# Identification and Management of Depression

## MSIII Psychiatry Clerkship

Tony Tu, MD/PhD
Clinical Instructor
Loyola University Medical Center

Assistant Program Director
Loyola Psychiatry Residency

tony.tu@lumc.edu

# Learning Objectives

1. Identify Major Depressive Disorder (MDD) and its specifiers
2. Distinguish between MDD and other etiologies that may resemble MDD
3. Recognize the scope and morbidity of depression within society
4. Contrast the multiple etiologies of depression syndromes
5. Differentiate the way depression manifests in unique clinical settings
6. Construct the biological, psychological, and social interventions to treat depression
7. Review the foundations of psychotherapy and discuss how its value in treating depression
8. Appraise the role of the psychiatrist in treating Major Depression
9. Participate in a team learning experience to enhance the above learning objectives.

# Lecture Outline

Part 1: Identification of Depression
Part 2: Treatment Considerations
Part 3: Biology of Depression and Introduction into Antidepressants
Part 4: Antidepressant Psychopharmacology
Part 5: Psychotherapy
Part 6: Enrichment section

# Part 1: Identification of Depression

# What is "depression"

- Depression is a generic term used quite often in society.  It may almost be accepted as part of everyone's daily life.
- As future physicians and for this clerkship, depression is meant to imply Major Depressive Disorder (MDD).  There is no single reliable marker of disease, and there are variations.

**DSM-5:**
**5 or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.  Do not include symptoms that are clearly attributable to another medical condition.**

**1. depressed mood**
**2. diminished Interest**
**3. significant weight loss**
**4. insomnia or hypersomnia**
**5. psychomotor agitation/retardation**
**6. fatigue or loss of energy**
**7. guilt or worthlessness**
**8. diminished concentration**
**9. suicidal thoughts**

# Burden of Depression

- Second leading disability in the world by 2020 (behind ischemic heart disease) - WHO
- Mortality: 35-40k suicides per year in the US.  This does not include the fatal accidents due to poor concentration and focus, as well as deaths due to self-neglect.
- Morbidity: suicide attempts, accidents, other illnesses, lost jobs and productivity, failures to achieve, substance use

# Burden of Depression

- Societal costs: dysfunctional families, absenteeism, decreased productivity, job related injuries, adverse effects on quality control in workplace and school settings

- Estimated 120 billion dollars per year lost to either the treatment of depression or how it affects society (similar to coronary artery disease or cancer)

# Epidemiology of Depression

- Lifetime prevalence in the US:
  - Major depression: 17%
  - Persistent depressive disorder (dysthymia): 3%
- Gender:
  - F:M prevalence is roughly 2:1
  - evens out to 1:1 post-menopausal
- Age:
  - Prevalence declines in older adults as they age
  - But, increases in older adults with greater burden of medical illnesses
- Family history:
  - concordance rate for depression in monozygotic twins is 37%

# Different Rates across genders

- **A combination of differences in hormonal makeup and perceptions in life.**

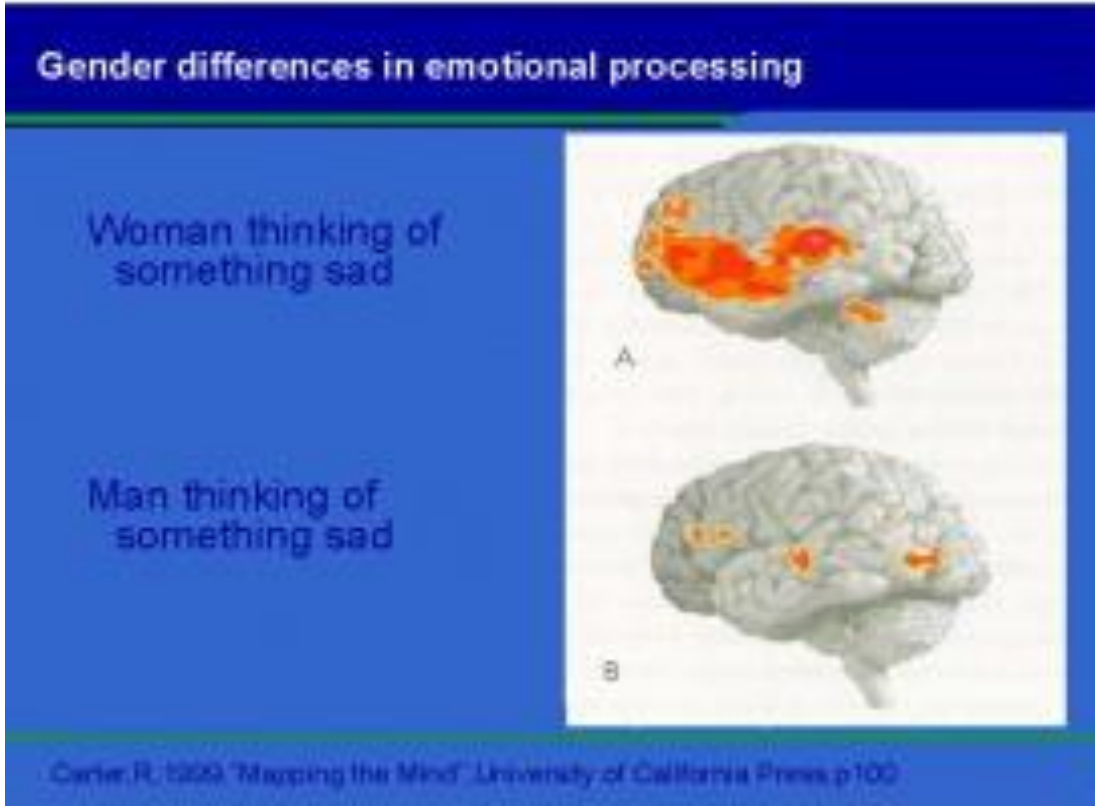
- It is thought that women's depressive episodes will most likely occur after perceived deficiencies in caring relationships and interpersonal loss.  Men's depressive episodes will most likely develop after perceived failures to achieve expected goals that lower self esteem (Kendler, 2014).

- It is thought that women are more likely to internalize negative events and have them present in somatic ways which include depressive symptoms and other bodily symptoms.

- However, men are more likely to experience and manifest depression with anger and aggression, substance abuse, and risk-taking.

- If you take these variations of symptoms together, the incidences of depression are

# Emotional processing is different



# Epidemiology of Depression

- Divorced, separated, unmarried - some risk
- Early parental losses, postpartum - higher risk
- Negative life events - highest risk

- Episodes can last for years (15%), most common duration is 8-18 months
- Recurrence rate is high (1 episode imparts 50%, 2 = 75%, 3+ = 95%)

- Physicians are just as vulnerable as the rest of the population to develop a depressive episode!
- The highest rate occurs during the internship year of residency

# Pathogenesis

- Multifactorial
- Polygenic
- depression is due to many genes, which contribute to the vulnerability towards depression
- additional non-genetic factors are involved culminating in the depressive disorder

# Why is there more depression?

## Many working theories

- Is it greater recognition and awareness?
- Is it that there's an increased genetic predisposition secondary to greater gene pooling?
- Is there greater expression of certain genes from exposure to increasingly chronic stress (epigenetics), which lead to neuronal connections that make people more susceptible to other modifiers?
- Is it the diet?  Omega-6-fatty acids vs omega-3-fatty acids
- Kindling theory?  with each episode of depression, an individual becomes primed, more prone to further depression with lessor stressors

# How good are we at identifying and treating depression?

- Stigma!
  - Only 50% of people ever get help from a professional
  - Only 35% will see a general MD
  - Only 15% ever see a psychiatrist
- Patient factors
  - Stigma
  - minimization of distress
  - reluctance to disclose symptoms
- Physician factors
  - time pressures, close-ended interviews, inadequate disease knowledge, uncomfortable discussing depression

# An example of the lack of depression identification

Young et al. 2001.

- A cohort of patients were surveyed over a 1 year period in a primary care clinic.
- 78% of these patients had some form of depression.
- All of the patients had an MD visit for a non-psychiatric reason
  - 18% referred to a mental health specialist
  - 21% received medication
  - 16% received adequate medication doses
  - 30% received some appropriate treatment

# Medical Systems Barriers

- Infrequent visits
- Total physician reliance
- Lack of close follow-up
- Lack of time to educate and advocate
- Lack of monitoring of adherence and outcomes
- Lack of time to support behavioral changes (exercise, problem-solving, etc)

# Confounders in identifying Depression

- While depression can present classically as neurovegetative symptoms (classic DSM 5), depression can also present atypically:
  - cognitive symptoms
  - impulse control problems - agitation, irritability
  - behavioral - family and friends
  - physical-somatic (e.g. gastrointestinal symptoms, fatigue, headaches)

# Other barriers in treatment

- Reasons patients relapse at 1 year:
  - not taking medications (non-compliance rate are similar to patients with any chronic disease, 50% by 6 months of treatment)
  - development of additional life stressors
  - loss of medication efficacy
  - absence of psychotherapy

# Why do patients stop taking their medications?

Demyttenaere, 2001

- Feeling better - 55%
- Adverse reactions - 23%
- Fear of drug dependency - 10%
- Lack of efficacy - 10%
- Feeling uncomfortable taking meds - 10%

- 76% of patients told their MD about noncompliance, correlated with strength of the doctor-patient relationship
- 59% of MDs had ego-defensive reaction (blaming, authoritarian)
- 10% of MDs avoided the issue
- 31% of MDs searched for a reason

# Withholding the truth

Sawada. 2012, J Clin Psych

- 70% of patients withhold some truth from their psychiatrist
- There is shame

  - daily life activities - 69%
  - symptoms - 53%
  - adherence to medications - 20%
  - alcohol/drug use - 16%

# Withholding the truth

Sawada. 2012, J Clin Psych

- I found it difficult to talk to my doctor
- I thought my doctor would not take it seriously if i told him or her
- I found it embarrassing to tell the truth

- What did the patients think would help them tell the truth
  - doctors need more time with patients (69%)
  - environment conducive to discuss issues (34%)
  - communication and explanation using letters (30%)

# Public perception of mental illness

- 71% - emotional weakness
- 65% - caused by bad parenting
- 45% - victim's fault - just will it away
- 43% - incurable
- 35% - consequence of sinful behavior

- there is an increasing awareness that depression and mental illness is brain/biologically based - 40%

# Part 2: Treatment Considerations

# Treatment Considerations

- Our goal is symptom remission, and restoring baseline functioning
- If we fully remit the symptoms, relapse is less likely to occur
- Treatment response defined as ≥50%improvement in a rating scale
- Disease remission defined as ≤ the rating scale for the normal range

# General Approach

- In general, "combination treatment" is more effective than monotherapy
- Clinical trials have not established the superiority of any specific medication/psychotherapy combination
- If there is more of an acute precipitant, and no prior history of Major Depression, then psychotherapy alone is the preferred first choice
- Psychotherapy avoids medication side-effects, and even after completion of the treatment course, patients often may remain well with benefits persisting, unlike medications

# Overview of psychopharmacology

- Which antidepressant?
  - different antidepressants are generally comparable clinically
  - no evidence that one antidepressant is superior in preventing relapse
- SSRI
  - Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
- SNRI
  - Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipran
- Atypical antidepressants
  - Bupropion, Mirtazapine
- Serotonin modulators
  - Vilazodone, Vortioxetine
- Older antidepressants
  - TCAs, MAOIs

# Overview of psychopharmacology

- Special considerations:
  - half-life
    - short vs long: paroxetine vs fluoxetine
  - clearance:
    - fecal excretion: sertraline and escitalopram

- In general, the "go-to" antidepressants are escitalopram and sertraline due to their ideal balance of efficacy and tolerability

- Treatment of **severe** MDD
  - SNRIs are first-line!

# DSM-5:  addition of severity specifiers

| Severity/course specifier | Single episode | Recurrent episode* |
|---|---|---|
| Mild (p. 114) | 296.21 (F32.0) | 296.31 (F33.0) |
| Moderate (p. 114) | 296.22 (F32.1) | 296.32 (F33.1) |
| Severe (p. 114) | 296.23 (F32.2) | 296.33 (F33.2) |
| With psychotic features** (p. 111) | 296.24 (F32.3) | 296.34 (F33.3) |
| In partial remission (p. 114) | 296.25 (F32.4) | 296.35 (F33.41) |
| In full remission | 296.26 (F32.5) | 296.36 (F33.42) |
| Unspecified | 296.20 (F32.9) | 296.30 (F33.9) |

- Treatment interventions will depend on the disease severity
- A patient needs to be assessed for mild, moderate, severe depression as well as the chronicity of the course
- Mild and moderate depression responds equally well to medication or psychotherapy.  Severe depression usually needs both arms, as well as more intensive levels of care (e.g. hospitalization) may also be indicated

# Differences in severity

- Mild (296.21) meets minimum criteria for MDD, and symptom intensity while distressing is manageable, with only minor impairment in social or occupational function

- Moderate (296.22) is the middle-ground between minimum and severe

- Severe (296.23) meets most if not all of the MDD criteria, and symptom intensity is seriously distressing and unmanageable, with social and occupational function greatly impaired

# Severe Major Depression

- Defined as having 7 to 9 depressive symptoms occurring nearly every day.
- Suicidal ideation is common
- Impairment of functioning is common
- Higher risk of psychotic or catatonic features
- Often requiring psychiatric hospitalizations

# Severe Major Depression

- combination treatment (pharmacology and psychotherapy)
- can also do pharmacology alone
  - favor SNRIs over SSRIs
  - include mirtazapine
  - include TCAs
  - include atypical antipsychotics combination with antidepressant
- ECT
  - suitable for patients with severe MDD who need a fast treatment response (actively suicidal, frequent life threatening behaviors)
  - RCTs have already demonstrated that ECT is more effective than any other treatment for severe major depression thus far...

# Severe Major Depression, and Psychotic Depression

- treatment time-frame with augmented treatment: 4-8 weeks
- ~50% of patients recover within 2-3 months, and the large majority recovery within 6-12 months
- functional impairment including social and occupational impairment unfortunately lags behind the recovery from the depressive and psychotic symptoms
- there are significantly more recurrences in severe major depression, and unsurprisingly significantly higher mortality rate.  However, the rate of complete suicides is similar between psychotic and non-psychotic depression
- Maintenance treatment:
    - continue antipsychotic augmentation for 4 months after initial recovery from the acute episode
    - continue antidepressant for a minimum of 2 years, possibly for a lifetime

# Biopsychosocial Etiologies

- In order to best treat depression, we need to better understand the various etiologies of depression
- Each episode of depression needs to be assessed from the biological, psychological, and social perspectives in order to provide the best possible treatment
- Each element will be present in different degrees
- Failure to recognize the above model leads to increased morbidity and treatment failure
- Each discipline will view this from different lens
    - "the art of psychiatry"

# Biopsychosocial Etiologies

- Depends on the presenting symptoms
- Also depends on unique characterizations of that individual
  - genetics, environments, stressors, psychological makeup, support, medical comorbidities
- There is no one treatment for all
- Treatment interventions need to be based on what the patient feels will help, and your understanding of what may or may not help the patients
- Focus of treatment is fluid, and may change over time

# Case to practice thinking Bio-Psycho-Social

- A 24 year old with a strong family history of depression in her mother and maternal grandmother presents with symptoms of sadness, irritability, loss of appetite, poor concentration, waking up early each morning, and low energy for 4 months. She had to move away from her family to take her first job as an accountant, and problems developed with her new roommate. She feels like she is a failure, and wishes she could just move back home. She has called in sick on 3 occasions because of feeling bad. She is drinking 4-6 cans of beer on most nights just to relax. She has not had previous mental health treatment.

# Biological-Psychological-Social

- A 24 year old with a **strong family history of depression in her mother and maternal grandmother** presents with symptoms of **sadness, irritability, loss of appetite, poor concentration, waking up early each morning, and low energy** for 4 months. She had to move away from her family to take her first job as an accountant, and problems developed with her new roommate. She feels like she is a failure, and wishes she could just move back home. She has called in sick on 3 occasions because of feeling bad. She is **drinking 4-6 cans of beer** on most nights just to relax. She has not had previous mental health treatment.

# Biological-Psychological-Social

- A 24 year old with a **strong family history of depression in her mother and maternal grandmother** presents with symptoms of **sadness, irritability, loss of appetite, poor concentration, waking up early each morning, and low energy** for 4 months. She had to **move away from her family** to take her first job as an accountant, and **problems developed with her new roommate**. She **feels like she is a failure**, and wishes she could just move back home. She has called in sick on 3 occasions because of feeling bad. She is **drinking 4-6 cans of beer** on most nights just to relax. **She has not had previous mental health treatment**.

# Biological-Psychological-Social

- A 24 year old with a **strong family history of depression in her mother and maternal grandmother** presents with symptoms of **sadness, irritability, loss of appetite, poor concentration, waking up early each morning, and low energy** for 4 months. She had to **move away from her family** **to take her first job as an accountant**, and **problems developed with her new roommate**. She **feels like she is a failure**, and **wishes she could just move back home**. She has **called in sick on 3 occasions** because of feeling bad. She is **drinking 4-6 cans of beer** on most nights just to relax. **She has not had previous mental health treatment**.

# Case:  estimating the severity index

- She has 5 symptoms of the 9 for MDD
- The symptoms are causing more than some minor impairment, as she had to miss work on 3 occasions, and is drinking excessive alcohol to relax, but she is still functional
- This would place her in the moderate category of MDD
- Therefore, interventions would best be medication and/or therapy

# Part 3: Biology of Depression and Introduction into Antidepressants

# The biology of depression, and antidepressants

## The monoamine hypothesis of depression

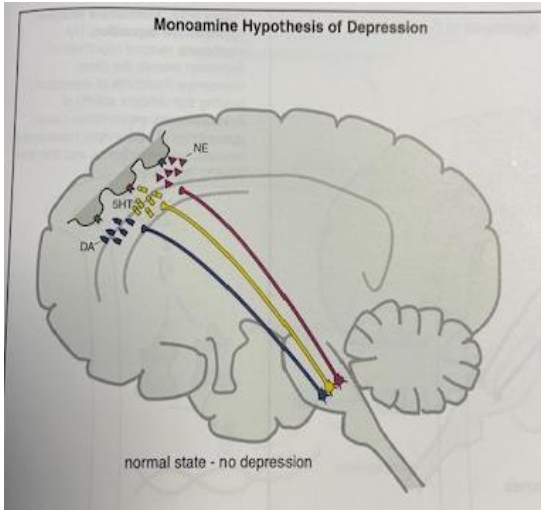
- Classic theory that depression is due to a deficiency of monoamine neurotransmitters (mania might therefore be the opposite)
  - Serotonin (5-hydroxytryptamine / 5-HT)
  - Norepinephrine (NE)
  - Dopamine

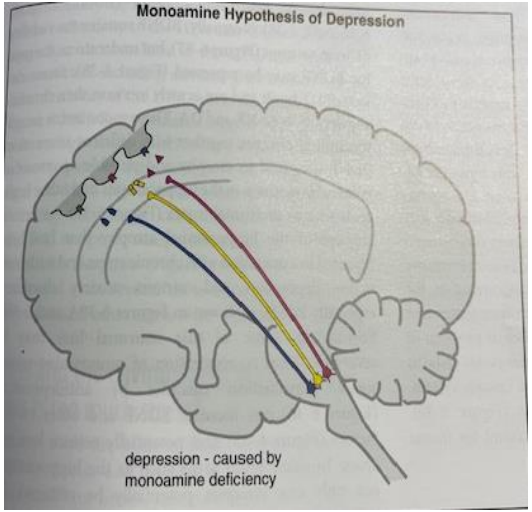
- Evidence to demonstrate this remains lacking
  - you don't precipitate depression with cyproheptadine
  - lacking direct evidence linking monoamine levels to mood

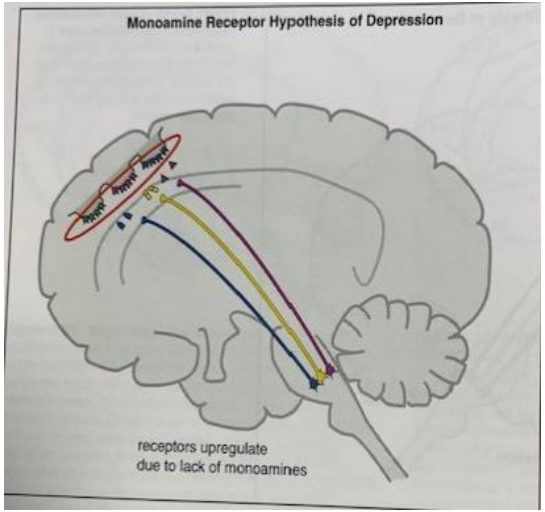
# The biology of depression, and antidepressants

## The monoamine RECEPTOR hypothesis of depression

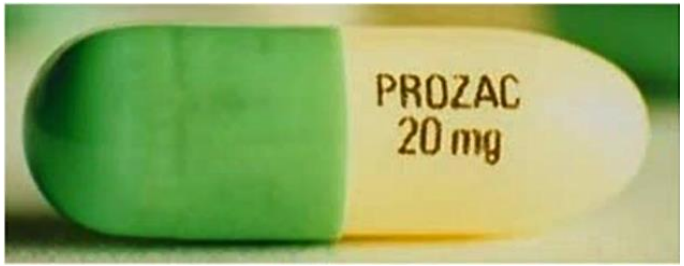
- Shifting focus from neurotransmitters to their receptors, and the downstream molecular events that these receptors trigger
  - gene expression, downstream neutrophic growth factors
  - brain circuit plasticity
  - epigenetics
- The Receptor hypothesis posits that an abnormality in the receptors for monoamine neurotransmitters leads to depression
  - reduced monoamine neurotransmitters occurs first
  - compensatory upregulation of postsynaptic neurotransmitter receptors
  - these postsynaptic receptors then lead to depression


Monoamine Hypothesis of Depression
NE
5HT
DA
normal state - no depression


Monoamine Hypothesis of Depression
depression - caused by
monoamine deficiency


Monoamine Receptor Hypothesis of Depression
receptors upregulate
due to lack of monoamines

# The biology of depression, and antidepressants


Prozac (fluoxetine)
- released in 1987, over 3 decades ago
- monumental in the treatment of depression because of how well it's tolerated

# Biological issues - antidepressants


- We live in a drug-driven society
- The idea that every type of malady can be "fixed" by a pill pervades western medicine
- "The Prozac generation"
- It is easier for patients to simply take a medicine
- It is easier for doctors to simply prescribe a medicine

# Biological issues - antidepressants

- Wasn't always this way
- TCA's introduced in the late 1950s was the first effective treatment
- ECT started in the 1930s
- TCAs encompass many different agents with many different side-effects
- Other uses besides depression developed over time, such as pain, sleep, migraines (amitriptyline)

# Biological - TCAs

- Effective 60-70% of the time
- Mechanism of action: NE, 5-HT reuptake inhibition
- noxious side effects due to the following mechanisms:
  - anticholinergic
  - antihistaminic
  - alpha-adrenergic antagonism
- Low fatality index: (arrhythmias)
- Used seldomly

# Biological - MAOIs

- Similar in the 1950s
- Blocks the breakdown of NE and 5-HT
- Good alternative to TCAs
  - Very activating
- Troublesome side-effect profile
  - Strict tyramine free diet, and potential fatal HTN led to very low usage
- Now available in a transdermal form (selegeline)

# Biological - SSRIs

- Release in the 1980s
- Fluoxetine (prozac) was a blockbuster release in 1987
- Heavily advertised
- Household names of other SSRIs: paxil, lexapro, zoloft
- They were no more effective than TCAs, but their side-effect profile and dosing were much easier leading to widespread use (100 million Americans)
- Cultural impact
  - destigmatization
  - changing of personalities
  - cosmetic boutique psychiatry
  - big business, big pharma

# Part 4: Antidepressant Psychopharmacology

# Antidepressant types

- **SSRI**
  - **Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline**
- SNRI
  - Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipran
- Atypical antidepressants
  - Bupropion, Mirtazapine
- Serotonin modulators
  - Vilazodone, Vortioxetine
- Older antidepressants
  - TCAs, MAOIs
- Ketamine
- Atypical antipsychotics

# Antidepressants:  SSRIs

- fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram

- Indications:
  - Mood: major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder
  - Anxiety: generalized anxiety disorder, panic disorder, social anxiety disorder
  - Eating disorders: bulimia nervosa, binge eating disorder
  - Other: post-traumatic stress disorder, obsessive compulsive disorder, body dysmorphic disorder, somatic symptom disorders

# Antidepressants:  SSRIs

- Side-effects:
  (side-effects from psychotropics in general arise from inadvertent neurotransmitter effects: adrenergic, serotonergic, histaminic, dopaminergic)
  (SSRI's are primarily serotonergic, hence serotonergic side-effects)
  - Sexual side-effects (the most common side-effect), and primarily with libido loss, and lack of orgasm
  - Drowsiness, dizziness, headaches
  - Insomnia
  - GI symptoms
  - Cardiac* (citalopram, QTC)
  - Weight gain*
  - Involuntary movements (akathisia)
  - Emotional numbing (can be discouraging, loss of creativity)

# Antidepressants:  SSRIs

- Patient psychoeducation:
  - discuss side-effects
  - time to response
  - drug-drug interactions
  - stopping the medications
- Suicide risk:
  - controversial topic
  - Evidence suggests an age-specific stratification
    - may raise risk of suicidality in ages 18-24
    - has no effect in ages 25-30
    - may lower risk in ages 31+
  - Must keep in mind that untreated depression also increases the risk of suicidality
  - Also keep in mind that SSRIs are quite safe in overdoses:
    - overdose on a single SSRI rarely causes death
    - Taking up to 30 times the daily dose produces minor or no symptoms

# SSRIs and pregnancy

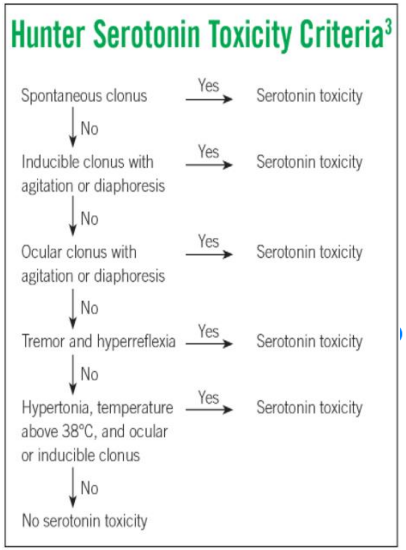
- Pregnancy and breastfeeding - Category C
  - *FDA pregnancy category C = animal studies have shown adverse effects on fetus, but there are no adequate and well-controlled studies in humans, and any potential benefits may warrant use despite potential risks*
- Slightly increased rate of early miscarriage, but also increased in pregnant women who are depressed
- Preterm delivery, with slightly higher perinatal complications, neonatal adaptation syndrome (NAS)
- Women exposed in 1st trimester slightly higher risk of autism
- SSRIs do passage through breast milk, leading to GI symptoms in the infant (sertraline is the best studied)
- BUT, consider, what does peripartum depression do to the fetus (increased cortisol exposure, R amygdala neuronal changes in the fetus)

# Serotonin discontinuation syndrome

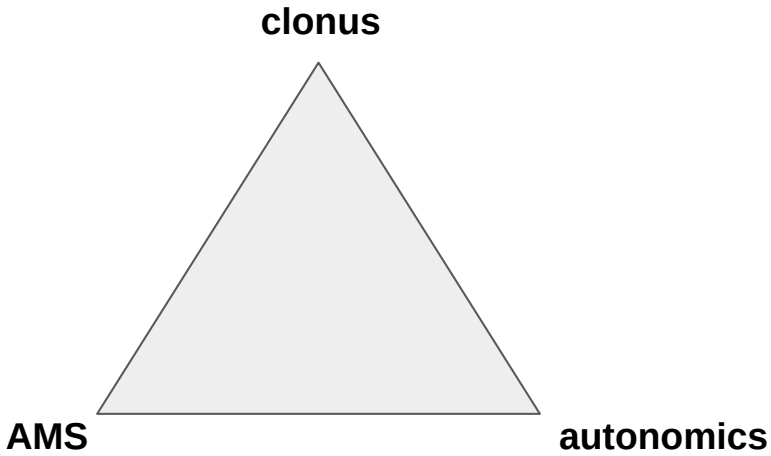
- more common with longer treatment: >6 months
- short-acting SSRI (paroxetine, fluvoxamine, venlafaxine)
- common symptoms:
  - flu-like symptoms
  - dizziness, fatigue, headache, nausea, anxiety, chills, diaphoresis, insomnia, irritability, myalgia
  - **lhermitte's sign***
- time-frame:
  - peaks 1-4 days s/p abruptly stopping SSRI
  - dissipates over 1-2 weeks
- treatment:
  - reassurance
  - restart SSRI (fluoxetine preferred), and taper slower

# Serotonin Syndrome

- Serotonin excess secondary to antidepressant dosage issues, drug-drug interactions, and intentional self-poisoning
- rapid onset: within 6-24 hours
- clinically diagnosed, no lab tests indicated
- treatment: stop all serotonergic agents, supportive care, benzos, cyproheptadine
- resolves quickly within 24 hours




| Sternbach Criteria | Hunter Criteria |
|---|---|
| ≥3 of the following required for diagnosis: | ≥1 of the following required for diagnosis: |
| Mental status changes (confusion, hypomania) | Spontaneous clonus |
| Agitation | Inducible clonus + agitation or diaphoresis |
| Myoclonus | Ocular clonus + agitation or diaphoresis |
| Hyperreflexia | Tremor + hyperreflexia |
| Diaphoresis | Hypertonic + temperature >38°C + ocular or inducible clonus |
| Shivering | |
| Tremor | |
| Diarrhea | |
| Incoordination | |
| Fever | |



# Antidepressant types

- SSRI
  - Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
- **SNRI**
  - **Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipran**
- Atypical antidepressants
  - Bupropion, Mirtazapine
- Serotonin modulators
  - Vilazodone, Vortioxetine
- Older antidepressants
  - TCAs, MAOIs
- Ketamine
- Atypical antipsychotics

# Antidepressants:  SNRIs

- venlafaxine, desvenlafaxine, duloxetine

- Indications:
  - Mood: major depressive disorder, persistent depressive disorder (dysthymia)
  - Anxiety: generalized anxiety disorder, panic disorder, social anxiety disorder
  - Chronic Pain syndromes: diabetic neuropathy, fibromyalgia, chronic MSK pain
  - Other: post-traumatic stress disorder, obsessive compulsive disorder, body dysmorphic disorder

# Antidepressants:  SNRIs

- Side-effects
  (due to effects on serotonin and norepinephrine receptors, and indirectly anticholinergic effects*)
  - Nausea (most common)
  - sexual dysfunction, headaches, dizziness, diaphoresis, dry mouth, constipation
  - weight gain*** (venlafaxine and duloxetine are especially known for this, usually seen with longer-term treatment more than 3 months)
  - blood pressure
- Suicide risk***
  - higher than SSRIs
  - rapid cycling
  - overdose is also more lethal than SSRIs

# Antidepressant types

- SSRI
  - Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
- SNRI
  - Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipran
- **Atypical antidepressants**
  - **Bupropion, Mirtazapine**
- Serotonin modulators
  - Vilazodone, Vortioxetine
- Older antidepressants
  - TCAs, MAOIs
- Ketamine
- Atypical antipsychotics

# Antidepressants:  atypical antidepressants

- Bupropion (dopamine-norepinephrine reuptake inhibitor)

- Indications:
  - Mood: major depressive disorder, seasonal affective disorder
  - ADHD
  - Tobacco dependence

- Stimulating
  - good for neurovegetative presentation
  - bad for high anxiety

- Side-effects:
  - Insomnia, dry mouth, GI symptoms (3 most common)
  - LOWERS SEIZURE THRESHOLD
  - No sexual side-effects, no weight gain

# Antidepressants:  atypical antidepressants

- Mirtazapine (alpha adrenergic modulator)
  - all neurotransmitters (serotonin, dopamine, norepinephrine) inhibit themselves ("negative feedback")
  - NE not only negative feedbacks itself but also serotonin via the presynaptic alpha-2 heteroreceptor
  - Mirtazapine blocks this negative feedback mechanism by blocking the alpha-2 heteroreceptor

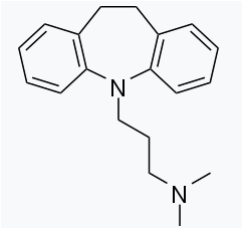
- Indications:
  - Major depressive disorder
  - Generalized anxiety disorder

- Side-effects:
  - Highly histaminic (affinity for H1 receptors) = weight gain, drowsiness, sedation

# Antidepressant types

- SSRI
  - Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
- SNRI
  - Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipran
- Atypical antidepressants
  - Bupropion, Mirtazapine
- Serotonin modulators
  - Vilazodone, Vortioxetine
- **Older antidepressants**
  - **TCAs, MAOIs**
- Ketamine
- Atypical antipsychotics

# Antidepressants:  TCAs




- Amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, doxepin
- Indications:
  - Mood: Major Depressive Disorder
  - Anxiety: GAD, panic disorder
  - Others: PTSD, OCD, bulimia, chronic pain
- No longer first-line because of the side-effect profiles especially in overdose situations
- Side-effects
  - cardiac!, QTC
  - seizure threshold
  - anti-cholinergic = constipation, dry mouth, urinary retention, blurred vision
  - anti-alpha adrenergic = orthostatic hypotension, diaphoresis
  - anti-histaminic = sedation, weight gain
- Suicidality
  - FATAL in overdose, as little as 10x the daily dose

# Antidepressants:  MAOIs

- Phenelzine, selegiline, tranylcypromine
- reserved for treatment resistant depression
- Side-effects
  - hypertensive crisis: "cheese reaction" because MAOIs block every MAO including the MAO in the gut.  After ingesting tyramine rich foods, the patient will have surge in tyramine leading to surge in blood pressure
  - serotonin syndrome

# Antidepressant selection

- Which factors do we consider when selecting an antidepressant?
  - safety
  - side-effect profile
  - activating effects
  - calming effects
  - drug-drug interactions
  - comorbid illness
  - ease of use
  - cost
- Patient's own medication history, and family history of response to medications may help, but limited evidence demonstrating improved outcomes thus far...

# Antidepressants, what to expect

- How long will it take to work?
  - earliest improvement at minimum is 1-2 weeks, and such early response may correlate with better chance of remission.  (studies show that among all patients who remitted, more than 90% were early responders)
  - traditional time frame = 4-6 weeks
  - mechanism: desensitization of the presynaptic neuron, i.e. overcoming the serotonin thermostat

# Antidepressants, what to expect

- How long does patient need to be on it?
  - traditional time frame = 6 months after response to medication to preserve and enhance remission and prevent relapse

- Maintenance treatment
  - Patients with risk factors for recurrence should consider maintenance treatment
    - childhood trauma
    - early age of onset of depression (<21 years old)
    - history of 2-3 or more major depressive episodes
    - persistent residual depressive symptoms
    - ongoing psychosocial stressors
  - traditional time frame = 1-3 years of continued treatment
  - Dosage is consistent with same dosage range for acute treatment

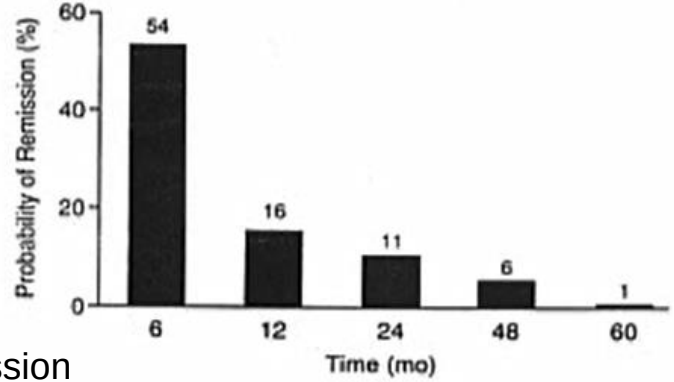
# Treatment goals

- Initial treatment response in 30-50% of patients taking antidepressants
- Overall response or remission in roughly 50-60% of patients
- If patient stays in treatment, >98% chance of symptom reduction

## What does remission mean?

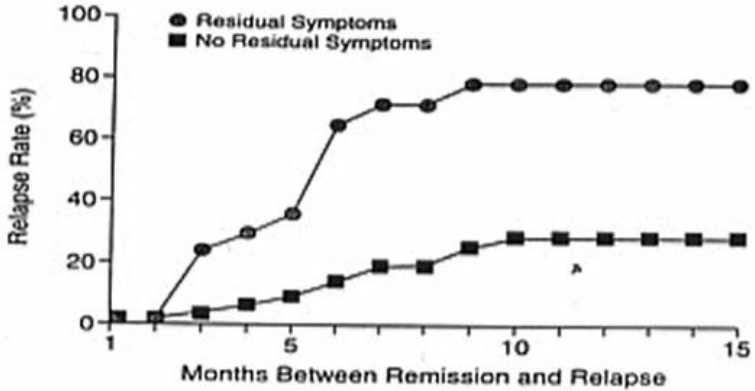
- Common practice to use some type of mood rating scale
- Presence of improved mental health: optimism, vigor, self-confidence
- Return to one's usual self, one's baseline
- General sense of well being
- Chance of relapse much higher without remission

Figure 3. Likelihood of Achieving Remission Over Time[a]




Duration of symptoms inversely proportional to probability of remission

Figure 2. Effect of Residual Depressive Symptoms on Relapse Rates[a]




Residual symptoms elevates the probability of relapse

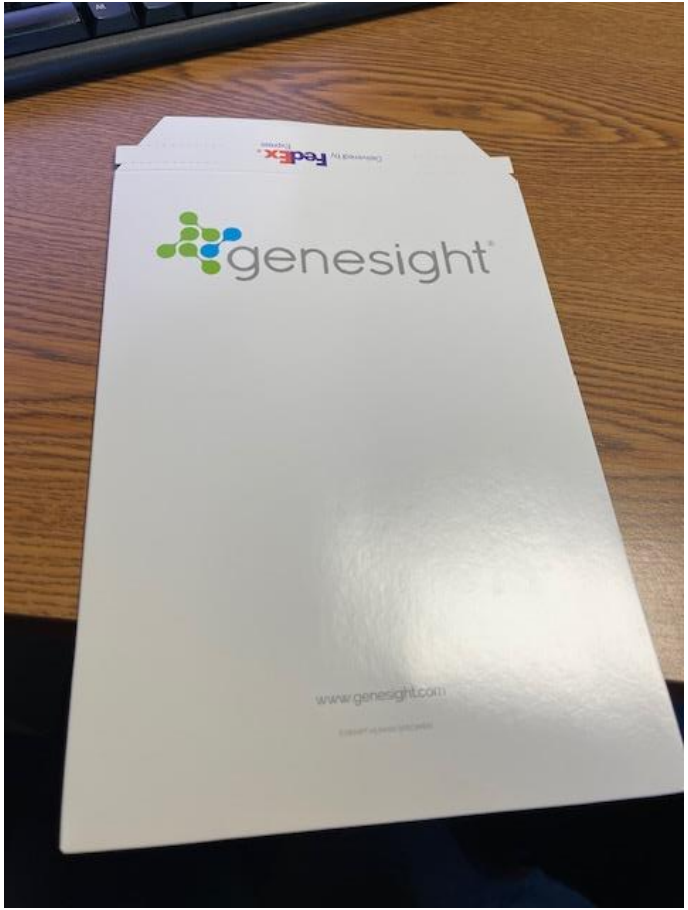
# Antidepressant augmentation

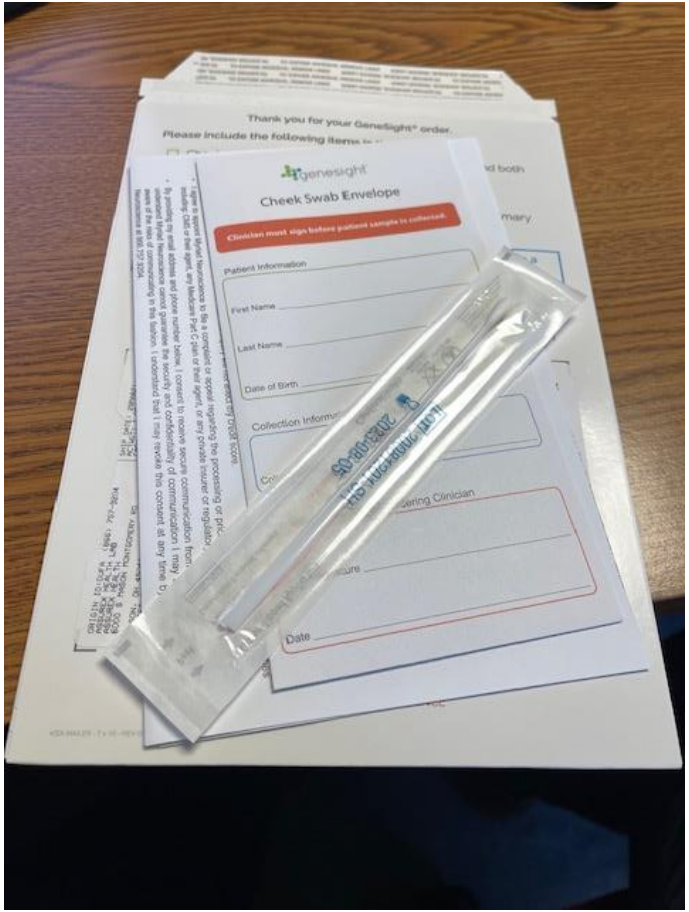
- What happens if the initial antidepressant doesn't work?
  - do we switch antidepressants, or do we augment?
  - some evidence suggests augmentation is superior to switching while other studies suggest both are comparable
  - therefore, it is suggested to first attempt medication augmentation when appropriate

- Augmentation options:
  - second generation antipsychotic (aripiprazole, brexpiprazole, quetiapine, olanzapine, risperidone)
  - lithium
  - second antidepressant (avoid MAOI, leverage distinct mechanisms)
  - thyroid hormone

# Pharmacogenetic Testing

- Pharmacogenetic testing is now deployed in clinical practice across the country including at Loyola for our outpatient psychiatry clinics
- Examines SNPs
- Covers both pharmacodynamic and pharmacokinetic genes
- Pharmacodynamic:
  - SLC6A4 transporter, HTR2A, HLA-A, HLA-B, MTHFR
- Pharmacokinetic:
  - CYPs: 2D6, 3A4, 1A2, 2B6, 2C19, 2C9
  - UGTs: 1A4, 2B15
- Guides prescribers:
  - which medications are less likely to work, eliminating medications that are "bad match"
  - optimal dosage


genesight
www.genesight.com


Thank you for your GeneSight® order.
Please include the following items
genesight
Cheek Swab Envelope
Clinician must sign before patient sample is collected.
Patient Information
First Name
Last Name
Date of Birth
Date

# PATIENT GENOTYPES AND PHENOTYPES

## PHARMACODYNAMIC GENES

PD

**SLC6A4** — **Reduced Response**

S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

---

**HTR2A** — **Increased Sensitivity**

G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

**HLA-B*1502** — **Lower Risk**

Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

---

**HLA-A*3101** — **Lower Risk**

A/A

This patient is homozygous for the A allele of the rs1061235 A>T polymorphism indicating absence of the HLA-A*3101 allele. This genotype suggests a lower risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

| NORMAL FOLIC ACID CONVERSION | REDUCED FOLIC ACID CONVERSION | SIGNIFICANTLY REDUCED FOLIC ACID CONVERSION |
|---|---|---|
| |  | |

**Note:** Serum levels of folate may be too low. Folate supplementation or higher daily intake of folic acid may be required.

## PATIENT GENOTYPE AND PHENOTYPE

| MTHFR | Intermediate Activity | C/T |
|---|---|---|
| This individual is heterozygous for the C677T polymorphism in the MTHFR gene. This genotype is associated with reduced folic acid metabolism, moderately decreased serum folate levels, and moderately increased homocysteine levels. | | |

# PHARMACOKINETIC GENES

PK

**CYP1A2** — **Ultrarapid Metabolizer**

-163C>A - A/A, 5347C>T - T/T

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

---

**CYP2B6** — **Extensive (Normal) Metabolizer**

*1/*1

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*1 allele enzyme activity: Normal

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

---

**CYP2C19** — **Extensive (Normal) Metabolizer**

*1/*1

CYP2C19*1 allele enzyme activity: Normal
CYP2C19*1 allele enzyme activity: Normal

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

---

**CYP2C9** — **Intermediate Metabolizer**

*1/*2

CYP2C9*1 allele enzyme activity: Normal
CYP2C9*2 allele enzyme activity: Reduced

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

---

**CYP3A4** — **Intermediate Metabolizer**

*1/*22

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*22 allele enzyme activity: Reduced

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

---

**CYP2D6** — **Intermediate Metabolizer**

*1/*4

CYP2D6*1 allele enzyme activity: Normal
CYP2D6*4 allele enzyme activity: None

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

---

**UGT1A4** — **Extensive (Normal) Metabolizer**

*1/*1

UGT1A4*1 allele enzyme activity: Normal
UGT1A4*1 allele enzyme activity: Normal

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

---

**UGT2B15** — **Intermediate Metabolizer**

*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*2 allele enzyme activity: Reduced

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

## ANTIDEPRESSANTS

| USE AS DIRECTED |
| --- |
| **desvenlafaxine** (Pristiq®) |
| **selegiline** (Emsam®) |

| MODERATE GENE-DRUG INTERACTION | |
| --- | --- |
| **amitriptyline** (Elavil®) | 1 |
| **bupropion** (Wellbutrin®) | 1 |
| **clomipramine** (Anafranil®) | 1 |
| **desipramine** (Norpramin®) | 1 |
| **doxepin** (Sinequan®) | 1 |
| **levomilnacipran** (Fetzima®) | 1 |
| **nortriptyline** (Pamelor®) | 1 |
| **trazodone** (Desyrel®) | 1 |
| **vilazodone** (Viibryd®) | 1 |
| **vortioxetine** (Trintellix®) | 1 |
| **citalopram** (Celexa®) | 1,4 |
| **escitalopram** (Lexapro®) | 1,4 |
| **sertraline** (Zoloft®) | 1,4 |
| **duloxetine** (Cymbalta®) | 2,7 |
| **imipramine** (Tofranil®) | 3,7 |
| **mirtazapine** (Remeron®) | 3,7 |
| **fluvoxamine** (Luvox®) | 2,4,7 |

| SIGNIFICANT GENE-DRUG INTERACTION | |
| --- | --- |
| **venlafaxine** (Effexor®) | 1,6 |
| **fluoxetine** (Prozac®) | 1,4,6 |
| **paroxetine** (Paxil®) | 1,4,6 |

### CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.

2: Serum level may be too low, higher doses may be required.

3: Difficult to predict dose adjustments due to conflicting variations in metabolism.

4: Genotype may impact drug mechanism of action and result in reduced efficacy.

6: Use of this drug may increase risk of side effects.

7: Serum level may be too low in smokers.

8: FDA label identifies a potential gene-drug interaction for this medication.

10: This medication does not have clinically proven genetic markers that allow it to be categorized.

## ANXIOLYTICS AND HYPNOTICS

| USE AS DIRECTED |
| --- |
| **temazepam** (Restoril®) |

| MODERATE GENE-DRUG INTERACTION | |
| --- | --- |
| **alprazolam** (Xanax®) | 1 |
| **buspirone** (BuSpar®) | 1 |
| **clonazepam** (Klonopin®) | 1 |
| **clorazepate** (Tranxene®) | 1 |
| **eszopiclone** (Lunesta®) | 1 |
| **lorazepam** (Ativan®) | 1 |
| **oxazepam** (Serax®) | 1 |
| **zolpidem** (Ambien®) | 1 |
| **propranolol** (Inderal®) | 3,7 |

| SIGNIFICANT GENE-DRUG INTERACTION | |
| --- | --- |
| **chlordiazepoxide** (Librium®) | 1,6 |
| **diazepam** (Valium®) | 1,6 |

### CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
10: This medication does not have clinically proven genetic markers that allow it to be categorized.

# ANTIPSYCHOTICS

## USE AS DIRECTED

**asenapine** (Saphris®)
**fluphenazine** (Prolixin®)
**ziprasidone** (Geodon®)

## MODERATE GENE-DRUG INTERACTION

| | |
|---|---|
| **cariprazine** (Vraylar®) | 1 |
| **iloperidone** (Fanapt®) | 1 |
| **paliperidone** (Invega®) | 1 |
| **perphenazine** (Trilafon®) | 1 |
| **quetiapine** (Seroquel®) | 1 |
| **lurasidone** (Latuda®) | 1,8 |
| **olanzapine** (Zyprexa®) | 2,7 |
| **chlorpromazine** (Thorazine®) | 3,7 |
| **clozapine** (Clozaril®) | 3,7 |
| **haloperidol** (Haldol®) | 3,7 |
| **thioridazine** (Mellaril®) | 3,7,8 |

## SIGNIFICANT GENE-DRUG INTERACTION

| | |
|---|---|
| **aripiprazole** (Abilify®) | 1,6 |
| **brexpiprazole** (Rexulti®) | 1,6 |
| **risperidone** (Risperdal®) | 1,6 |
| **thiothixene** (Navane®) | 2,7 |

## CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
10: This medication does not have clinically proven genetic markers that allow it to be categorized.

## MOOD STABILIZERS

### USE AS DIRECTED

**lamotrigine** (Lamictal®)
**oxcarbazepine** (Trileptal®)
**valproic acid/divalproex** (Depakote®)

### MODERATE GENE-DRUG INTERACTION

**carbamazepine** (Tegretol®) 1

### SIGNIFICANT GENE-DRUG INTERACTION

### NO PROVEN GENETIC MARKERS

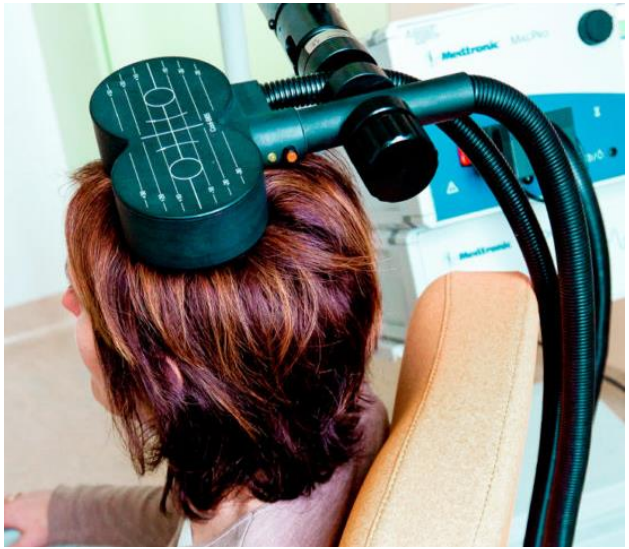
**gabapentin** (Neurontin®) 10
**lithium** (Eskalith®) 10
**topiramate** (Topamax®) 10

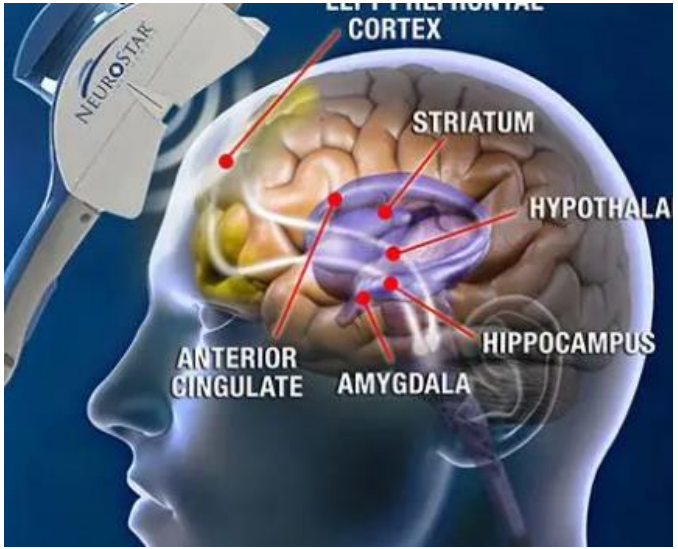
CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
10: This medication does not have clinically proven genetic markers that allow it to be categorized.

# Procedural interventions

- ECT
  - still one of the best interventions, especially for the elderly, and severely ill mood disorders including bipolar, regardless of age
    (ask the Hines program coordinator during your clerkship, Hines VA has a robust ECT treatment center where you can observe and participate)
- TMS
  - moderate depression especially if there are medication side-effects. Insurances now cover.
- DBS
  - effective but invasive
- Ketamine
  - S and R enantiomers, psychiatry uses the S enantiomer
  - NMDA receptor antagonism + AMPA receptor agonism = glutamate modulation, and other receptors including opioid receptors
  - dissociative state, very powerful experience, but reserved only for treatment resistant depression






We do TMS at Loyola!

# Part 5: Psychotherapy

# Psychological Issues

- When a person experiences depression, he or she will naturally try to understand why it is happening

- Many different psychological reasons why a person might be depressed:
  - loss
  - guilt
  - embarrassment, humiliation
  - dependency, entrapment
  - anger, danger
  - trust

# Psychological Issues

- Most "depression" can be managed through dealing with the issues in some sort of psychotherapy
- Ask patients their theories as to why they are depressed
- Ask patients what they think it will take for them to improve
- Work off of those ideas for best compliance and recovery

# Suggested indications for psychotherapy alone

- Patient preference
- Mild-to-moderate depression
- Mild-to-moderate functional impairment
- Acute onset related to adverse events
- First depressive episode
- Availability of competent therapists

# More about psychotherapy for depression

- **Structured (time-limited) therapies**
  - **cognitive behavioral therapy**
  - **interpersonal therapy**
  - **behavioral therapy**
  - can do outcome studies (evidence-based)
  - training is homogeneous
  - makes sense in a rationed care world
  - as effective as medications in mild to moderate depression
  - very useful augmentation to medications
  - best prognosis in combination treatment

# More about psychotherapy for depression

- **Cognitive Behavioral Therapy (broad applicability)**
  - here and now
  - very little exploration of the person
  - correction of abnormal thought connections due to one's experience
  - main topics: catastrophic thinking, black and white thinking, overvaluation, etc
  - homework
  - repetition

# More about psychotherapy for depression

- **Interpersonal Therapy (narrower applicability)**
  - here and now
  - use the relationship with you as a vehicle
  - main topics: grief, role transition, role dispute, interpersonal deficits are the main areas of focus
  - patterns of past poor interpersonal interactions
  - redefine one's relationship with others
  - often "practice" and "role-play" with patients

# More about psychotherapy for depression

- **Behavioral Therapy**
  - learning models, healthy eating
  - relaxation models
  - exercise - one of the best tools for depression
  - specific techniques and general techniques
  - very effective for anxiety disorders and many types of stressors
  - common for all of us to use some of this

# More about psychotherapy for depression

- **Solution-focused therapy (positive psychology)**
  - determine what should change for the patient to feel better
  - look at what strategies and skills the patient already has from the past that might prove helpful again
  - build upon the patient's strengths to develop better ways to manage
  - try to change external situations to the betterment of the patient's condition
  - "positive psychology" focusing on the positives of the patient rather than the negatives

# More about psychotherapy for depression

- **Mindfulness-based therapies**
  - present-centered, thought awareness, acknowledging each thought, each feeling, each sensation and accepting them
  - self-regulation while adopting curiosity
  - optimizes the prefrontal cortex to better regulate the amygdala


Mind Full, or Mindful?

# More about psychotherapy for depression

- **Insight Oriented Therapy**
  - very powerful, but lengthy process of therapy
  - less used because of modern healthcare and insurance
  - based on Freud and childhood developmental traumas
  - very hard to determine outcome
  - personality change and mindset is part of the therapy
  - expensive and not for everyone
  - predominant form of therapy from the 1920-1970s

# More about psychotherapy for depression

- Other therapies
  - psychoanalysis
  - family systems work
  - experiential therapies
  - group therapy

- Most people use a mixture of different therapies

- Supportive psychotherapy is used by far the most
  - you are already are doing this with your patients!

# Social Environmental Issues

- Important to identify the social environmental issues in the context of the depression

- Intervention to correct these factors should be attempted

- Examples
  - Job loss
  - Poverty
  - Homelessness
  - marital problems
  - children problems
  - substance abuse

# Normal Life Processes can contribute to depression

- Many of life's events can lead to symptoms of depression
  - Loss of loved one (mourning - grieving)
  - Breakup (adjustment disorders)
  - Being laid off
  - Being diagnosed with medical illnesses
    - anhedonia, suicidal thoughts, hopelessness - are especially important to screen here

- Identifying these processes, and distinguishing between this reactive depression vs MDD is important

# Other types of depression

- Disruptive Mood Dysregulation Disorder (296.99)
- Persistent Depressive Disorder (300.40)
- Premenstrual Dysphoric Disorder (625.4)
- **Substance/Medication Induced Depressive Disorder (292.84)**
- Depressive Disorder Due to Another Medical Condition (293.83)
- Other specified depressive disorder (311)
    - Recurrent brief, short duration depressive episode with insufficient symptoms

# Substance-induced Mood Disorder

- A. Prominent and persistent mood disturbance that is characterized by depressed mood and markedly diminished interest in pleasure in most activities
- B. There is evidence from history, physical, or labs that of both 1. Mood disturbance developed soon after use of the substance and 2. the substance is known to cause mood disturbance
- C. The disturbance is not better explained by a depressive disorder that is not substance/medication induced
- D. Does not occur exclusively during Delirium

# Specifiers for MDD and other depressive disorders

- with anxious distress
- with mixed features
- with psychotic features
- with melancholic features
- with catatonia
- with peripartum onset
- with seasonal mood pattern
- with atypical features

# Melancholic features

- Classic depressive syndrome thought to be predominantly biological based due to the severity and symptom presentation
- A. During worst of the depression either loss of all pleasure or lack of reactivity to usually pleasant things
- B. 3 or more of the following:
  - Distinct quality of depressed mood
  - Depression worse in the am
  - Early am awakening ( 2hours before normal)
  - Marked psychomotor agitation or retardation
  - Significant weight loss
  - Excessive or inappropriate guilt

## Variations in presentations across age and culture

- Be aware of different presentations in different groups of the population
- Elderly: somatic, irritable
- Adolescents: behavioral changes, changes in friends, grades, use of drugs
- Different cultures: Asian and African American populations tend to be stoic, minimization

# Comorbidities

- It is not uncommon for MDD to occur along with other psychiatric disorders in the same patient
- More than 60% of the time, another psychiatric diagnosis is found
- 25% of the time, 3 or more psychiatric disorders are diagnosed
- Identifying the other disorders will make treatment of the MDD easier
- The more the co-morbidities, the worse the prognosis
- The longer the depression goes untreated, the more the co-morbidity

# Comorbidities

- Common comorbid disorders to MDD
  - substance abuse
  - anxiety disorders
    - panic
    - GAD
    - social anxiety
  - somatic disorders
  - OCD
  - eating disorders
  - personality disorders
  - trauma

# Recurrent Major Depression

- Chances of recurrence increase with each recurrence
  - 1 episode 50%
  - 2 episodes 90%
  - 3 episodes 95%

- Kindling Model:
  - on a molecular level, once MDD has occurred, the brain is much more susceptible to further depression even if the stresses are proportionally much less

- This leads to the topic of maintenance therapy

# Maintenance Therapy

- The need for maintenance therapy has been well documented
- However, physicians and the public are not versed or inadequately trained about this model

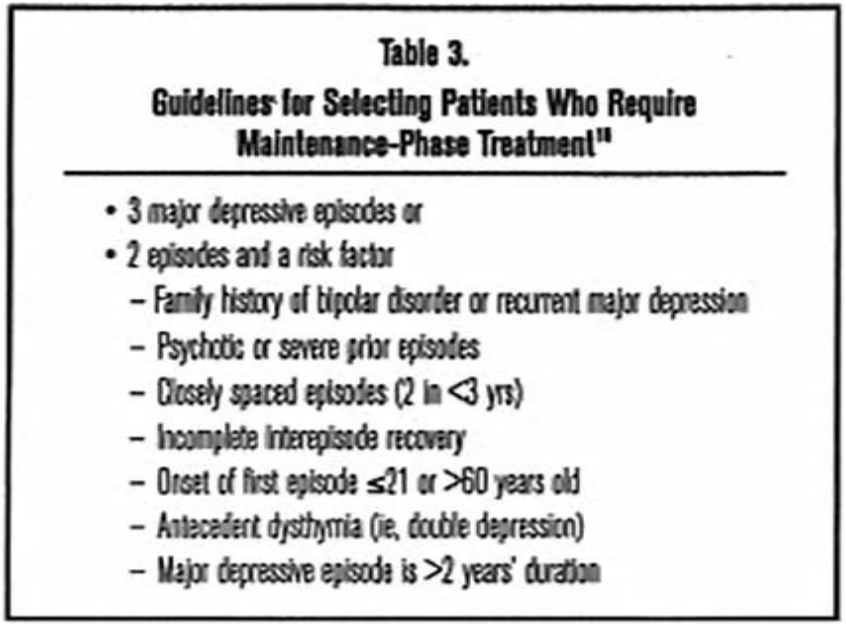


**Table 3.**

**Guidelines for Selecting Patients Who Require Maintenance-Phase Treatment[11]**

- 3 major depressive episodes or
- 2 episodes and a risk factor
  - Family history of bipolar disorder or recurrent major depression
  - Psychotic or severe prior episodes
  - Closely spaced episodes (2 in <3 yrs)
  - Incomplete interepisode recovery
  - Onset of first episode ≤21 or >60 years old
  - Antecedent dysthymia (ie, double depression)
  - Major depressive episode is >2 years' duration

## Summary

- Depression is very common, and still under-treated for many reasons
- With identification and good treatment adherence, the vast majority of episodes can be improved if not put into remission
- All physicians need to screen and be aware of the signs of depression
- Psychiatrists are involved with the more challenging patients
  - Primary care should be comfortable as to when to refer

**Part 6: Enrichment section:**

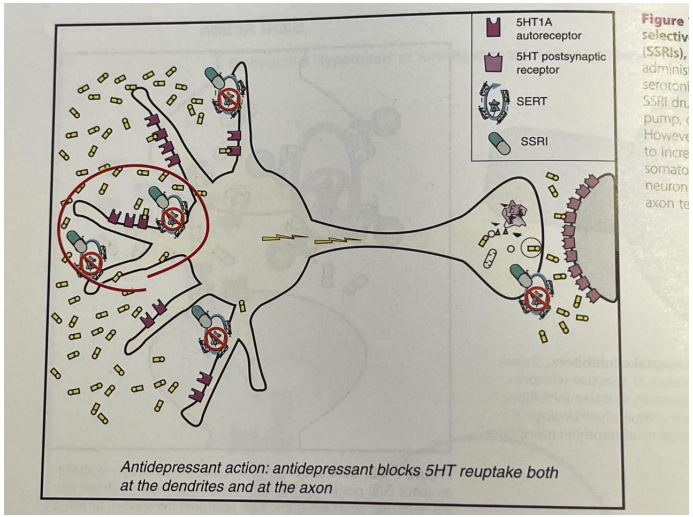
**Deeper understanding of SSRIs and psychopharm**

**Theories on Depression**

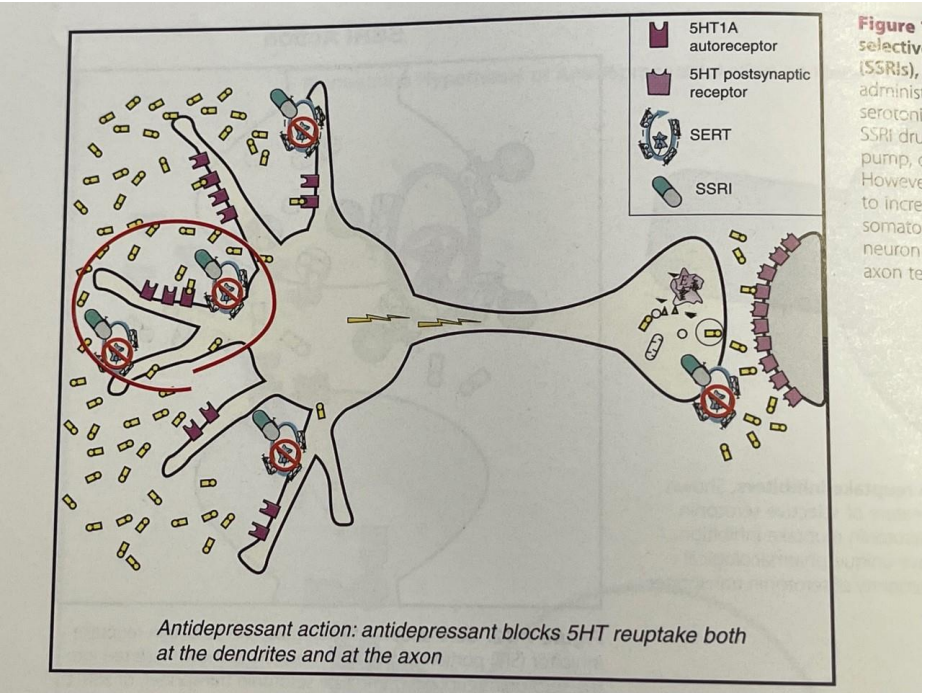
**Mind-Body Medicine**

# Understanding SSRIs deeper

- SSRIs all have one thing in common: inhibition of the serotonin transporter
- SSRIs actually initially block the body/dendrites of the presynaptic neuron rather than the axon or synapse

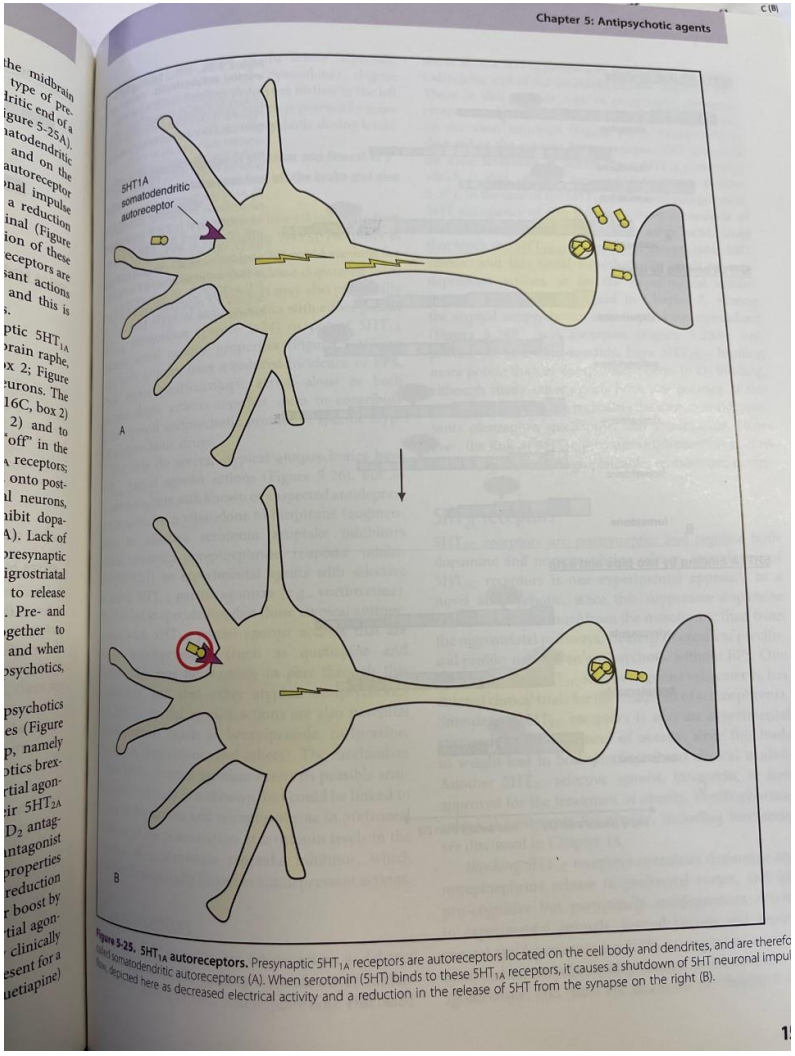



Stahl's Essential Psychopharmacology




*Antidepressant action: antidepressant blocks 5HT reuptake both at the dendrites and at the axon*

- when SSRI is given, the 5-HT rises due to blockade of the serotonin transporter
- but, blocking the transporter does NOT immediately increase serotonin in the synapse
- instead, the 5-HT increases in the somatodendritic area of the presynaptic neuron
- thus, we focus on this area of the presynaptic neuron rather than the synapse




- The serotonin receptors in the cell body (somatodendritic region) of the presynaptic neuron are different from the conventional serotonin receptors in the synapse.
- They are the presynaptic "autoreceptors" most famous one = 5-HT1A.
- These autoreceptors shut down serotonin production.
- But, SSRIs paradoxically trigger these to increase serotonin production!  How!?!

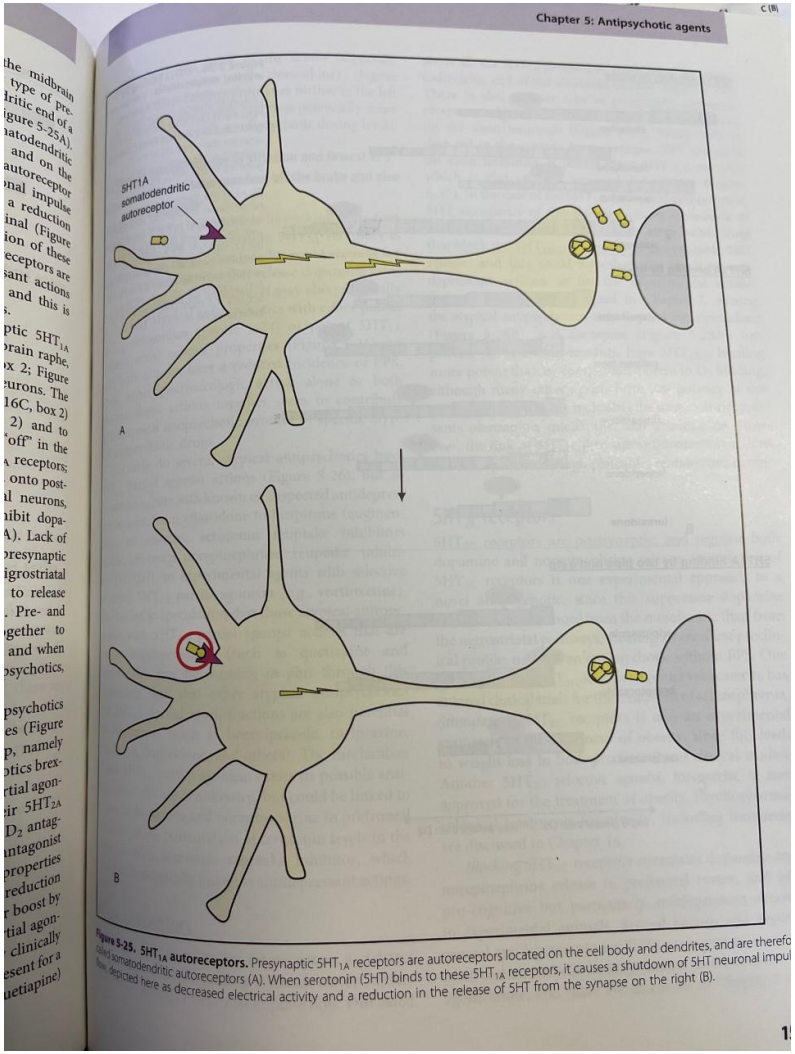



**Figure 5-25. $5HT_{1A}$ autoreceptors.** Presynaptic $5HT_{1A}$ receptors are autoreceptors located on the cell body and dendrites, and are therefo called somatodendritic autoreceptors (A). When serotonin (5HT) binds to these $5HT_{1A}$ receptors, it causes a shutdown of 5HT neuronal impul flow, depicted here as decreased electrical activity and a reduction in the release of 5HT from the synapse on the right (B).

**Key point = desensitization!**

**SSRIs ultimately increase serotonin production by first de-sensitizing these autoreceptors on a genomic level.**

1. SSRIs increase 5-HT
2. 5-HT binds to presynaptic autoreceptor
3. initially, serotonin production decreases
4. over time, the 5-HT1A autoreceptors signal into cell nucleus, resulting in downregulation and desensitization of 5-HT1A and other autoreceptors
5. once these inhibitory autoreceptors are desensitized, 5-HT can no longer effectively turn off its own release
6. the presynaptic neuron becomes disinhibited
7. the disinhibited presynaptic neuron finally starts dumping serotonin like crazy into the axon/synapse
8. this process precisely correlates with the delayed onset of SSRIs

# From where does depression arise?

- Stress-diathesis model (genetic vulnerability or predisposition)
- Life experiences trigger epigenetic mechanisms, to activate or silence genes that regulate cognition, behavior, and even mental disorders
- Activation of these stress response genes results in the production of inflammatory signals that alter the processing of the brain
- Yes, you outrun the bear, but at what cost?
- The bear is now gone, but I'm left with maladaptive circuits

# Neurobiology

- Atrophy of the hippocampus (selective memory, learning, problem-solving)
  - atrophy: loss of number of neurons, and reduced dendritic connections
  - this atrophy could be premorbid and/or a sequelae from chronic depression
- Overactivity of amygdala (fear response, emotions) and under-activity of the prefrontal cortex (executive functions and cognitions)
- However, results do not have good enough specificity to be a biological marker for depression

# Molecular biology of depression

- Ongoing stress leads to CRF (corticotropin releasing factor) which elevates cortisol

- Chronic elevations of cortisol reduces neurogenesis, increases neurotoxicity especially in the hippocampus

- Greater neuronal loss with longer duration of illness leading to more severe symptoms and treatment resistance

- Balance of neurogenesis vs neurodegeneration

# Molecular biology of depression

- In utero exposure to high levels of cortisol leads to persistent cognitive, behavioral, and physical defects, and increased rates of later depression (King 2005).

- Programming hypothesis: neonates of depressed mothers have the similar biochemical abnormalities as their mothers and show inferior performance on neurobehavioral development measures (Markus et al. 2009).

- Increased cortisol exposure leads to R amygdala neuronal changes in the newborn on MRI (Qiu et al. 2013).

# Molecular biology of depression

- Neurogenesis is downregulated by: stress, steroids, age, opioids
- Neurogenesis is upregulated by: enriched environment, exercise, learning, estrogen, antidepressants
- Potential theory: increased neurotransmitters > increased cAMP > increased CREB (cAMP responsive binding protein) > increased BDNF (brain-derived neurotrophic factor)
- IV ketamine rapidly treats depression but no effect on BDNF, but rather on activation of glutamatergic receptors

# Molecular biology of depression

- Neurogenesis is downregulated by: stress, steroids, age, opioids
- Neurogenesis is upregulated by: enriched environment, exercise, learning, estrogen, antidepressants
- Potential theory: increased neurotransmitters (from antidepressants) > increased cAMP > increased CREB (cAMP responsive binding protein) > increased BDNF (brain-derived neurotrophic factor) > neurogenesis
- IV ketamine rapidly treats depression but no effect on BDNF, but rather on activation of glutamatergic receptors

# Inflammatory models of depression

- Elevated levels of interleukin-1B, IL-6, TNF-a found in the prefrontal cortex of teenage suicide victims (Pandey et al. 2012).

- Subgroups of patients with early life adversity may be more predisposed to developing depression in reaction to other life modifiers especially obesity.  These individuals respond poorly to antidepressants and therapy.  Some novel anti-inflammatory approach is needed such as recent trials of COX-2 inhibitors (Raison et al. 2014).

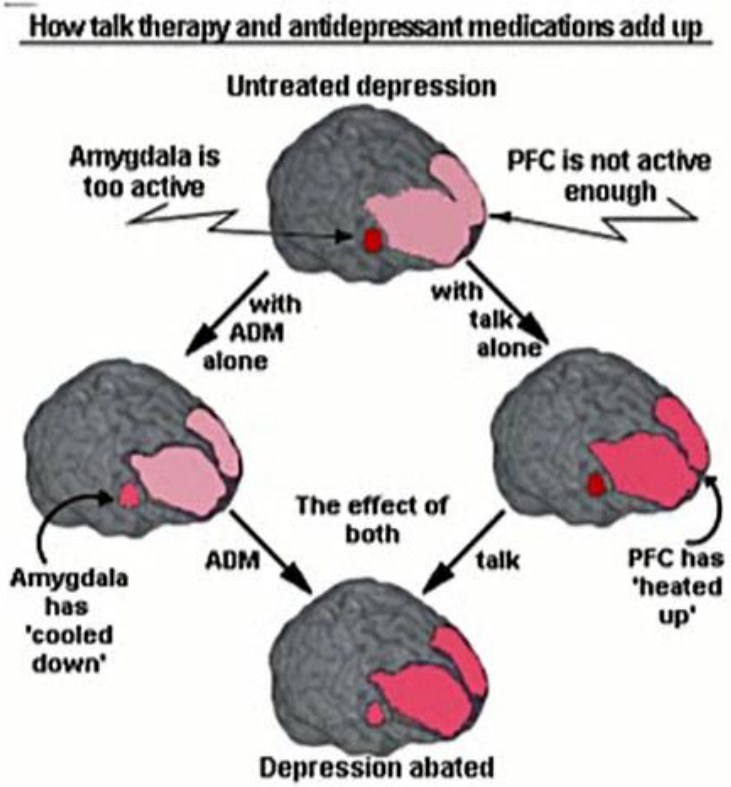
- Inflammation may be a cause in treatment refractory cases

# Network hypothesis of depression

- Observations that antidepressants act permissively to facilitate environmental influence on neuronal network reorganization.  This provides a plausible neurobiological explanation for the enhanced effect of combining antidepressants with psychotherapy.

- Recovery from depression is a gradual process that develops slowly and is facilitated by structured guidance and rehabilitation.

# Therapy is top down
# Medication is bottom up

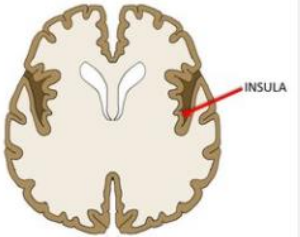


# Can we predict treatment response?

- Patients with insula hypometabolism screened via PET scan respond to CBT psychotherapy, but poorly to escitalopram.

- Patients with insula hypermetabolism respond to escitalopram, but not CBT psychotherapy (McGrath et al. 2013).

- The anterior insula is crucial in mediating the translation of visceral experiences to subjective feelings.  The insula is intimately linked to the brain regions responsible for emotional self-awareness, decision making, and cognitive control.



# Neurotrophic Hypothesis of Depression

- The fronto-limbic circuitry which includes the prefrontal cortex, hippocampus, amygdala, striatum, and insula are highly involved in the regulation of emotion

- fMRI and postmortem biopsy shows significant volumetric and grey matter reduction in the prefrontal cortex, hippocampus, and striatum, and an increase in volume and grey matter in the amygdala and insula

- Exposure to chronic stress mediates the deterioration of the fronto-limbic circuitry (Rao et al. 2014)

# Protective factors for depression

- Higher spirituality (but not greater church attendance) increases cortical thickness in bilateral parietal lobes and occipital regions, which is protective if an individual is at high risk (strong genetic linkage), but otherwise shows no protective advantage

- Those with family history of depression have significantly thinner cortex predevelopment of their illness (Miller et al. 2014).

# Why is exercise an effective intervention?

- Not only does exercise motivate people by being active and accomplishing a goal, but:
  - A protein called FNDC5 is produced in muscle cells and released in circulation in a form called "irisin" (Kerman et al. 2012)
  - Irisin crosses blood brain barrier to stimulate BDNF production
  - BDNF then helps maintain healthy neurons, and thereby improve depressive symptoms as well as cognition

# Mind-Body Medicine

- People with MDD have decreased immunity (especially NK activity) leading to greater bacterial and viral infections

- 20-50% of patients with CVAs, seizures, MS, and parkinsonism develop depression (Kanner 2003).

- 25% of patients prior to 1st onset of a seizure have a depressive episode

# Mind-Body Cardiac

- The most evidence for a strong clinical association
- Depression is now considered a moderate risk factor for developing MI/CAD/CHF (Kimmel 2001)
- Depression imparts 2x the risk of mortality in CABG patients
- Use of prophylactic SSRIs even in non-depressed patients is a discussion that goes on in cardiology outpatient appointments

# Why is depression a cardiovascular risk factor?

- **Biological:**
  - Platelet aggregation
  - Heart rate variability
  - proinflammatory cytokines
  - Endothelial dysregulation

- **Behavioral:**
  - Health habits
  - Smoking
  - Alcohol
  - Nonadherence to diet, exercise
  - Nonadherence to medical treatments

# Depression and Diabetes

- Older individuals with non-severe depression, persistent depression, or untreated depression have a 65% greater risk of developing diabetes over a 5 year period

- No evidence of antidepressant etiology

- Theories
  - obesity
  - lack of physical activity
  - poor self-care
  - chronic stress-hypercortisolemia (Campayo et al. 2010)

# Illnesses that don't follow the rules

- Chronic fatigue syndrome
- Fibromyalgia
- Irritable bowel syndrome
- Chronic pain syndrome
- Somatic symptom disorders

- These may have depressive components

- Mind-body integrative approaches are the best hope for these patients, as well as alternative medicine approaches

# References


- Castren,E. Neuronal Network Plasticity and Recovery from Depression, JAMA Psychiatry, 2013;70(9), p983-989
- Demyttenaere,K, et al. Compliance with Antidepressants in a Primary Care Setting, J Clin Psychiatry 2001;62 ( suppl 22) p 30 –33
- Duman, RS, Structural Alterations in Depression: Cellular Mechanisms Underlying Pathology and Treatment of Mood Disorders, CNS Spectrums 2002; 7(2) p 140-146
- Dunlap,BW, et al. The Role of Dopamine in the Pathophysiology of Depression, Archives of Gen Psych 64:2007 p327- 337
- Gorman, JM; To Adhere or not to Adhere: An Important Decision, CNS Spectrums 11(2): 2006 p 81-82
- Greden, JF; The Burden of Recurrent Depression; J Clin Psychiatry 2001;62 (suppl 22) p 5-9.
- Hasin,DS, et al. Epidemiology of Major Depression Disorder, Archives of Gen Psych 62:2005 p1097-1106
- Hasser,C, et al, SSRI use During Pregancy, Current Psychiatry 5(4): 2006 p 31-40
- Kanner,AM, et al. The Impact of Mood Disorders in Neurological Diseases, Epilepsy and Behavior 4:2003 p 3-13
- Kerman, IA. New Insights into BDNF Signaling, Am J of Psychiatry, 2012; 169(11), p 1137-1139
- King, S, Negative Consequences of Prenatal Stress are Long Lasting, CNS News, 8:2005, p 12
- Kirkcaldy,RD, et al Depression Screening in a VA Primary Care Clinic, Psychiatric Service 57:2006 p1694-1696
- Kronish,JM, et al. Persistent Depression affects adherence to secondary prevention behaviors after acute coronary syndromes, J Gen Internal Med. 21:2006 p1178-1183
- McGrath,CL, et al Toward a Neuroimaging Treatment Selection Biomarker for MDD, JAMA Psychiatry 2013,70(8), p821-829
- Miller, Craig, What are the Real Risks of Antidepressants? Harvard Mental Health Letter, 21(11):2005 p 1 –8
- Miller, L, et al. Neuroanatomical Correlates of Religiosity and Spirituality, JAMA Psychiatry, 2014; 71(2): p 128-135
- Nemeroff,CB, et al. Pharmacological Differences among the SSRI's, CNS Spectrums, 9 (Supp 4): 2004 p 23-31
- Olfson,M, et al. Continuity of Antidepressant Treatment for Adults with Depression in the United States, Am J of Psych, 163(1):2006 p 101-108
- Pandey,GN, et al. Proinflammtory Cytokines in Teenage Suicide Victims, J of Psychiatric Research, 2012(46), p 57-63
- Raison,CL, Inflammatory Depression:A Trifecta of Trouble, J of Clinical Psychiatry;2014;75(6), p 663-664
- Rao, M, et al. Dissecting melancholia with evidence-based biomarkers, Current Psychiatry, 2014; 13(2), p41-57.
- Sapolsky,RM; Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders; Arch Gen Psychiatry 57:2000 p925-935.
- Tanskanen,A, et al. Fish Consumption and Depressive Symptoms in the General Population in Finland, Psych Services, 52(4): 2001 p 529-531
- Tyssen,R, et al. Mental Health Problems among Young Doctors: An Updated review of Prospective Studies, Harvard review Psychiatry, 10:2002 p154-165
- Young AS, et al. The Quality of Care for Depressive and Anxiety Disrders in the United States, Arch Gen Psychiatry 58:2001, p55-61.