;

DA & NT are the implicated neurotransmitters;

Hypofunction in the PFC;

Sex differences: boys more likely to have hyperactive Sx, girls more likely to have primarily inattentive symptoms.

We do know that the frontal lobes are involved, specifically the PFC and ADHD some say, maybe should be renamed “RIDD” or response inhibition deficit disorder”

The cerebellum, interestingly, is also implicated; might have something to do with chronobiology, as we know that ADHD patients have a really bad sense of time.

So while psychosocial and psychoeducational treatments are important, we have to start from the premise that a biological disorder deserves a biological treatment.

Meds for ADHD

Common Medications

Type of medication	Brand name	Generic Name	Duration
Short-acting amphetamine stimulants	Adderall	Mixed amphetamine salts	4 to 6 hours
	Dexedrine	Dextroamphetamine	4 to 6 hours
	Dextrostat	Dextroamphetamine	4 to 6 hours
Short-acting methylphenidate stimulants	Focalin	Dexmethylphenidate	4 to 6 hours
	Methylin	Methylphenidate (tablet, liquid, and chewable tablets)	3 to 5 hours
	Ritalin	Methylphenidate	3 to 5 hours
Intermediate-acting methylphenidate stimulants	Metadate CD	Extended-release methylphenidate	6 to 8 hours
	Ritalin LA	Extended-release Methylphenidate	6 to 8 hours
Long-acting amphetamine stimulants	Adderall-XR	Extended-release amphetamine	10 to 12 hours
	Dexedrine Spansule	Extended-release amphetamine	6+ hours
	Vyvanse	Lisdexamfetamine	10 to 12 hours
Long-acting methylphenidate stimulants	Concerta	Extended-release methylphenidate	10 to 12 hours
	Daytrana	Extended-release methylphenidate (skin patch)	11 to 12 hours
	Focalin XR	Extended-release dexmethylphenidate	8 to 12 hours
	Quillivant XR	Extended-release methylphenidate (liquid)	10 to 12 hours
Long-acting non-stimulants	Intuniv	Guanfacine	24 hours
	Kapvay	Clonidine	12 hours
	Strattera	Atomoxetine	24 hours

Products are mentioned for informational purposes only and do not imply an endorsement by the American Academy of Pediatrics. Your doctor or pharmacist can provide you with important safety information for the products listed.

Limitations of stimulants:
(1) Insomnia
(2) Tics
(3) Abuse potential

Non-stimulants:
(1) ADHD-specific (atomoxetine/Strattera) = NSRI
(2) Anti-hypertensive meds
(3) Anti-depressant meds

Overall, efficacy slightly lower than stimulants (50 – 60 % vs. 60 – 90 %).

Meds for treating addictions

- AUD incidence in US: 14%
- AUD prevalence in US: 30%
- c. 100,000 alcohol-related deaths per year in US
- APA recommends MAT for moderate to severe AUD
- **Naltrexone** – avoid if on opiods
- **Acamprosate** – renally excreted
- **Disulfiram** – "aversive" treatment
- **Gabapentin** – "anti-craving Rx" ?
- **Topiramate** – weight loss s/e

Comprehensive, evidence-based treatment for AUD includes:

- Inpatient or outpatient Tx
- CBT
- 12 step and 12-step-facilitated Tx
- M.E.T.
- C.R.T.
- Medication Tx
- No Tx

5 medicines are recommended: 3 are FDA-approved, 2 are "off-label";

[Say out loud the Brand Names of the five medicines]

Reward circuitry & reward deficiency hypothesis

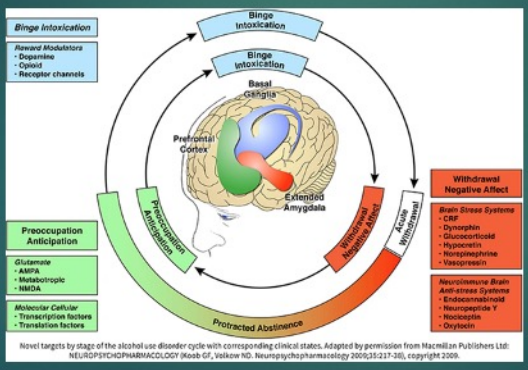
It was hard to find a single good slide off an internet google search illustrating all the brain mechanisms associated with addictive behavior, but we know that rats will press a lever to obtain DA, and some drugs that activate DA regions in the brain, but not for other chemicals and not for saline. If the lever is attached to an electrode that stimulates a few key brain structures, the rat will basically ignore the outside world and keep pressing the level until exhaustion, which is not a bad model for addiction.

The central reward structures in rat and man alike, include limbic structures: VTA and Nacc. Many other brain structures are involved including importantly alerting and memory structures amygdala and hippocampus – after all, you have to be alert to where you might be able to get your fix and remember where and how and with whom you can get high, and to some extent the frontal areas, involving in planning, procuring, and protecting your supply.

However, all this together is called a 'compulsivity circuit' because it trains itself to bypass, or "hijack" the sane, rational, future-oriented frontal regions of the brain. That's why we say the addict's brain (more precisely, the higher part, or human part, of the brain) it "hijacked" in addiction.

One way or another, all drugs of abuse ultimately stimulate DA and the reward centers of the brain. It's hypothesized that – either through genetics or epigenetic experiences or both – people prone to addiction have a deficient reward circuitry, are therefore vulnerable to seeking exogenous drugs or reward-generating behavioral routines (food, sex, shopping, gambling, etc.), in order to squirt out enough DA to feel okay. This is known as the "reward deficiency hypothesis" of the addictive brain.

Neurobiology of alcohol abuse: neurocircuitry & neurotransmitters



Novel targets by stage of the alcohol use disorder cycle with corresponding clinical states. Adapted by permission from Macmillan Publishers Ltd: NEUROPSYCHOPHARMACOLOGY (Koob GF, Volkow ND. Neuropsychopharmacology 2009;35:217-38), copyright 2009.

More recently, the NIAAA is focused on looking at 3 neurocognitive states that characterize the addicted brain in order to target drug development for addictive disorders:

Intoxication

Withdrawal

Craving & pre-occupation

Each state has a corresponding NT and circuitry

Provides targets for treatment

Explains why the addicted person you're talking rationally with one moment throws all that out the window the next moment: which "brain" are you really talking to?

There's a medicine called "contrive" for weight loss and a patient of mine remarked

offhand, “funny, since I started the contrive, I don’t have any desire to drink alcohol any more” (Bupropion + Naltrexone).

In great literature or drama, there is always a Protagonist and an Antagonist; but in the Wonderful World of Psychopharmacology, there are only Agonists, Antagonists, and "Partial Agonists": ….

Naloxone = Antagonist

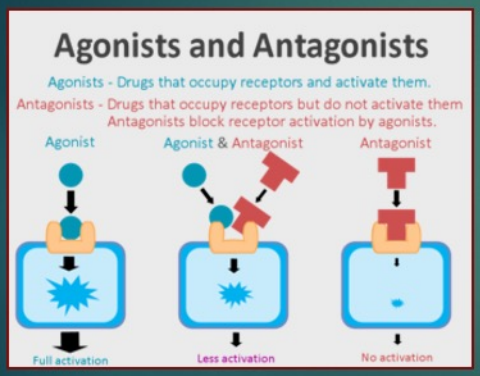
- Short-acting
- Strips the opiate off the opiate receptor
- For "opioid-reversal" in acute overdose
- Reverses respiratory depression
- Opiate blockade lasts for 30 minutes
- Therefore overdose with long-acting opoids (e.g., Methadone) may require repeated (IV, IM, Intranasal) doses of Naloxone
- Brand name = Narcan
- Side effects: immediate opiate withdrawal, hepatic effects

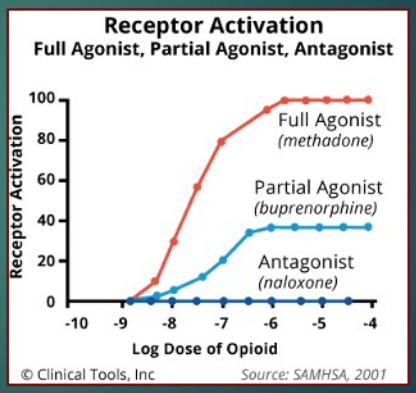
Naltrexone = Antagonist

- Used for relapse prevention
- Takes hours to take effect
- Opiate blockade lasts for 24 to 48 hours

- Orally effective
- Brand name = ReVia

The Wonderful World of MAT for Opiates: agonist - antagonist –partial agonist





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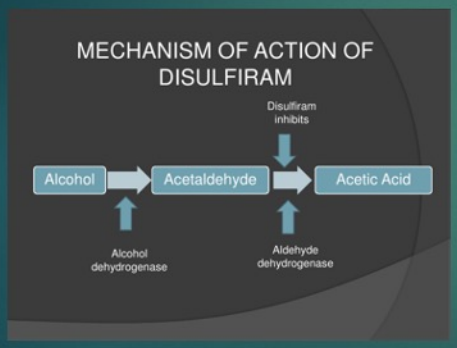
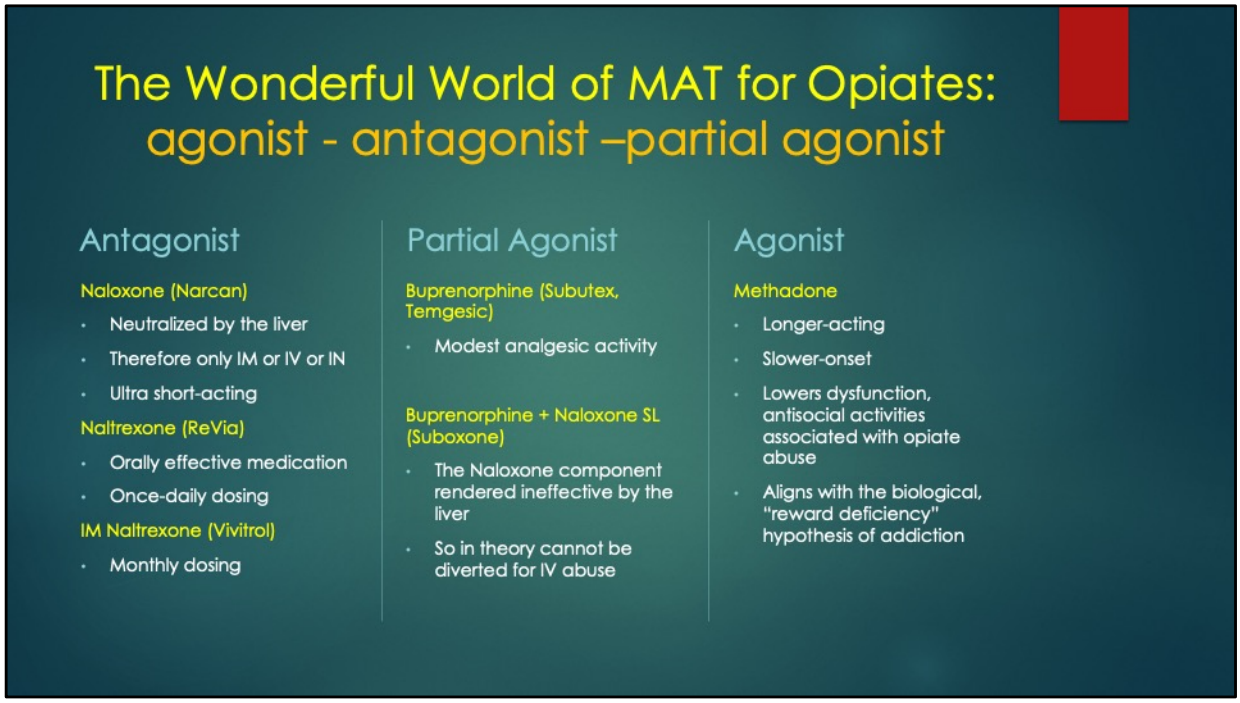
Disulfiram (Antabuse)



- Does NOT target the main NT's involved in addiction
- Blocks alcohol metabolism leading to accumulation of a toxic intermediary metabolite like formaldehyde
- Symptoms include nausea, vomiting, tachycardia, weakness, hypotension, splitting headache, or seizures
- Should be taken daily
- Also blocks DA-decarboxylase; can result in psychosis in vulnerable patients

Disulfiram is unlike other anti-dipsotropics



In great literature or drama, there is always a Protagonist and an Antagonist; but in the Wonderful World of Psychopharmacology, there are only Agonists, Antagonists, and "Partial Agonists": ….

Trick question: which of these are considered "narcotics" ?

Naloxone = Antagonist

- Short-acting
- Strips the opiate off the opiate receptor
- For "opioid-reversal" in acute overdose
- Reverses respiratory depression
- Opiate blockade lasts for 30 minutes
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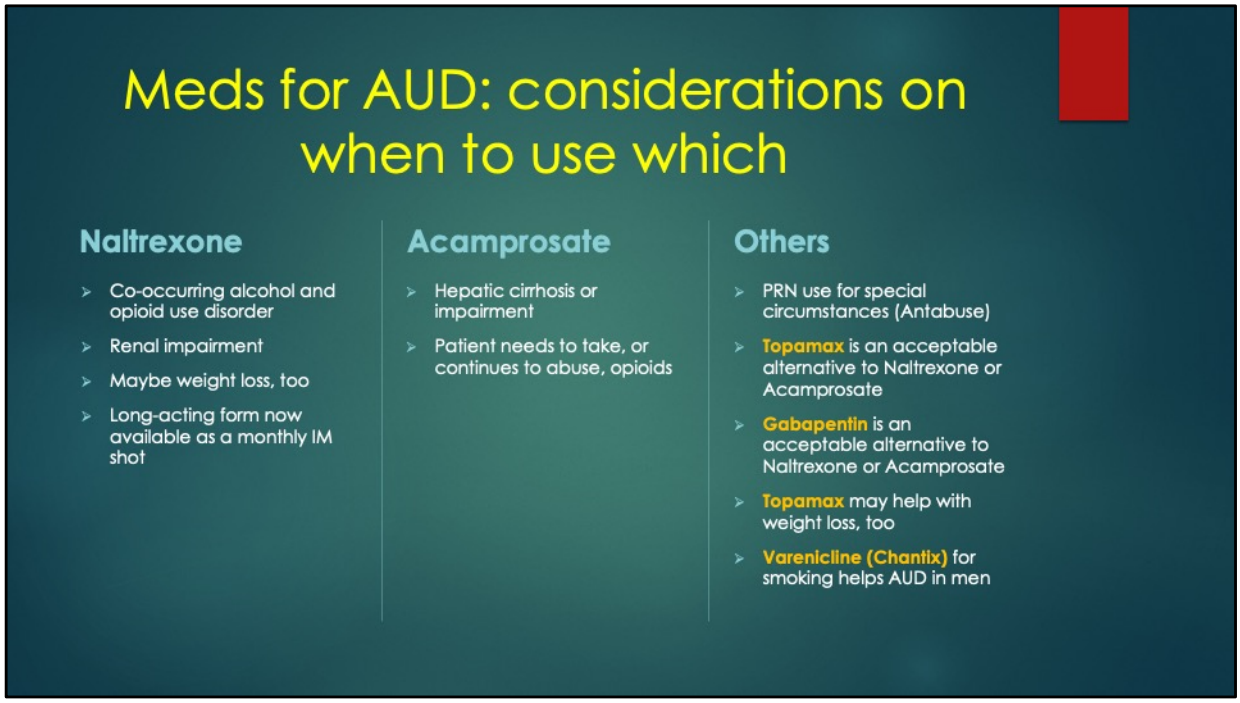
- Brand name = Narcan
- Side effects: immediate opiate withdrawal, hepatic effects
- Oral to parenteral ratio = 50:1, meaning that Naloxone is effectively eliminated from the body by "first pass" metabolism in the liver

Naltrexone = Antagonist

- Used for relapse prevention
- Takes hours to take effect
- Opiate blockade lasts for 24 to 48 hours
- Orally effective
- Brand name = ReVia
- Extended-release injectable = Vivitrol



Alcohol / AUD pharmacology involves:

Opioid pathways (opioid agonists, antagonists, and partial agonists)

GABA and Glutamate pathways (Benzo's & Acamprosate)

None of the above: Antabuse (an "aversive" = targets two-step metabolism of alcohol: alcohol & aldehyde dehydrogenase)

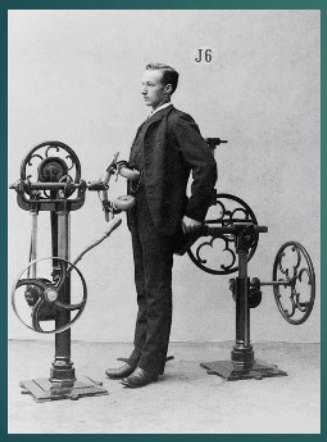
APA (psychiatry) practice guidelines for medication Tx of AUD, Jan 2018

Naltrexone FDA approved 1994 (a commentary on the pace of assimilation of medical knowledge and practice)

Campral (Acamprosate) FDA approved 2004

Antabuse FDA approved around 1948

Case history



Questions?


NOW SHE CAN COOK BREAKFAST AGAIN
. . . WHEN YOU PRESCRIBE NEW
MORNIDINE


Ritalin
Helps relieve chronic fatigue and apathy quickly
CIBA


MAKES CHILDREN AND ADULTS AS FAT AS PIGS.
No Cure No Pay
Price 50 Cents
GROVE'S
TASTELESS CHILL TONIC
ON THE MARKET OVER 20 YEARS
1½ MILLION BOTTLES SOLD LAST YEAR


OLD DICK
You'll also like
POT-O-HONEY

Sleep

Approaching insomnia

- FDA approves drugs for "primary insomnia"
- "Primary insomnia" accounts for 10 to 15% of all insomnia
- 85 to 90 % of insomnia is associated with an underlying condition
- Look for the underlying condition and treat it
- Always use counseling
  - Sleep hygiene
  - Holistic approach from the moment of awakening
- What makes for an ideal "hypnotic"?

One should never begin with the notion of addressing insomnia by prescribing a pill; rather, one should take a strategic and holistic approach to insomnia.

What makes an ideal hypnotic

- Rapid onset of action
- Long – but not too long – duration
- Normal sleep architecture
- Safe in overdose
- No daytime "hangover"
- Doesn't interact with other psychotropics
- Non-addictive
- Does not cause parasomnias
- "Good for chronic as well as acute insomnia"

Medicines for sleep and medicines for anxiety overlap a lot

- **FDA approved for insomnia**
  - Benzo's
  - "Z" drugs (formerly "BRA" drugs)
  - Ramelteon (melatonin-like)
  - Doxepine
  - Suvorexant (anti-Orexin)
- **"Off-label" hypnotics**
  - Sedating antidepressants
  - Sedating antipsychotics
  - Sedating anticonvulsants
  - Antihistamines

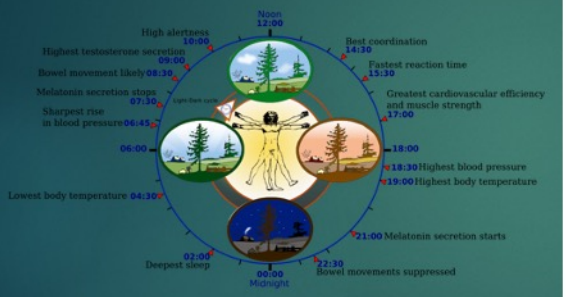
The “Z” drugs are “BRA” drugs = benzodiazepine receptor agonists or “BRA” ; it becomes obvious why they changed the nickname to the “Z” drugs =

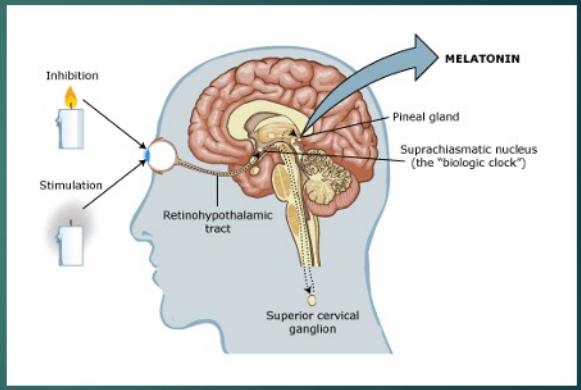
Zolpidem

Zaleplon

Zopiclone & Eszopiclone

Melatonin, Orexin, Ghrelin





Some hormones the brain manufactures only while awake, sleeping, or in darkness:

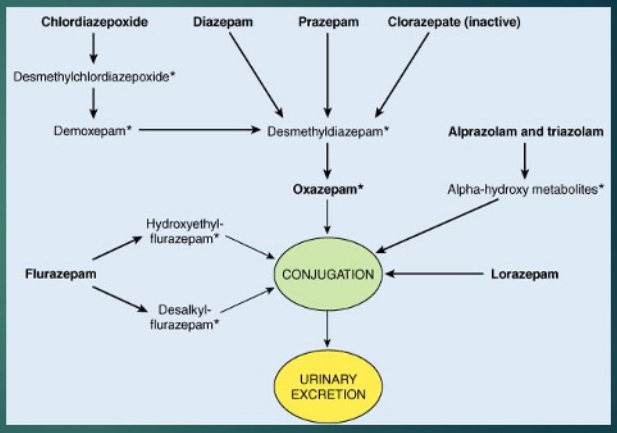
Melatonin

Orexin (Hypocretin)

Ghrelin

Benzodiazepines

- Over 50 BZ's on the market
- "Biotransformation" = common active, intermediate metabolite
- Some BZ's bypass this metabolite and don't show up on urine screening
- Half-life fiascos:
  - **Flurazepam (Dalmane)** 40-80 Hrs
  - **Triazolam (Halcion)** 2-5 Hrs
- Ultra-short acting: **Midazolam**
- **Flunitrazepam = Rohypnol**



Midazolam = Versed

Flunitrazepam = severe amnesia & psychomotor impairment

Benzo adverse effects

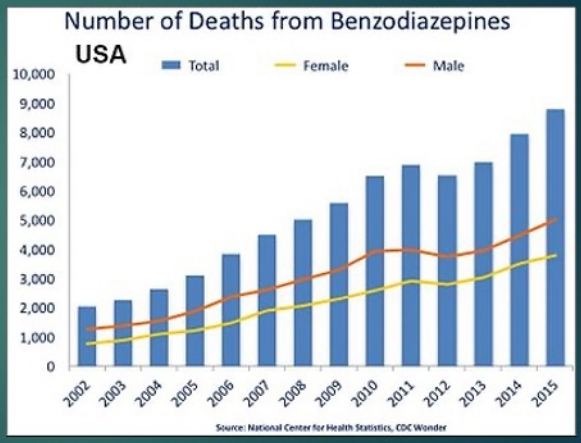
- Daytime sleepiness
- Decreased psychomotor performance
- Anterograde amnesia
- Rebound insomnia
- Abuse & dependence
- Respiratory depression & death

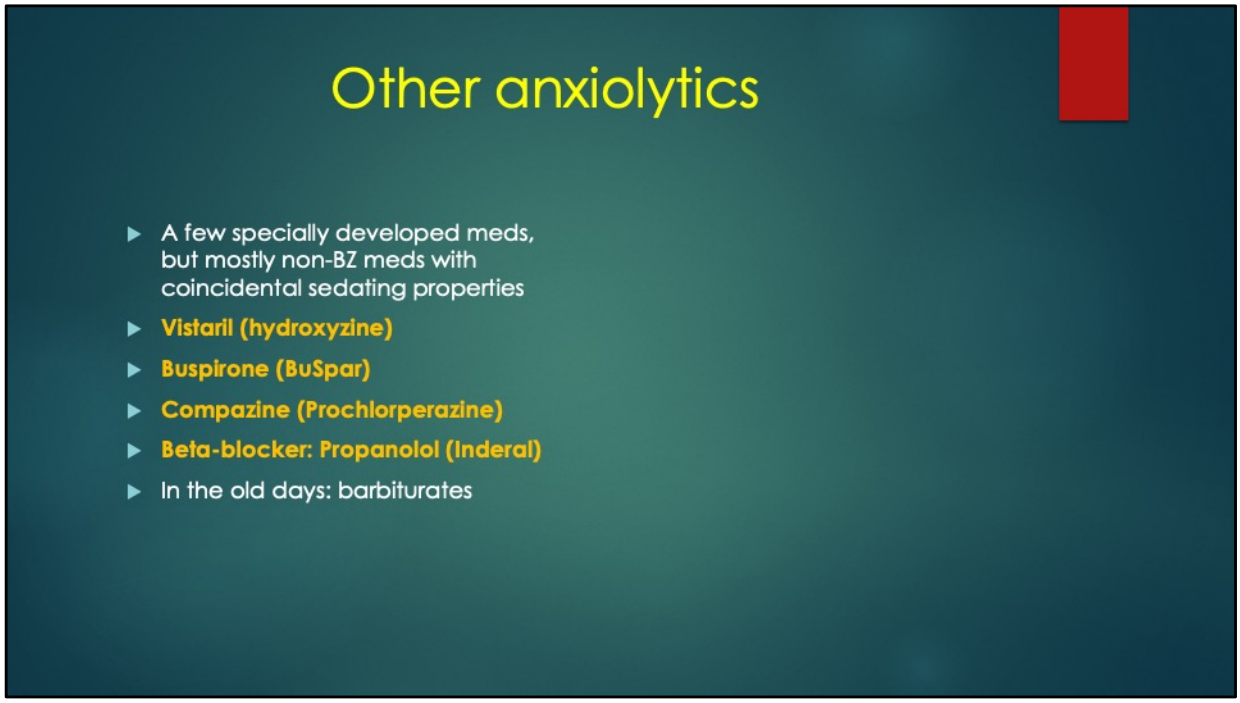
- **Modafinil (Provigil)** = a "wakefulness-promoting agent"
  - DA agonist

Predator on benzo's: not exactly King of the Jungle

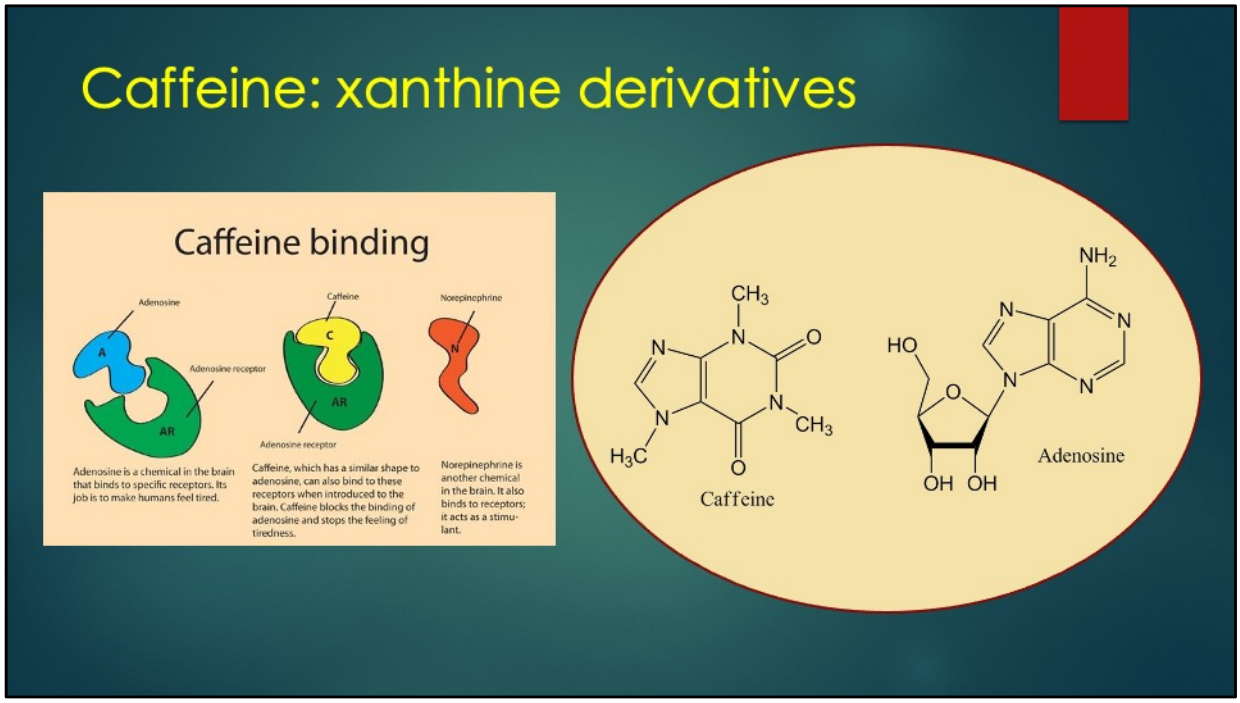
The hidden epidemic

- Opiate overdoses making headlines
- Benzodiazepine overdoses have increased over the same time period
- Most common drugs involved in lethal overdose include
  - Opiates (heroin)
  - Benzodiazepines
  - alcohol





BuSpar: odd mechanism, DA & 5HT activity; takes weeks to take effect; with MAO-I's get hypertensive crisis; considered too mild for some.



Occurring naturally in more than 60 plants, caffeine is a bitter substance that when consumed has stimulant properties.. Caffeine is the most widely consumed stimulant drug in the world. Caffeine induces feelings of alertness and increased energy as a result of its interactions with adenosine receptors in the brain. Caffeine is also commonly added to pain relief medication because of the role of adenosine in headaches and migraines.

Adenosine is an inhibitory neurotransmitter in the CNS that regulates sleep-wake cycles. When you are awake, adenosine accumulates in the brain and eventually causes drowsiness by attaching to cells in the basal forebrain and inhibiting their activity. Adenosine stimulates signals that tell your body it is time to rest, and activates the responses necessary to engage in full and sustained sleep.

Caffeine and Adenosine

Caffeine's effects of increasing energy and making you feel more alert are due to its interaction with adenosine receptors in the brain. Both caffeine and adenosine are neurotransmitters belonging to a chemical group known as xanthine. In your brain, caffeine appears as adenosine to nerve cells and is able to bind to adenosine receptor sites. As a result, your brain does not detect adenosine, and nerve activity does not

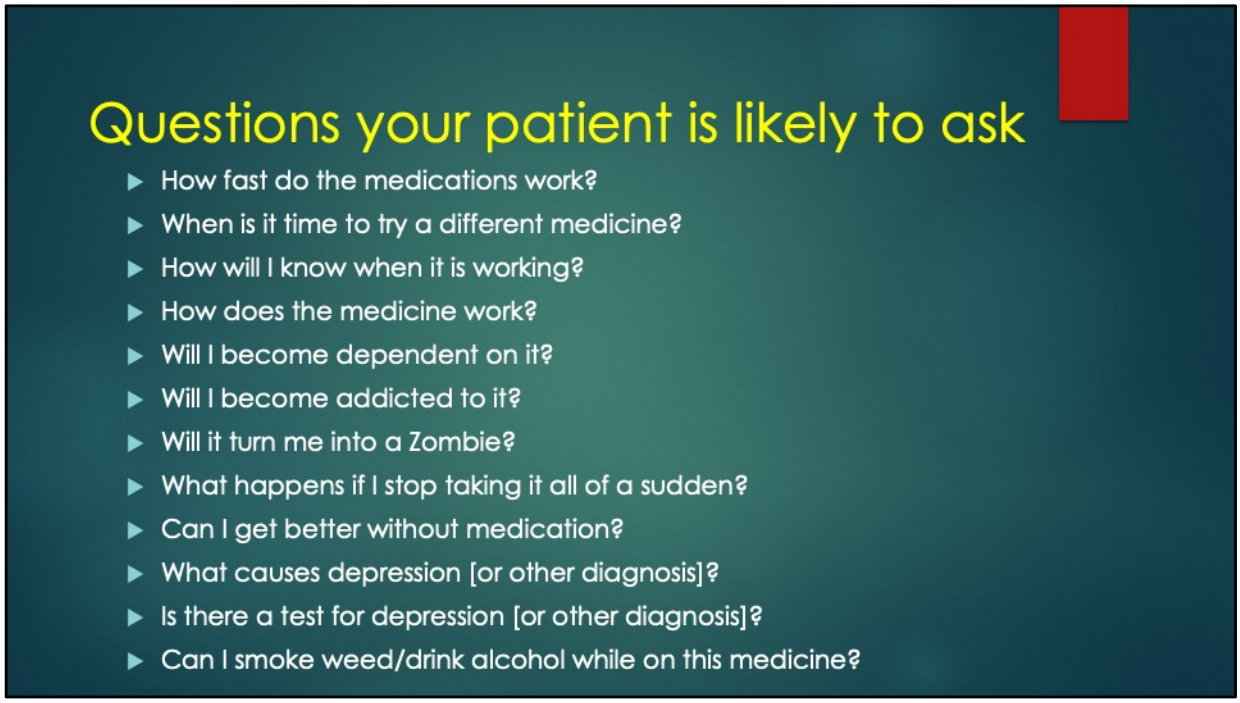
slow down. Instead, caffeine increases brain activity, making you feel more energetic and less sensitive to your body's natural rhythms of wakefulness and sleep.

Your body responds to blocked adenosine by increasing neural activity

Coffee, by the way, is the number one source of anti-oxidants in the US diet. Antioxidants prevent oxidative, or free radical, damage to cells. Coffee contains anti-oxidant phenols, esters, and chlorogenic acid and prevents cancer, cognitive decline, and diabetes.

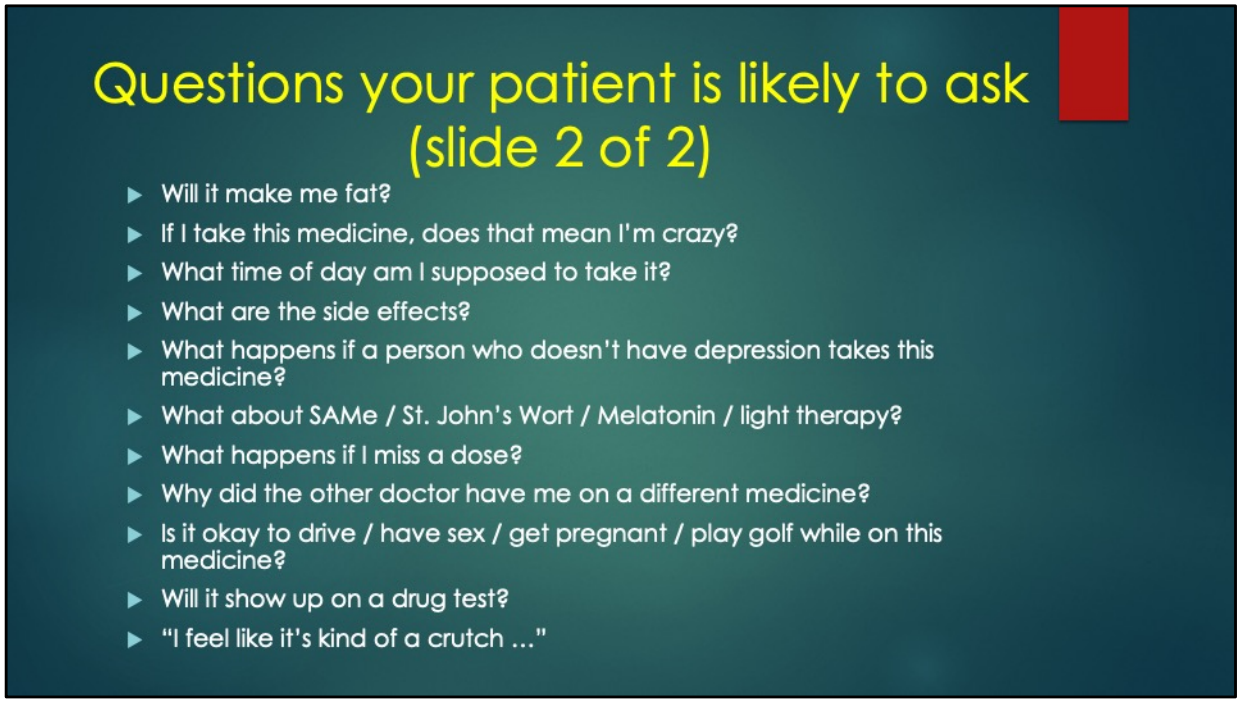
Part 4:
The end

- ✓ INTEGRATING PSYCHOLOGICAL AND BIOLOGICAL PERSPECTIVES
- ✓ QUESTIONS PATIENTS WILL ASK YOU, THE DOCTOR
- ✓ THE PSYCHOLOGY OF PSYCHOPHARMACOLOGY (NON-ADHERENCE)

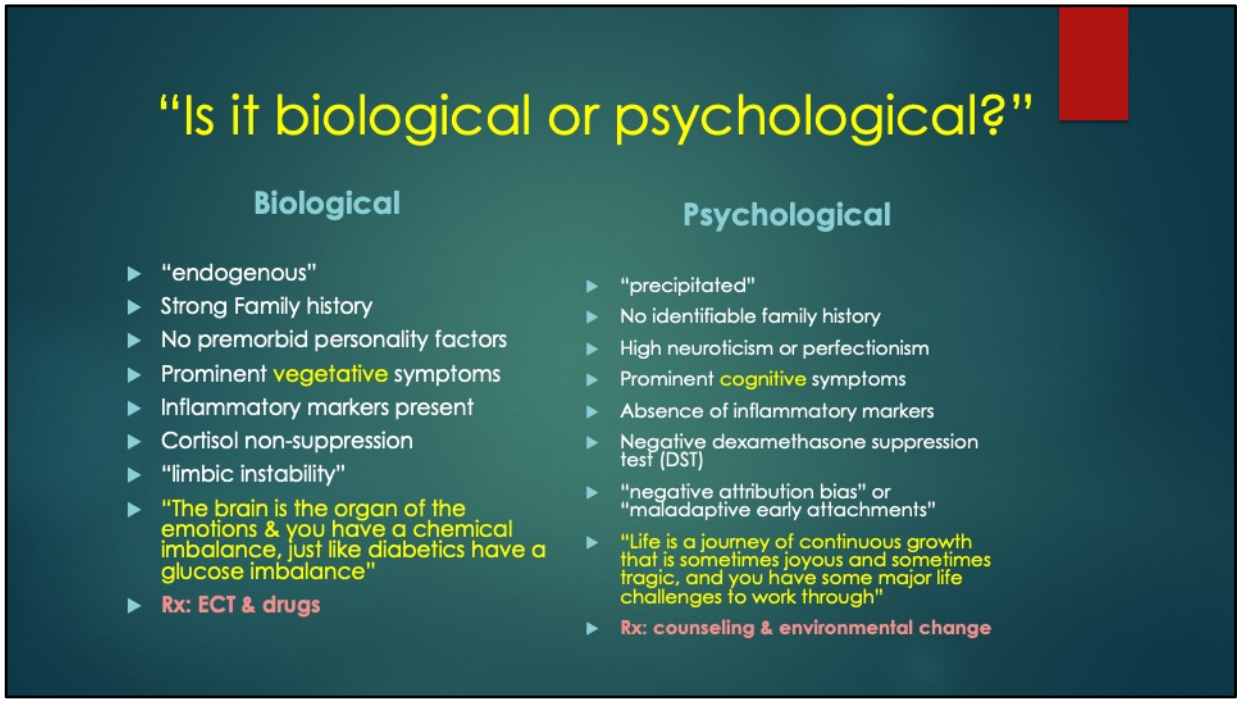


One study from the British Journal of Psychiatry found that over 50% of patients, when asked if they have any questions, have none at all; of a sample of 200 patients, 57% of patients diagnosed with unipolar depression had no questions about their medication; the group with the most questions about meds was, not surprisingly, those diagnosed with an anxiety disorder: only 7% percent of that sample had no questions about meds for their doctor.

So be prepared not only to answer a variety of questions, but also for the possibility your patient will ask no questions at all.



"If I take this medicine, does that mean I'm crazy?" = gets at the issue of "stigma" associated with mental illness.



Systemic inflammation: cytokines, TNF, Interleukins, CRP,ESR

Vegetative symptoms: appetite, energy, psychomotor changes, diurnal variation

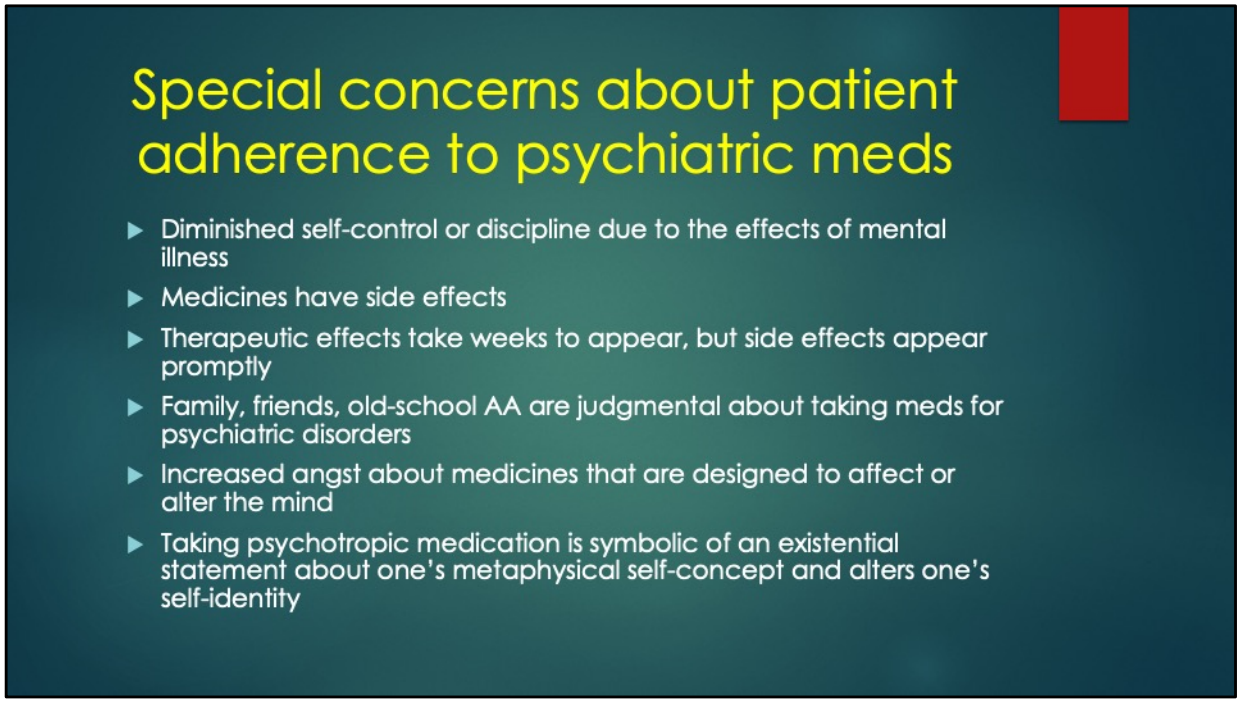
"positive DST" = can't turn off the stress hormone cortisol; may be correlated with probability of relapse, risk of suicide. Un-moderated Cortisol causes apoptosis of neurons in the hippocampus ("excitatory neurotoxicity of limbic structures"); ketamine, Magnesium, Lithium induce synaptoneogenesis of cortical and hippocampal neurons.

Psychological theories of depression are varied; they include learned helplessness, needs-fulfillment, interpersonal theories (including role strain, interpersonal conflict, and loss), negative self-concept and/or negative cognitive bias.

Biological theories include the biogenic amine hypothesis, fronto-limbic imbalance, inflammatory states, and the neurotrophic hypothesis.

This is an antiquated dichotomy and "the truth is somewhere in between". Mind and brain are more integrated; psychological experience modifies brain structures and

connections (e.g., hippocampal atrophy in PTSD) and biological variables impact psychological experience (e.g., oxytocin production and interpersonal trust and comfort).



RX:

(1) Normalize the challenges of daily meds compliance

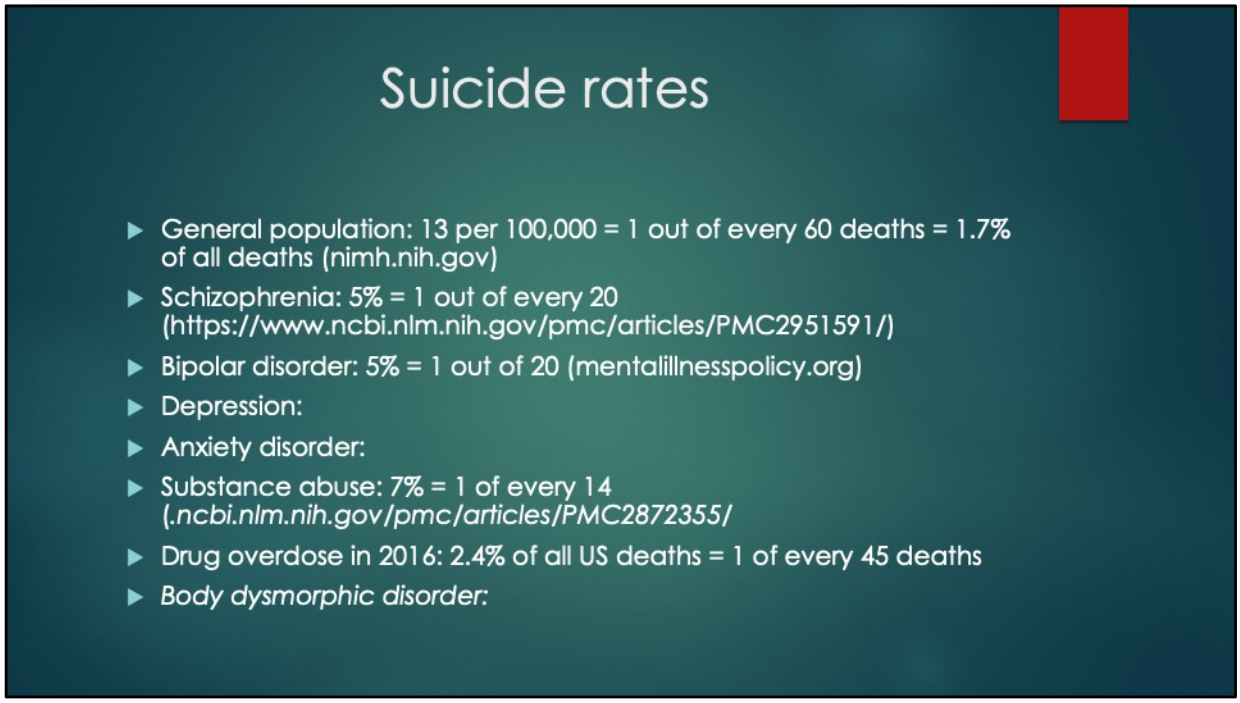
(2) Use "MI" techniques to assess patient's readiness for daily compliance ("on a scale of 1 to 10, how likely are you to take it each day?" …."what are the reasons pro and con to take or not take your medications" …"what are the possible obstacles or impediments to taking your meds each day" ….

(3) "why do you think it that you've got this whopping depression on your hands?

(4) "what are your concerns about being on meds?

(5) "what does it mean to you to be a person taking medicine to treat depression?"

(6) Provide encouragement: we're all born with diferent brains; all brains have pluses and minuses; (compare to a heart or a larynx or a GI tract); we've got to learn to live with and work with the brain we were born with …"



U.S. death rate overall = 824/100,000 (source: https://www.cdc.gov/nchs/fastats/deaths.htm)