# Antidepressants

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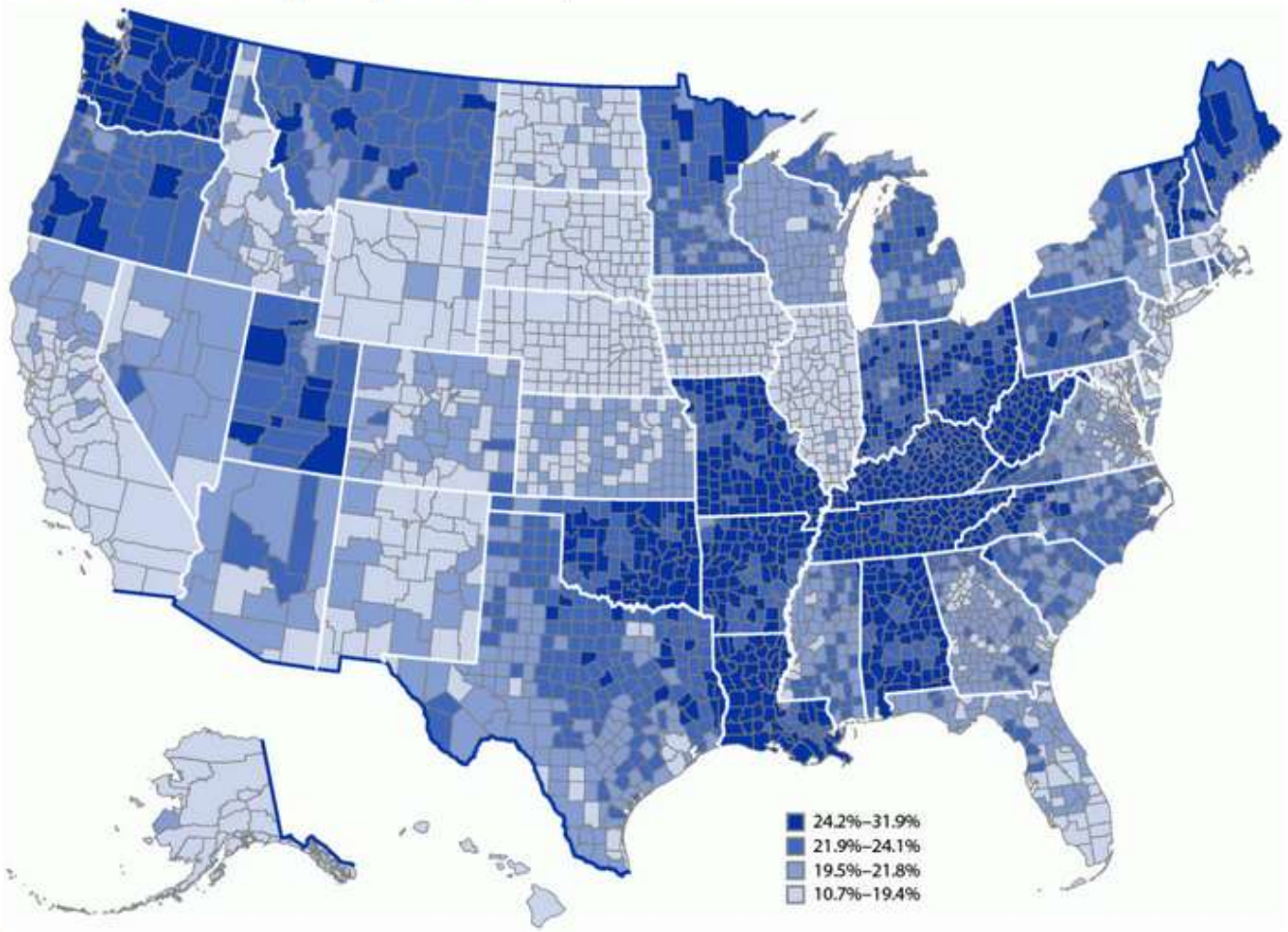
# Overview

# Prevalence of Depression

**FIGURE. Model-based age-standardized* county estimates of the percentage† of adults aged ≥18 years self-reporting a lifetime diagnosis of depression§ — Behavioral Risk Factor Surveillance System, United States, 2020**



# Comorbidies

- Other mental health disorders
  - Anxiety disorders
  - PTSD
  - Substance abuse disorders
- Medical disorders
  - CVD
    - Depression confers 3-5 x risk of cardiac-related death at 6, 18 months after MI
    - In 51,119 pts who suffered a stroke, pts dx with mental illness 1 mo after stroke had 33% greater chance of dying within 3yrs, even though they were younger and had fewer chronic conditions
    - 1/3 heart attack survivors experience depression vs 1/20 of adults in general population
    - In PM women, symptoms of depression were 50% more likely to develop or die from heart disease than those w/o such symptoms, even w/o hx of heart disease

# Comorbidies

- Medical disorders
  - IBS
  - Pain Disorders
  - Cancer
  - Neurodegenerative disorders
  - Autoimmune disorders
  - Fibromyalgia
  - Metabolic syndrome
  - DMII
  - Dementia
  - Migraine headaches

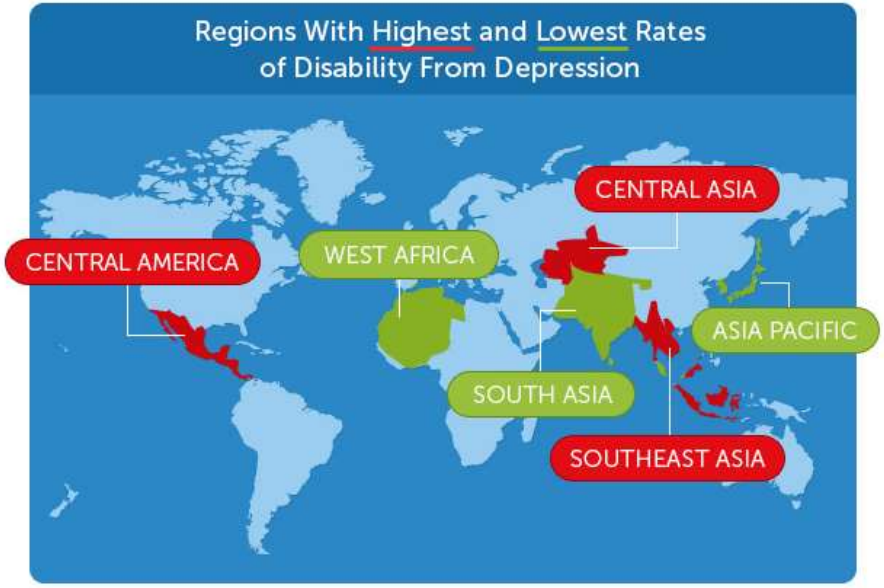
# Epidemiology

- Lifetime prevalence about **15%** overall
- May be as high as 25% in **women,** who almost universally have a **two-fold greater prevalence** of MDD than men
- Incidence is increasing in children/adolescents
- Mean age onset is 40 years old
- More common in those who are divorced or separated
- More common in rural areas
- May be underdiagnosed in minorities, as prevalence isn't associated with race or socioeconomic background
  - Except the unemployed—3X's more likely to have MDE
- 40% of patients with MDD also meet criteria for dysthymia

# Mental Health and Disability

## DEPRESSION: A LEADING CAUSE OF DISABILITY WORLDWIDE

Depression has inched up to No. 2 in worldwide rankings as a cause of disability.



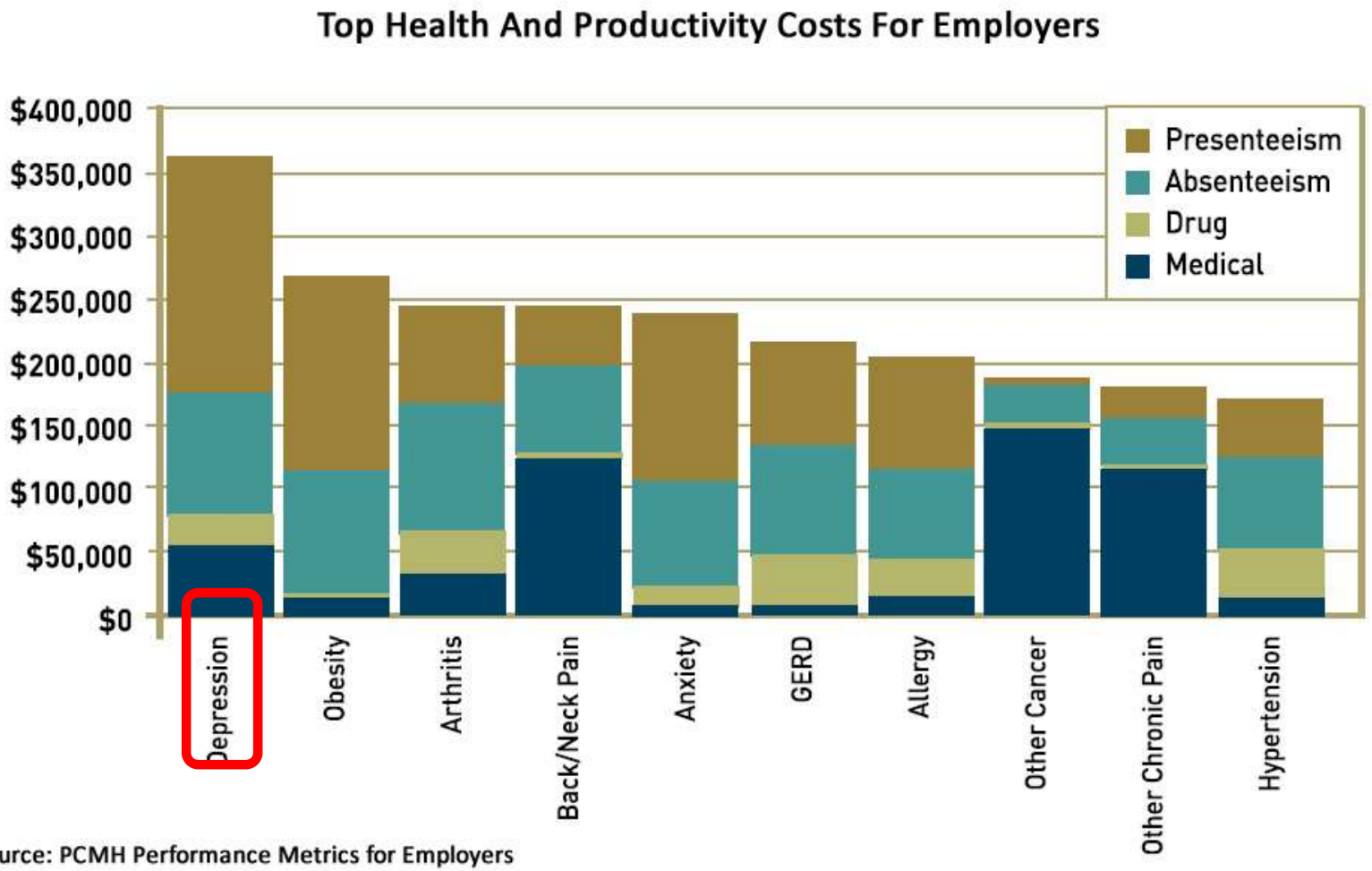

### More Facts About Depression and Disability

- Globally, an estimated 298 million people had depression in 2010.
- Population growth and aging are said to be responsible for a 37.5% increase in depression-related disability from 1990-2010.
- Women and people of working age – especially those in their twenties – were found to be most affected by depression-related disability.

~ 1 million lives are lost yearly due to suicide
(≈3000 suicide deaths daily)

Burden of Depressive Disorders by Country, Sex, Age and year. Findings from the Global Burden of Disease Study 2010. PLOS Medicine Nov 2013 and WHO 2012

# Cost of Depression




Sherman, B., et al. Patient-Centered Medical Home and Employer Metrics. Patient- Centered Primary Care Collaborative

# Course of Disease

- In general, mood disorders tend to have **long courses** and **relapses**
- In 20 years, mean number of episodes is 5-6
- **Untreated** episode lasts **6-13 months**
- **Treated** episodes last about **3 months**
- Risk of recurrence
  - 1 episode: <50% will have future episode
  - 2 episodes: 50-90% will have future episode
  - 3 episodes: >90% will have future episode
- As the disorder progresses, episodes become more frequent, more severe, more resistant to tx, and last longer
- Dysthymia
  - Usually suffer with the disorder for a decade before seeking help
  - Only 10-15% are in remission a year after their initial dx
  - About 25% attain complete recovery

Paykel ES et al. Psychol Med 1995;25(6):1171-1180

# Course of Disease

- Good prognostic factures
  - Hx of solid friendships during adolescence
  - Stable family functioning
  - Generally sound social functioning for the past 5 years
  - Absence of comorbid psychiatric disorder (including PD)
  - No more than 1 hospitalization

# Course of Disease

- Poor prognostic factors in depression
  - Long duration of episodes
  - Psychotic symptoms
  - Poor premorbid social adjustment
  - Male (more likely to experience chronically impaired course)
  - **Dysthymia**
  - **Substance** misuse
  - **Anxiety** symptoms

# Suicide

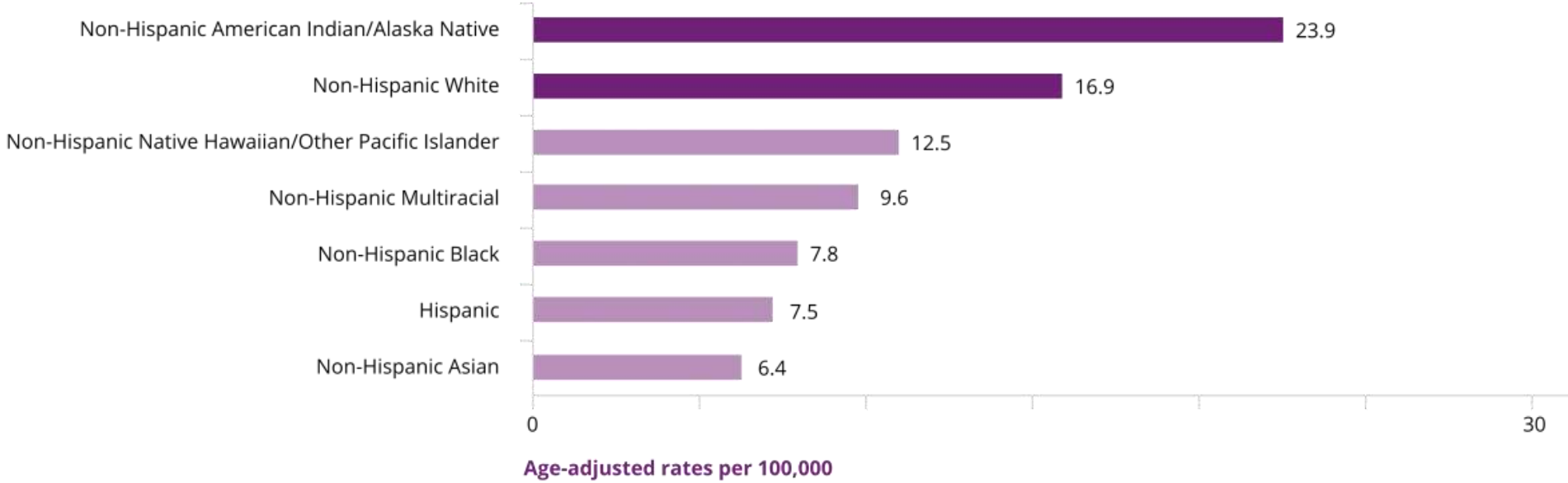
- **Are women or men at higher risk?**
  - More women attempt suicide (3:1) but more men complete suicide (4:1)

| Suicide Method | Males (%) | Females (%) |
|---|---|---|
| Firearms | 57 | 32 |
| Suffocation | 23 | 20 |
| Poisoning | 13 | 38 |

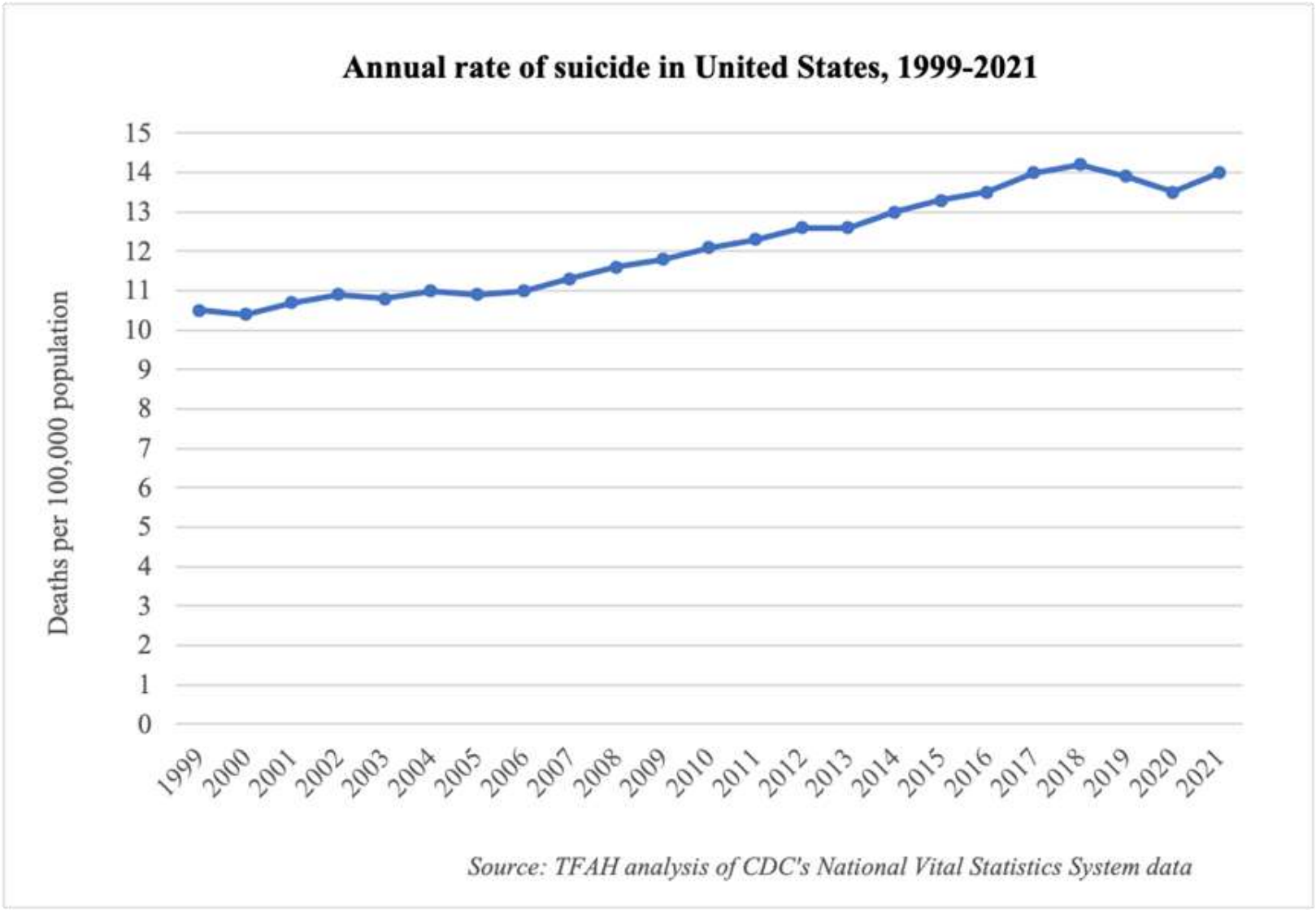


Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) www.cdc.gov/ncipc/wisqars

# Suicide Rates by Race/Ethnicity, United States, 2020



# Suicide rates increased 36% between 2000-2018, declined briefly, and are increasing again



# Pathophysiology

# Theories of Pathophysiology of Depression

**Genetic / epigenetic / environmental / diet**

**Monoamine Deficiency**

**Neurotoxic / neuroendocrine effects**

**Reduced GABA**

**Impaired circadian rhythm**

# Pathophysiology of Depression

- Centered in the limbic system circuit of Papez
  - Atrophy of dendritic spines
  - Decrease in neurotrophic factors like BDNF
  - Reduced size of the prefrontal cortex, hippocampus; decreased neuronal synapses
  - Decrease in overall metabolic neuronal activity in the limbic system by 30-40%
- Genetically vulnerable individual encounters an ongoing stressor
- Limbic system goes further and further out of homeostasis
- Chronic unpredictable stress
  - Cortisol release -> decrease in BDNF in the prefrontal cortex and hippocampus
  - Decreases neurogenesis, dendrite complexity, spine density in the prefrontal cortex
  - Hypertrophy in the nucleus accumbuns
- Limbic system function deteriorates to the point where modulatory neurons in the raphe nuclei and locus ceruleus no longer have the capacity to push the limbic system back into homeostasis
- Depressive symptoms emerge

# Pathophysiology of Depression

- Damage shown to reverse with
  - Ketamine
  - ECT
  - Antidepressants
  - Botulinum toxin
  - Neurohormones (ie allopregnanolone)
  - Dietary changes (omega-3 FAs, decreased processed foods, whole grains, olive oil, etc)
  - Exercise
  - Environmental changes
- Moderating effects
  - Coping styles
  - Genetic predispositions
  - Epigenetics like childhood adversity

# Pathophysiology of Depression

- Mediating effects
  - Limbic HPA alterations
  - Reduced glucocorticoid receptor function
  - Altered glucose tolerance and glucose sensitivity
  - Excitotoxicity
  - Intracellular calcium
  - Oxidative stress
  - Pro-inflammatory milieu
  - Lower levels of counter-regulatory neurosteroids (ie pregnanolones)
  - Pain
- NOT typically a chemical imbalance / monoamine deficiency except:
  - Neurodegenerative diseases (AD, PD, Alcoholic Korsakoff syndrome)
  - Epilepsy
  - Tumors
  - Stroke
  - Multiple sclerosis
  - Neurosyphilis

# Pathophysiology of Depression

- Primary problem is not in the modulatory system but in the end organ
  - Heart disease is not a failure of the autonomic system, however inotropic medications can help
  - Limbic system disease in not a failure of MAO system, however antidepressants can help
- Antidepressants
  - Only 1/3 of patients recover from depression
  - 1/3 respond
  - 1/3 no response
  - Positive effect often not permanent when medication is withdrawn or if withdrawn too soon
- Ketamine and ECT
  - Stimulate synaptogenesis
  - Turn on rapid response genes that activate structural genes in the limbic system neurons and start replacing receptors and transport systems within the cells
- Psychotherapy, life/environmental changes, improved resilience
  - Positive effect more likely to be long lasting, however can take 6-18 months for effect to occur

# Diagnosis and Assessment

# MDD DSM-5 Diagnostic Criteria

- Major depressive episode
  - **Five** of the following on most days within 2 weeks
  - Must have (1) of the top two symptoms
    - Depressed or irritable mood nearly all day occurring most days
    - Anhedonia
    - Substantial weight loss or gain (≥5% of body weight)
    - Insomnia or hypersomnia
    - Fatigue or low energy
    - Poor concentration or ability to think or indecisiveness
    - Feelings of worthlessness or inappropriate guilt
    - Psychomotor agitation or retardation
    - Recurrent thoughts of death or suicide with or without plan

# MDD DSM-5 Diagnostic Criteria

- Major depressive episode, continued
  - Symptoms cause distress or functional impairment
    - Such as social, educational, occupational
  - Symptoms not better explained by
    - Another medical condition
    - Effects of a substance
- Symptoms are not better explained by psychotic disorder
- There has never been a manic or hypomanic episode

# Medical Causes of Depressive Symptoms

- Hypo-, hyper-thyroidsm
- Diabetes mellitus
- Parkinsons (50-75%)
- Epilepsy (30% SA)
- Multiple schlerosis (25-30%)
- Alzheimer's disease
- CAD/CVA/MI/CHF
- HIV/AIDS
- Cancer
- Fibromyalgia/pain disorder
- Rheumatoid arthritis
- Lupus
- Adrenal disorders
- Vitamin/mineral deficiencies
  - B12, B6, B1, folate, D, C, Mg, Zn
- Anemia
- Lyme disease
- Testosterone deficiency
- Wilsons disease
- Others

# Medication Causes of Depressive Symptoms

- **FDA Black Box Warning**
  - Antdepressant class (2004)
    - Includes APs approved for MDD/BPD
  - VMAT2 inhibitors (HD only) (2008)
  - Mefloquine (2013)
  - Montelukast (2020)
- ***Warning Removed***
  - Varenicline
- Other leukotriene Inhibitors
  - Zafirlukast
  - Zileuton
- Antipsychotics
- Benzodiazepines
- Naltrexone
- Antiparkinsonian
- Antiepileptic Drugs
- Oral contraceptives
- H2-blockers
- GLP-1 RA
- Clonidine
- Beta-blockers (propranolol)
- Methyldopa
- Corticosteroids
- Interferon alpha
- Indomethacin
- Analgesics (opioids, tramadol)
- Antineoplastics
- Isotretinoin
- Oseltamavir
- Zanamivir
- Antiretrovirals
- Ciprofloxacin
- Roflumilast

# Patient Assessment

- Evaluate target symptoms of depression
- D SIG E CAPS
  - **D**epressed mood
  - **S**leep: increased or decreased
  - **I**nterest: loss or interest in activities (anhedonia)
  - **G**uilt/feelings of worthlessness
  - **E**nergy: decreased
  - **C**oncentration: decreased
  - **A**ppetite: decreased or increased
  - **P**sychomotor: agitation or retardation
  - **S**uicidal ideation

# Patient Assessment

- Rating Scales
  - Patient rated (PHQ-2, PHQ-9), Clinician rated (QIDS)
- Comorbidities and PMH
- Family and personal psychiatric history
- Medication history
- Laboratory findings
  - TSH
  - CBC (Hb, MCV)
    - B12/Folate (more for the elderly, alcoholism, atypical or vegan diets)
    - Iron
  - Chemistry
    - Calcium (hypo/hyper can cause depression)
    - Sodium (SRIs can induce hyponatremia)
  - Substances: UDS, EtOH, GGT, PEth
  - Vitamin D
- Suicidality

# Differential Diagnosis

- Rule out other psychiatric diagnoses as treatment may be different
  - PTSD
    - Similar medications are indicated though ADs are less effective
    - Hypervigilance and nightmares have different treatments
    - Therapy is different (ie CPT)
  - ADHD
    - Treatment is stimulant
  - OCD
    - May respond to same medications but there are subtle differences in dosing and algorithm slightly different
  - Personality disorders
    - Medication unlikely to help
  - Adjustment disorder
    - Medication unlikely to help
  - Substance abuse
    - Substance abuse treatment, naltrexone, etc
    - ADs not indicated

# Differential Diagnosis

- Bipolar disorder
  - Antidepressants are not indicated and may harm patient
  - Kraeplin described 18 subtypes under manic depressive illness
    - This model of mania and depression on a spectrum predominated until the 1960s
    - Many with MDD have subclinical DSM 5 hypomanic symptoms
      - Up to half may have mixed states
      - Up to a third may have hyperthymic or cyclothymic temperaments
        - Cyclothymia (Type II ½?) may be confused with Borderline PD
        - Hyperthymic temperment with depressive episodes (Type IV?)
      - Psychomotor agitation, anxiety, and anger may be associated with hypomania
      - Up to half of patients with peri-partum depression may have BD
      - Antidepressant use often associated with these symptoms (Type III?)
      - Substance-induced mania (Type III ½?)
    - Treatment is a mood stabilizer

# Differential Diagnosis

- Soft Signs of bipolar disorder
  - Patients often initially present with depression
  - Multiple factors below should raise your suspicion for BD
    - Family hx of BD
    - Thyroid dysfunction
    - Anxiety, irritability, depression on antidepressants
    - Mood symptoms beginning 15-20
    - Post-partum depression (especially psychosis)
    - Psychotic depression
    - Atypical depression
    - Substance use disorder
  - Consider scales
    - Bipolarity index (long) (90% sensitivity, 90% specificity)
    - Rapid mood screener (short) (90% sensitivity, 80% specificity)

# Assessment of Suicide Risk

- Presence of suicidal or homicidal ideation, intent, or plans
- History and seriousness of previous attempts
- Access to means for suicide and the lethality of those means
- Presence of severe anxiety, panic attacks, agitation, and/or impulsivity
- Presence of psychotic symptoms, such as command hallucinations or poor reality testing
- History of psychiatric diagnoses
- Presence of alcohol or other substance use
- Family history of or recent exposure to suicide
- Absence of protective factors

# Treatments

# Treatments

- Lifestyle Recommendations
- Psychotherapy
- Complementary therapies
- Somatic therapies
- Antidepressants

# Lifestyle Recommendations

- Nutrition
  - Mediterranean diet, DASH, low-carb, keto, protein, fiber Fresh veggies and fruits
    - Whole grains, fish, limited meat and dairy
    - Reduce/eliminate ultra-high processed foods
      - Added sugars, omega-6 FAs, trans fat
    - Healthy fats
      - Omega-3 FAs, MUFAs, saturated FAs, (MCTs)
        - sdLDL vs lbLDL
- Physical Activity
  - 30+ minutes cardio per day 5-7 times per week
  - Resistance training 2-3x's/wk (prevent muscle loss)
  - Decrease sedentary behavior

# Lifestyle Recommendations

- Decreased/elimination of toxins
  - Tobacco, alcohol, drugs
  - Trans fats, (fructose)
- Adequate Sleep
- Decreased Stress
- Healthy relationships
- Spending time in nature
- Continue to learn new things (ie reading)
  - Pursuit of hobbies

# Psychotherapy

- Types
  - Cognitive Behavioral Therapy
    - Equally effective as pharmacotherapy for mild-moderate depression
    - Combo with med best for moderate to severe depression
    - Additional 31% of patients recovered when added to antidepressants (STAR*D trial)
  - Interpersonal therapy
  - Group therapy
  - Psychodynamic psychotherapy
- Compared to medications
  - Remission takes longer (up to 12-18 months)
  - Remission more likely to persist after treatment concludes
- Limitations
  - Cost, time investment, patient resistance, limited availability

# Rejoyn® (2024)

- First FDA cleared prescription smartphone therapy app-based digital therpeutic
- Classed as a medical device
- For MDD
- Intended for use in tandem with medication
- 6 week program
- Brain training exercises
- Short skills-based therapy lessons
- >=22 years old
- Phase III trial
  - MADRS 28->19 vs 21 for placebo
  - Not statistically significant
- Will insurance cover?

# Complementary and Somatic Therapies

- Complementary Therapies
  - Vitamins and minerals
  - St. Johns Wort
  - L-methylfolate
  - SAMe
- Somatic Therapies
  - Electroconvulsive therapy (ECT)
  - Phototherapy
  - Vagal nerve stimulation
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Cranial Electrotherapy Stimulator

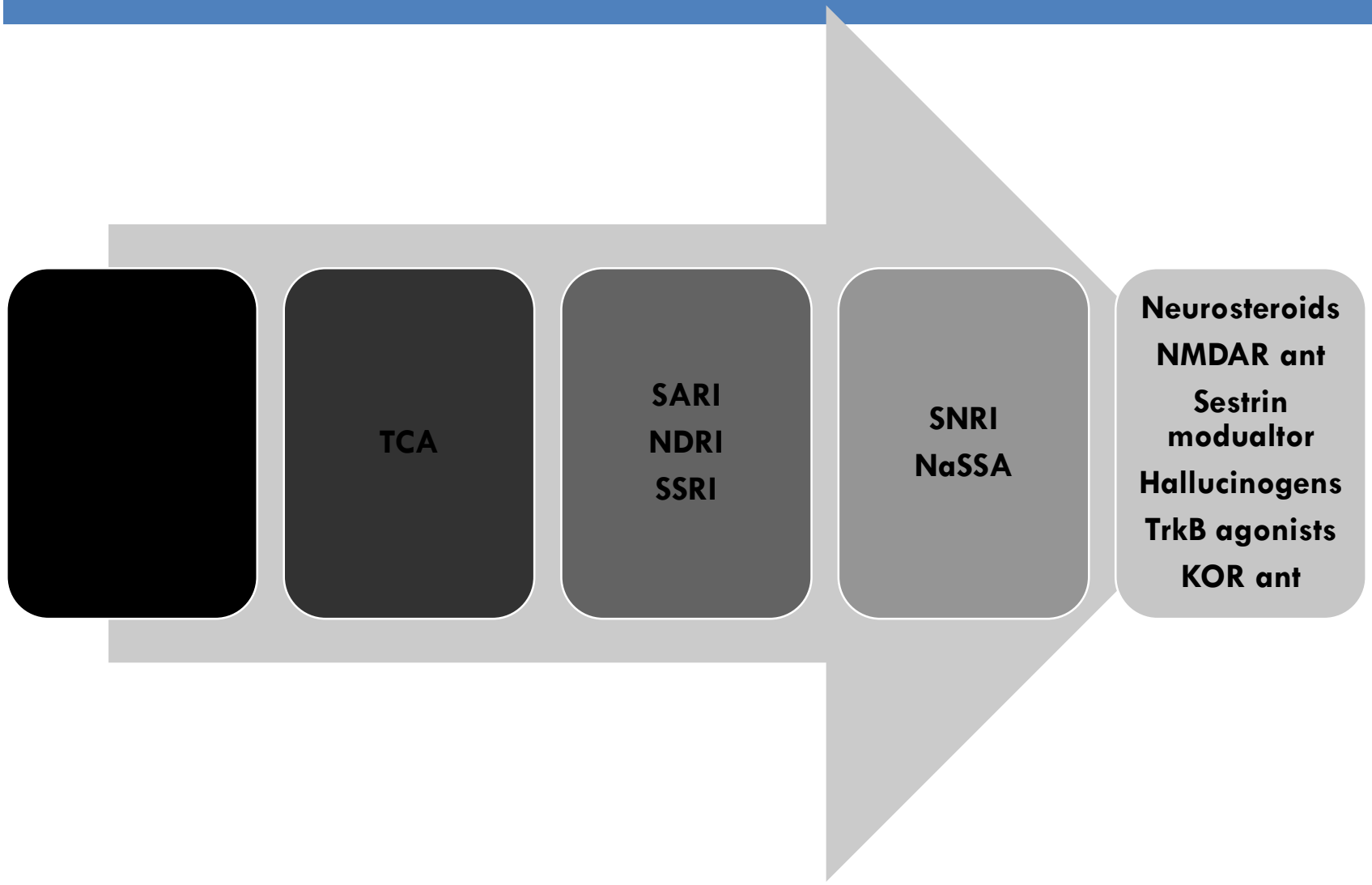
# Antidepressant Medications

# Pharmacologic History of Depression Treatment

- Prior to 1950s: Opioids and amphetamines
- 1950s: Patients thought of as anxious and neurotic
  - Affluent treated with psychoanalysis
  - 10% of Americans were treated with barbiturates
    - Meprobamate (Miltown®) (1955)
      - Less potent/sedating than barbiturates
      - Prodrug of carisprodol
      - First blockbuster psychotropic drug in US hx
      - Widely used and promoted by celebrities
      - Tantrums, stammering, "school headaches"
      - Pregnancy
      - Menstrual cycle
- 1960s: Chlordiazepoxide (Librium®) marketed as safer than barbiturates
  - Many advocated its use as an antidepressant
  - 10% used as well



# Development of Antidepressants



# American Psychiatric Association Practice Guidelines

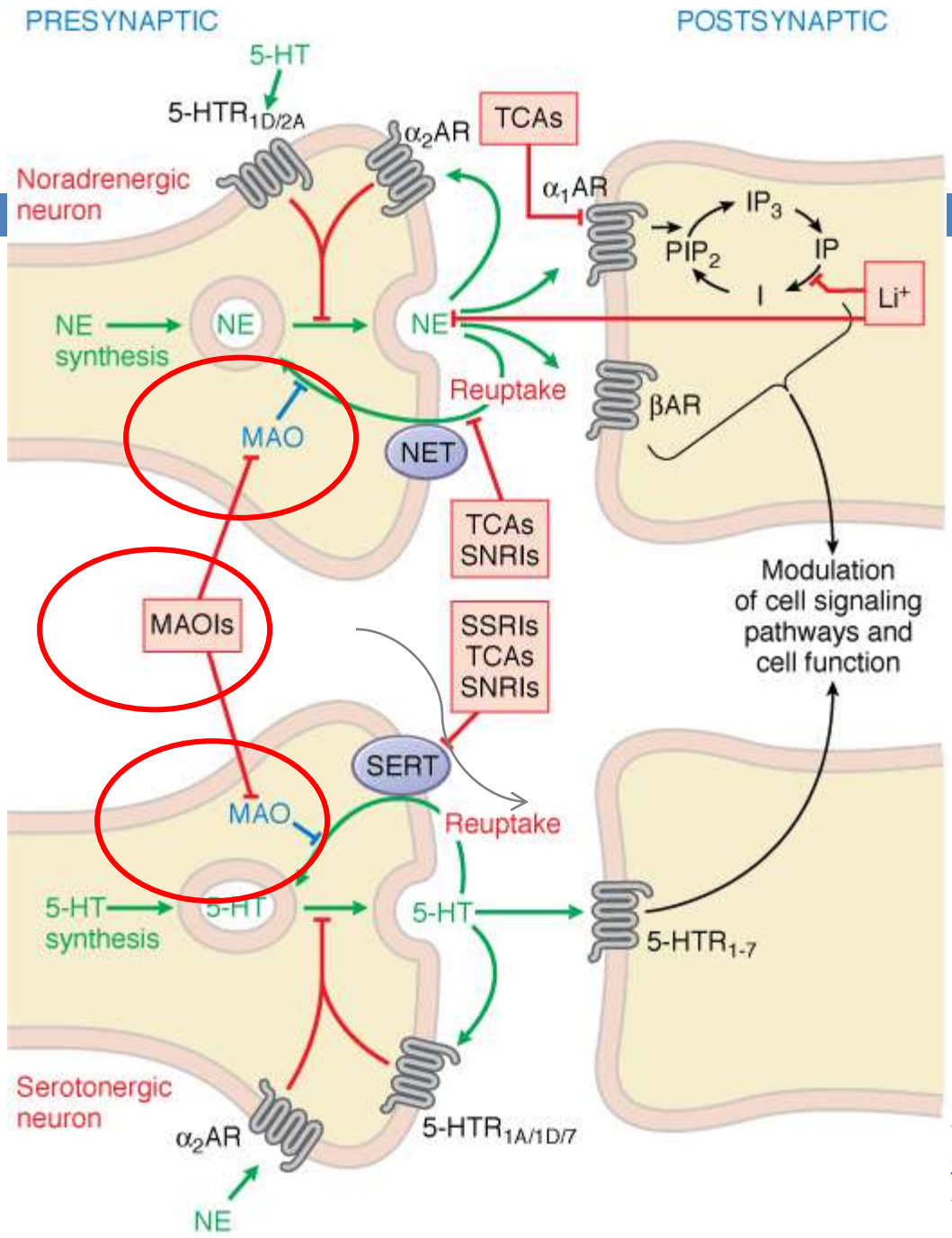
- **Level I Recommendations**
  - SSRIs, SNRIs, bupropion, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are comparable in effectiveness
  - SSRI, SNRIs, mirtazapine and bupropion are optimal for most patients
  - MAOIs and TCAs typically reserved for treatment-resistance

# Antidepressant Mechanism of Action

- Inhibition of MAO
- Blockade of reuptake of monoamines (5-HT, NE, DA)
  - Happens quickly (hours) and can lead to initial anxiety/AEs
    - Inhibition of 5-HT reuptake **raises synaptic 5-HT** levels at dendrites and axon
  - Delayed response (weeks) leads to improved mood/ AEs
    - Increased 5-HT leads to
      - **Autoreceptor downregulation / desensitization**
        - Leads to more release of 5-HT at the axon
      - Post-synaptic receptor downregulation / desensitization
        - Decreased synthesis of receptors
        - Neurogenesis
        - Increased synthesis of BDNF
        - Increase synthesis of various proteins
- Agonism of specific 5-HT receptors

# Mechanism of Action for Antidepressants

**Tyramine (diet)**




Increase in NE
Increase in BP
Also increase 5HT, DA

# Monoamine Oxidase Inhibitors

# Monoamine Oxidase Inhibitors

- Non-selective, irreversible (last 2 weeks after stopping)
  - Iproniazid
    - Originally developed for tuberculosis
    - Antidepressant properties discovered in 1952
    - First monoamine-related antidepressant
    - Withdrawn in most of the world in 1960s due to hepatitis
  - Isocarboxazid (Marplan®) (1959)
  - Phenelzine (Nardil®) (1961)
  - Tranylcypromine (Parnate®) (1961)

# Monoamine Oxidase Inhibitors

- MAO-Ai
  - Moclobemide (reversible, not in US, not as effective)
  - Linezolid (antibiotic)
  - Methylene blue (treatment for methemoglobinemia)
- MAO-Bi
  - Selegiline (Deprenyl® 1989) (EMSAM® 2006)
    - Selective up to 6mg
  - Rasagiline (Azilect®) (2006)
    - Selective up to 1mg
  - Kavalactones

# Mechanism of Action

- MAO-A breaks down
  - Serotonin
  - Norepinephrine
  - Dopamine
  - Melatonin
  - Tyramine
    - Tyramine is converted into octopamine, a false transmitter which causes massive release of NE and may result in hypertensive crisis
- MAO-B breaks down
  - Phenethylamine
  - Benzylamine
  - Dopamine
  - Tyramine (less so)

# Adverse Effects (MAOIs)

- CNS: Sedation/insomnia, headache, disorientation, switch from depression to mania
- CV: **Orthostatic hypotension** (worse with phenylzene), decreased HR, hypertensive crises
  - Effect to prevent the release of norepinephrine from sympathetic nerve endings similar to bretylium
- Endocrine: Anorgasmia/sexual impotence, SIADH
- GI/GU: Dry mouth, constipation, urinary hesitancy, weight gain, diarrhea, dyspepsia
- Selegiline patch specific ADR
  - Application site reaction from glue
    - Can treat with diphenhydramine or lidocaine gel
    - Use of alcohol swab and/or soap and water to remove glue

Schatzberg AF, Cole JO, DeBattista C. Manual of Clinical Psychopharmacology; 1997.

# Hypertensive Crisis

- Nonselective inhibition of MAO enzyme limits dietary restriction of foods containing tyramine
- Definitely Avoid
  - Homemade beer and red wine, aged cheeses, sauerkraut, dry sausage, cured meats, fava or Italian green bean pods, smoked fish, liver, aged soy sauce and soy products, brewer's yeast (vegemite), sourdough bread, pickled/fermented foods
  - While taking and 2 weeks after stopping
- May be problematic
  - Overly ripe avocado/bananas, dried fruits, yogurt, alcohol, caffeine, sour cream, chocolate, peanuts, cream cheese
- Most are safe
  - Unaged, unfermented, unspoiled, pasteurized, fresh products of above
  - Domestic bottled/canned beer, white wine, spirits at 1 standard drink
- Combination may lead to hypertensive crises → severe HA, CVA
- Treat with IV phentolamine or chlorpromazine (alpha blocker)

# Drug Interactions

- Serotonin syndrome may occur with combining certain medications with MAOI
  - Due to ↑ central 5-HT activity by either concomitant meds or conditions
  - Meperidine (Demerol®), epinephrine (often given during surgery), other MAOi, ketamine, dextromethorphan, SRI, TCAs (amitriptyline, imipramine, clomipramine), brompheniramine, chlorpheniramine, SAMe, l-tryptophan, St. John's Wort, cocaine, MDMA, LSD, ziprasidone, lumateperone
  - Will discuss in more detail later with SSRIs
- For EMSAM® only
  - Carbamazepine → increased level of drug and metabolite found
  - All interactions with other MAOIs as well as cyclobenzaprine, tramadol, methadone, propoxyphene, oxcarbazepine

# Contraindications (all MAOIs)

- Pheochromocytoma
- Hepatic or renal dysfunction
- Cerebrovascular defect
- Cardiovascular disease
- Patients undergoing elective surgery (should not be)
- Concomitant sympathomimetic (epinephrine) therapy
- Do not use within 5 ½-lives of SRI (~1-2 weeks)
  - 3 weeks of discontinuing vortioxetine (32 days for BMI >=35)
  - 5 weeks of discontinuing fluoxetine
  - Can bridge with
    - Stimulant, benzo, trazodone, mirtazepine
    - Atypical antipsychotic other than ziprasidone or lumateperone
- Do not use SRI within 2 wks of stopping MAOi
  - Due to time needed for mitochondria turnover

# MAOI Summary

## Advantages

- Inexpensive
- Treatment-resistant depression
- Atypical depression
- Social anxiety disorder
- Panic disorder
- Anxious distress
- Patch may be preferable for some

## Disadvantages

- Drug-food, drug-drug interactions
- Side effects
- Contraindications
- Generally reserved as last line
- Difficult to switch between different antidepressants
- Selegiline patch
  - Dietary advantage (6mg dose only) likely isn't effective for treatment resistance

# MAOi FDA Indications

| Medication | MDD | Parkinson's Disease |
|---|---|---|
| Isocarboxazid | ✓ | |
| Phenelzine | ✓ | |
| Tranylcypromine | ✓ | |
| Selegiline | ✓ | ✓ |
| Rasagiline | | ✓ |

# Isocarboxazid (Marplan®) (1959)

- **Less activating** than other MAOIs
- Less studied than other MAOi's so less information on comparable efficacy
- Monitor **LFTs**
- Dosing
  - Start with 10 mg test dose on the first day
  - Increase to 10 mg TID over the first week
  - Then add 10 mg weekly until limited by side effects or reach max dose of 50 mg daily

# Phenelzine (Nardil®) (1961)

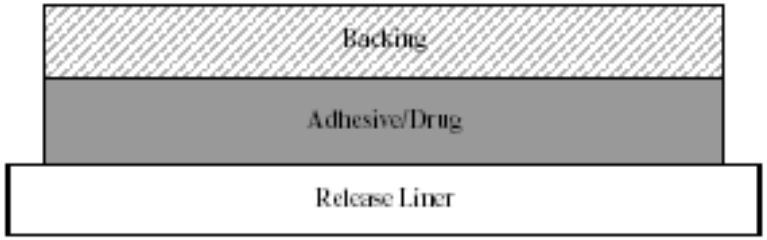
- Most often used MAOi
- Also a GABA transaminase inhibitor
  - Good for panic, anxious distress
  - Twice as effective for social anxiety as SSRIs
  - Sedating
- Can use with amoxapine if started simultaneously
- Most **anticholinergic** and **sedating** of the MAOIs
- Most weight gain, hypotension, and sexual dysfunction
- Can cause B6 deficiency
- Monitor **LFTs**
- Dosing
  - Give a test dose of 15 mg the first day
  - Then increase to 15 mg TID over the first week
  - Then add 15 mg weekly till you are limited by side effects or reach max dose of 90 mg

# Tranylcypromine (Parnate®) (1961)

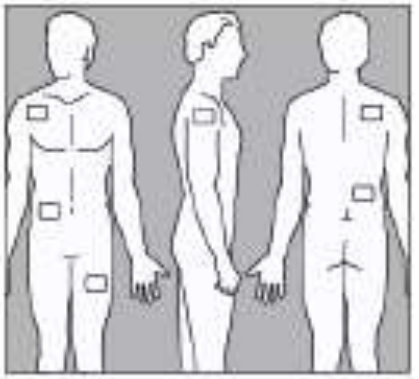
- May have faster onset of action
- **Most activating** MAOI with more insomnia—can tx with Trazodone
  - Has amphetamine properties (dopaminergic) at higher doses
    - UDS will be positive for amphetamines
  - Activating
  - Melancholic/apathetic depression
- Better tolerated than phenelzine and equally effective
- Positive reports for its use in **bipolar depression**
- Dosing
  - Start with 10 mg test dose on the first day
  - Increase to 10 mg TID over the first week
  - Then add 10 mg weekly until limited by side effects or reach max dose of 40-60 mg daily

# Selegiline (EMSAM®)

- Matrix-type transdermal system with 3 layers (backing, adhesive/drug, release liners)
- 1mg per $cm^2$ delivers ~0.3mg of selegiline per $cm^2$ over 24 hours
- No studies for treatment-resistance for the patch (only oral)
- Available in 20mg/20$cm^2$, 30mg/30$cm^2$, 40mg/40$cm^2$
  - Deliver on average of 6, 9, 12mg over 24 hours, respectively

# Selegiline (EMSAM®)



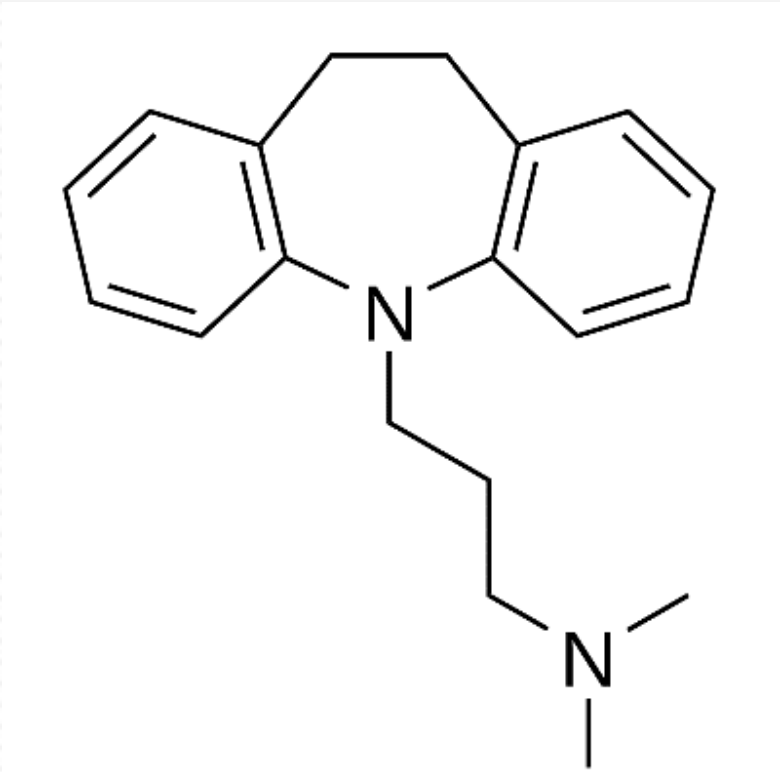
- Application of EMSAM
  - Apply to dry intact skin on upper torso (below neck, above waist), upper thigh or outer surface of upper arm
  - Alternate application site
  - Do not touch sticky side, med can come off
  - External heat sources may result in ↑ drug absorption
    - Saunas, heating pads, prolonged sunlight, etc.
- No dose adjustment for hepatic or renal dysfunction
- Dietary Modifications
  - Modified diet required for 9mg and 12mg doses (and for at least 2 weeks after discontinuation of higher dose or reduction to 6mg dose)
    - Effect still likely less than with oral selegiline
  - 6mg dose likely no more effective than other antidepressants
  - Medication restriction required at all doses
- Activating
- UDS will be positive for amphetamines

# Neuroreceptors

| Site of Action | Consequences of Blockade |
|---|---|
| Histamine-1 (H1) | Sedation, antipruritic/allergic effect, weight gain, hypotension |
| Muscarinic acetylcholine (mACH) | Dry mouth, blurry vision, constipation, urinary retention, sinus tachycardia, memory impairment, sedation; anti-EPS, but worsens TD |
| Norepinephrine transporter (NET) | Antidepressant efficacy, increased blood pressure, tremors, diaphoresis |
| Serotonin transporter (SERT) | Antidepressant efficacy, nausea, loose stools, insomnia, anorgasmia |
| Dopamine transporter (DAT) | Attention, appetite, mood, addiction |
| 5-HT1A | Anxiety (busprione is an agonist), memory, learning, depression, anti-analgesia, aggression |
| 5-HT1B | Cerebral arteries dilate (triptans are agonists), aggression, bone mass |
| 5-HT1D | Cerebral arteries dilate (triptans are agonists) |
| 5-HT1E | Unknown |
| 5-HT1F | Migraines (lasmiditan is an agonist) |
| 5-HT2A | Depression (dcr by agonist and antag), REM sleep, anti-anxiety, anti-EPS, anti-neg sx of schizo, sleep (trazodone), Agonist: Improve sexual SEs (mirtazepine), psycheldelia (LSD) |
| 5-HT2B | Cerebral arteries dilate |
| 5-HT2C (was 5-HT1C) | Anxiety, mood (agonist and antag), sleep, appetite (AAPs, mirtazepine), penile erection, sexual behavior (mirtazapine), decreased motor restlessness |
| 5-HT3 | Anti-nausea (ondansetron), counter the activity of excessive dopamine, (GI side effects from SSRI due to increased serotonin action here) |
| 5-HT4 | anti-GI Motility (cisapride is an agonist), anti-memory/learning, depression |

| Site of Action | Consequences of Blockade |
|---|---|
| 5-HT5A | Memory consolidation |
| 5-HT5B | Functions in rodents, pseudogene in humans |
| 5-HT6 | Mood (agonist and antag), anxiety, cognition |
| 5-HT7 | Mood, anxiety, cognition (vortioxetine, lurasidone) |
| $\alpha 1^{A,B,D}$ adrenoceptor | Orthostatic hypotension, sedation, dizziness, tachycardia, priapism, GI upset, blurred vision, sexual/ejaculation dysfunction, nasal congestion (ie –zosins, trazodone, TCAs) |
| $\alpha 2^{A,B,C}$ adrenoceptor | Antidepressant efficacy, arousal, increased libido, anxiety, tachycardia, dilated pupils, tremor, sweating; Agonist: hypotension, sedation (clonidine, tizanidine) |
| β1 adrenoceptor | Bradycardia, Hypotension (ie -lol drugs), mostly in heart and kidneys |
| β2 adrenoceptor | Smooth muscle relaxation throughout autonomic nervous system |
| β3 adrenoceptor | Relaxation of the bladder (-begron drugs are agonists) |
| GABA-A | Agonist: sedation, anxiolytic, anticonvulsant, muscle relaxant (ie benzos, alcohol, z-drugs) |
| GABA-B | Agonist: sedation, anxiolytic, anticonvulsant, muscle relaxant (ie baclofen, GHB, phenibut) |
| Glutamate | AMPA (EtOH, barbiturates), NMDA (ketamine, DXM, PCP), mGLUr, KAR. Agonist: excitatory |
| Sodium fast channels | Delayed repolarization leading to arrhythmias, seizures, delirium (TCAs) |
| D1 | Memory, learning, addiction |
| D2 | Positive symptoms of schizophrenia improvement, EPS, prolactin elevation |
| D3 | Psychosis, movement |
| D4 | Psychosis, movement |

# Tricyclic Antidepressants



# Tricyclic Antidepressants (TCAs)

- Discovered through exploration for H1 antagonists
- Chlorpromazine discovered through this search and approved in 1954
- Imipramine the first antidepressant discovered through this research
- Tricyclic
  - Tertiary amines (Nitrogen with 3 alkyl groups attached)
    - Imipramine (Tofranil®) (1959)
    - Amitriptyline (Elavil®) (1961)
    - Doxepin (Sinequan®) (1969): Amitriptyline with an oxide in the central ring dep
    - Trimipramine (Surmontil®) (1979): Imipramine with extra methyl group
    - Clomipramine (Anafranil®) (1990): Imipramine with a chloride group
    - *Cyclobenzaprine (Flexeril®) (1977): very similar structure to amitriptyline but not a TCA
  - Secondary amines (Nitrogen with 2 alkyl groups attached)
    - Desipramine (Norpramin®) (1963): Imipramine metabolite (demethylated)
    - Nortriptyline (Pamelor®) (1964): Amitriptyline metabolite (demethylated)
    - Protriptyline (Vivactil®) (1966): Nortriptyline with single vice double bond
- Tetracyclic
  - Maprotiline (Ludiomil®) (1974)
  - Amoxapine (Asendin®) (1992)

# TCA FDA Indications

| Medication | Depression | Anxiety | Enuresis (Peds) | OCD | Pruritis | Insomnia | Bipolar Disorder (Depression) |
|---|---|---|---|---|---|---|---|
| Imipramine | ✓ | | ✓ | | | | |
| Amitriptyline | ✓ | | | | | | |
| Doxepin | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| Trimipramine | ✓ | | | | | | |
| Clomipramine | | | | ✓ | | | |
| Desipramine | ✓ | | | | | | |
| Nortriptyline | ✓ | | | | | | |
| Protriptyline | ✓ | | | | | | |
| Maprotiline | ✓* | | | | | | |
| Amoxepine | ✓ | | | | | | |

*No longer available in the US

# TCA off-label uses

- Neuropathic pain
- IBS pain
- Functional dyspepsia
- Chronic fatigue syndrome insomnia/pain
- Cyclic vomiting syndrome
- Fibromyalgia
- Migraines/tension headaches
- Postherpetic neuralgia
- Sialorrhea
- ADHD
- Diabetic neuropathy
- Insomnia

# TCAs and Receptors

- SERT: improved mood/anxiety, adverse sexual effects
  - Tertiary amines are stronger except Doxepin and Trimipramine
- NET: help with pain, concentration
  - Secondary amines are stronger
- 5-HT2A: sedation
  - Tertiary amines except imipramine
- 5-HT2C: weight gain
  - Amitriptyline, nortriptyline, amoxapine
- α-1: orthostasis
  - Tertiary amines are stronger
- H1: weight, sedation
  - Most except desipramine
- mACh: hot as a hare, red as a beet, blind as a bat, dry as a bone, mad as a hatter, full as a flask
  - Secondary amines and tetracyclic are less except for protriptyline
- Sodium fast channels: delayed repolarization leading to arrhythmias, seizures, delirium
- Half-life
  - Protriptyline is very long (54-92 hrs)

# Receptor Binding Affinity (Ki): TCAs

| TCA | SERT | NET | 5-$HT_{2A}$ | 5-$HT_{2C}$ | $\alpha_{1B}$ | $D_2$ | $H_1$ | $M_1$ |
|---|---|---|---|---|---|---|---|---|
| Imipramine | **1.4** | 37 | 115 | 120 | 61 | 1310 | 24 | 68 |
| Amitriptyline | **4.3** | 35 | **24** | **4** | **26** | 1230 | **1.03** | **13.8** |
| Doxepin | 68 | **29.5** | **26** | 200 | **24** | 1380 | **0.21** | 52 |
| Trimipramine | 149 | 2450 | **32** | | **24** | 180 | **0.27** | 58 |
| Clomipramine | **0.28** | **38** | **27** | 64 | **38** | 190 | **31** | **37** |
| Desipramine | 17.6 | **0.83** | 315 | 244 | 115 | 3400 | 85 | 132 |
| Nortriptyline | 18 | **4.37** | 43 | **8.5** | 58 | 1885 | **8.2** | 94 |
| Protriptyline | 19.6 | **1.41** | 70 | | 130 | 2300 | **25** | **25** |
| Maprotiline | 5800 | **11** | 51 | 122 | 90 | 500 | **1-2** | 570 |
| Amoxapine | 58 | **16** | **0.5** | **2** | 50 | **4** | **7.9** | 1000 |

# Adverse Effects (TCAs)

- Side effects common with all TCAs
  - Sedation, anticholinergic symptoms, orthostasis, sexual dysfunction, weight gain, lower seizure threshold, switch to mania
  - Cardiovascular toxicity
    - Orthostatic hypotension, tachycardia, bundle branch block and other arrhythmias
    - Patients with preexisting AV block may be treated with SSRI or bupropion
- More adverse effects with tertiary TCAs than secondary TCAs

# Adverse Effects (Anticholinergic)

- Hot as a hare (hyperthermia)
- Red as a beet (cutaneous vasodilation)
- Blind as a bat
  - Relaxation of the ciliary muscles
    - Blurry vision, loss of accomodation (falls, car accidents, difficulty reading)
  - Relaxation of the iridocorneal angle
    - Acute angle closure glaucoma (avoid in narrow angle glaucoma)
- Dry as a Bone
  - Xerostomia
    - Dental problems (tooth decay, gum inflammation, halitosis)
  - Xerophthalmia
  - Decreased mucus in the lungs (clogged airways, worsened asthma)
  - Anhidrosis (overheating)

# Adverse Effects (Anticholinergic)

- Mad as a hatter (confusion, restlessness, delirium, hallucinations)
- Full as a flask (urinary retention)
  - UTI
  - Renal/bladder damage
- And the heart runs alone
  - Tachycardia
  - Decreased/absent bowel sounds
    - Constipation (bowel obstruction, paralytic ileus)

# Dangers of TCA Overdose

- Delayed repolarization of sodium fast channels cause cardiac and neurologic effects
- Cardiovascular
  - Conduction abnormalities (↑ PR, QRS widening, ↑ QTc, AV block, torsades de pointes, ventricular tachycardia)
  - Hypotension
- Neurologic
  - MS changes, lethargy, confusion, coma, seizures
- Respiratory depression, anticholinergic effects, rhabdomyolysis, renal failure
- Not preferable in suicidal patients
- Dose >1000mg/day is toxic; dose >2000mg/day is lethal
- Get blood levels
- Decrease dose in elderly and avoid tertiary amines

# Blood levels

- Check 8-12 hours after last dose, wait five ½-lives
- Toxic: 500ng/mL
- Linear therapeutic window
  - Imipramine: 150-300ng/mL
  - Amitriptyline: 100-250ng/mL
  - Desipramine: 150-300ng/mL
  - Doxepin: 120-250ng/mL
  - Clomipramine: 220-500ng/mL
  - Trimipramine: 150-300ng/mL
  - Protriptyline: 150-500ng/mL
- Inverted U-shaped therapeutic window
  - Nortriptyline: 50-150ng/mL (depression worse outside of this)

# Drug-Drug Interactions

- Pharmacokinetic Interaction
  - CYP2D6 inhibitors
    - Can affect all TCAs
  - CYP1A2, CYP2C19 inhibitors
    - May inhibit metabolism of tertiary amines
- Pharmacodynamic
  - Serotonin syndrome
    - Caution with other serotonergic agents, MAOIs
  - Additive effects with other agents
    - Anticholinergic agents
    - Hypotensive agents
    - Sedating agents

# Contraindications

- Cardiac
  - Recovering from an MI
  - QTc prolongators/Hx of QTc prolongation
  - Cardiac arrhythmias
  - Uncompensated heart failure
  - Pheochromocytoma
  - Cisapride
- Metabolism
  - 2D6 inhibitors/reduced function/poor metabolizers
  - Within 2 weeks before or after MAOi
- Seizure disorders

# Caution

- Anticholinergic sensitivity
- With drugs that cause bradycardia
- With hypokalemia, hypomagnesemia, or drugs that cause
  - Diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids
- Bone marrow suppression
- Orthostatic hypotension
- CV disease
- Diabetes
- Hepatic/renal impairment
- Mania
- Prior to surgery
- Risk of seizure
  - Head trauma, CNS abnormalities, alcoholism

# TCA Indications

- Melancholic depression (details at the end)
- Antidepressant Augmentation (nortriptyline is best)
  - Start low and go slow, particularly because some SSRIs raise TCA levels through 2D6 inhibition
- Preventing depression after ECT
  - Nortriptyline + $Li^+$ is recommended
- Chronic pain (particularly amitriptyline)
  - Headache, neuropathic pain, fibromyalgia, migraine, neck pain, lumbago
- Depression with IBS (particularly amitriptyline and imipramine)
  - May be more effective than SSRIs
- OCD (only clomipramine)
  - Slightly more effective than SSRIs
- Insomnia
- Treatment-resistant depression
  - Probably not better than newer antidepressants
  - Older studies with TCAs used sicker patients

# TCA Summary

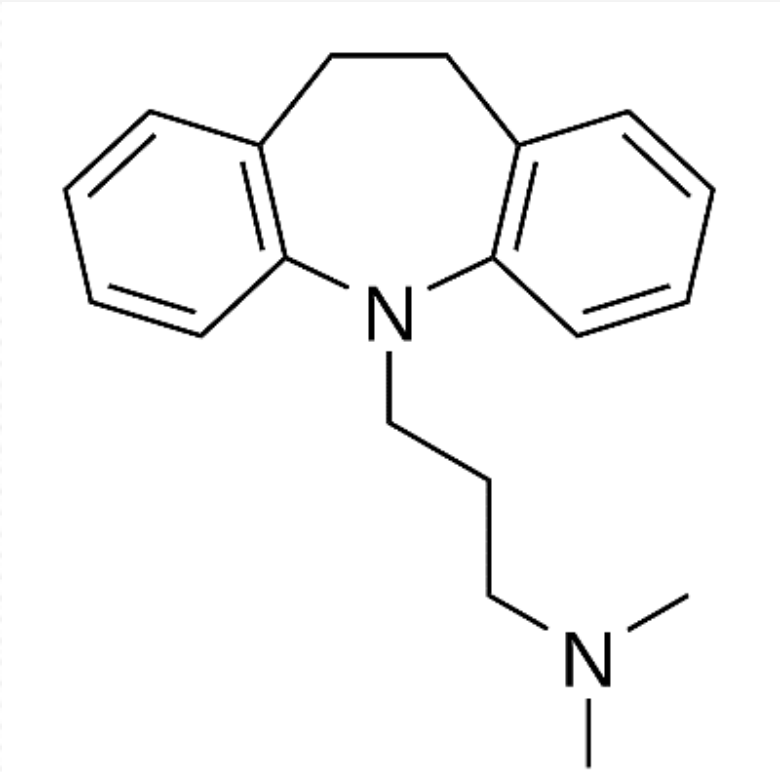
## Advantages

- Inexpensive
- Long history of use
- Therapeutic blood levels can be measured
- Insomnia
- Neuropathic pain

## Disadvantages

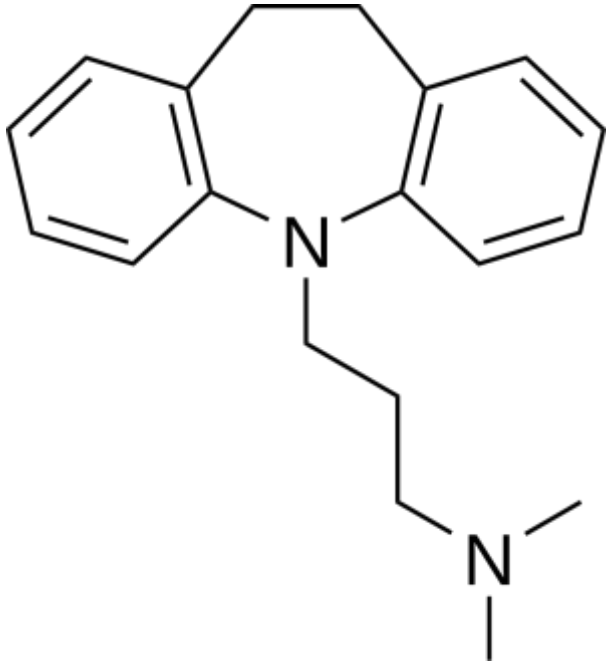
- Very lethal in overdose
- Cardiac toxicity
- Lower seizure threshold
- Many adverse effects
- Caution in BPH, glaucoma, elderly, concomitant medications
- Children and Elderly
- Weight gain
- 7% of population has reduced activity of 2D6 making TCA a poor choice
- Do not mix with 2D6 inhibitor
- Anticholinergic effects
- Avoid concurrent with ECT

# Tertiary Amines



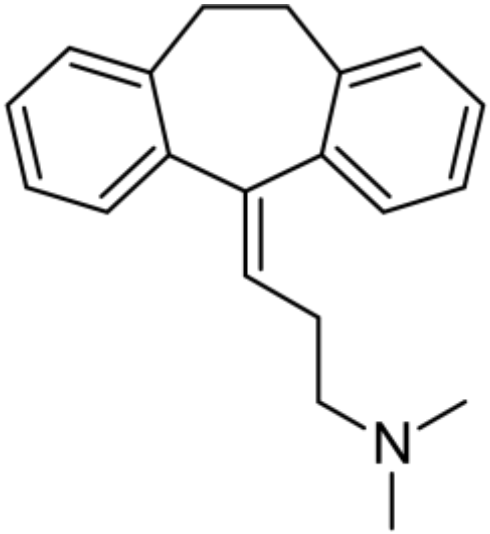
# Imipramine (Tofranil) (1959®)

- A search for new H1 blockers was undertaken
  - Chlorpromazine was discovered and then found to have calming properties
  - Imipramine was later discovered and found to have antidepressant properties
- Etymology: imi(de)+pr(opyl)amine
  - Basically it contains an N linked to another N by a propyl group
- Currently FDA approved for
  - MDD
  - Pediatrics
    - Depression
    - Enuresis
- Used off label for
  - Functional dyspepsia
  - IBS-associated pain
  - Chronic neuropathic pain
  - ADHD



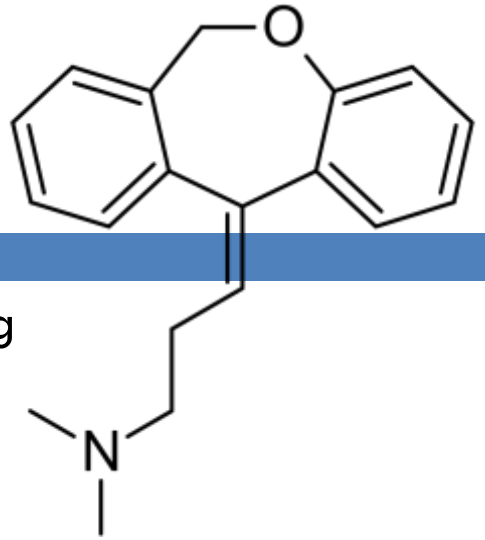
# Amitriptyline (Elavil®) (1961)

- Most anticholinergic of the TCAs
- Differs chemically from imipramine by one less N
- Etymology: ami(no)+tri+(he)ptyl+ine
  - Basically there's an N, 3 rings, and a heptane ring
- Approved for MDD
- Used off label for several conditions
  - Pain syndromes / neuropathic pain
  - GI discomfort syndromes
  - Headaches
  - Insomnia
  - Sialorrhea




- Combined formulation with chlordiazepoxide (Limbitrol®) (1977)
  - Withdrawn from the market in 2023 but generic my still be available
  - Approved for depression and anxiety
- Combined formulation with perphenazine (Triavil®) (1970)
  - Approved for depression and anxiety AND schizophrenia with depression

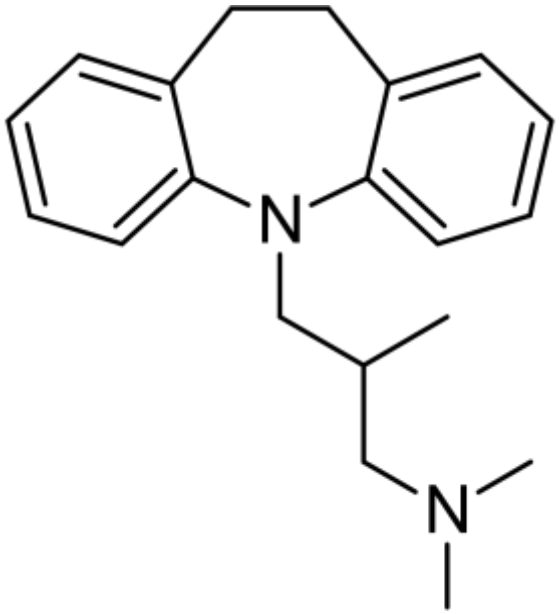
# Doxepin (Sinequan®) (1969)




- Sturcture resembles amitriptyline with an O in the middle ring
- Etymology: -oxepin is the center ring with the O
  - "D" may refer to di- (the other 2 rings)
- Approved for
  - MDD
  - Anxiety
  - Bipolar disorder, depressive episode (though not recommended)
  - Insomnia (Silenor®) (2010)
    - Dosed only at 3-6mg QHS versus lowest dose of doxepin of 10mg
    - To save money one can give 10mg dose of doxepin
    - Though doxepin comes in a capsule it may be possible to empty half out if 3-6mg dose is desired
    - Branded Silenor® is around $22/pill
    - Generic Silenor® is around $4-17/pill
    - Generic doxepin is around $0.30-0.70/pill
  - Pruritis (Prudoxin®, Zonalon®)
    - Up to 8 days of atopic dermatitis or lichen simplex chronicus
- Increases Ramelteon by 66%

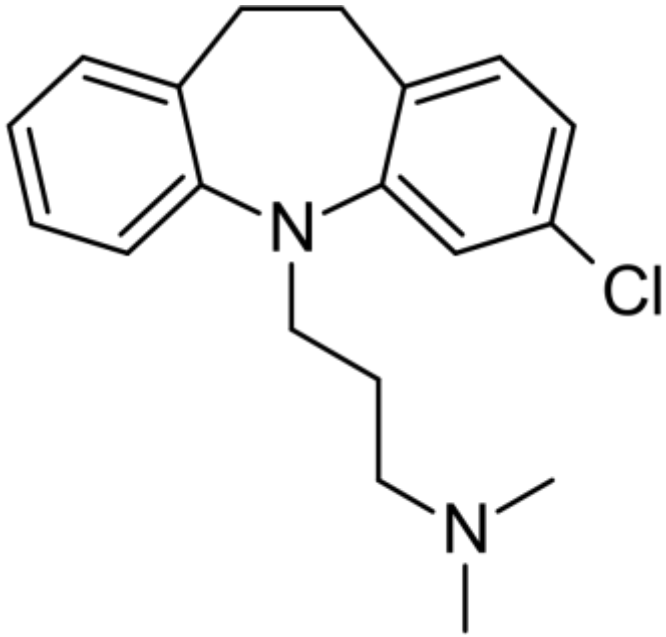
# Trimipramine (Surmontil®) (1979)

- Etymology: tri+(i)mipramine
  - Similar to imipramine with a 3rd methyl group (tri-)
- Approved for
  - MDD
- Relatively weak at SERT and NET making it an atypical antidepressant
- Relatively stronger at receptors that cause adverse effects
  - One of the worse agents for QTc prolongation
- Rarely used

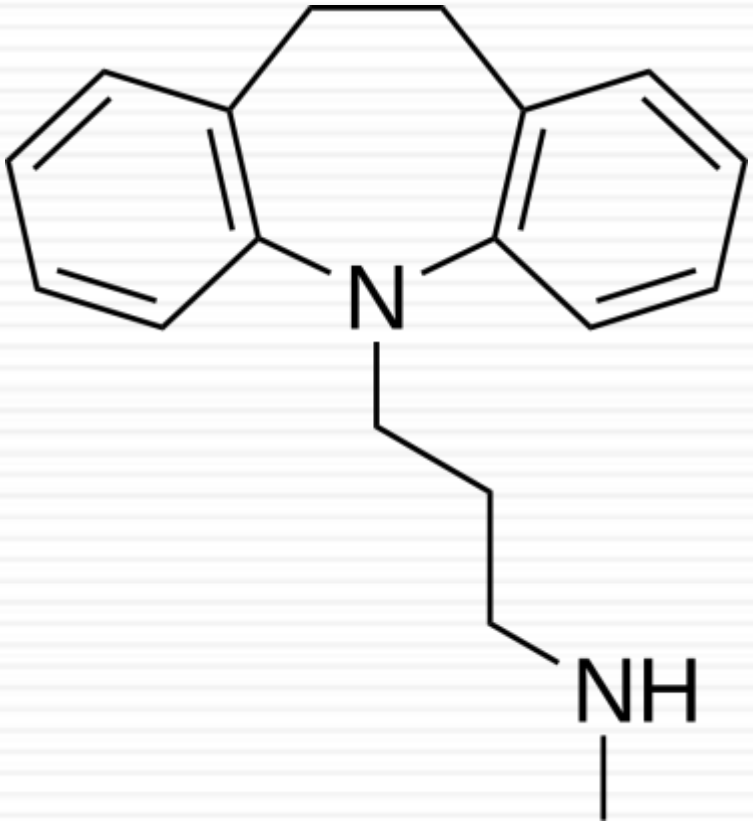


# Clomipramine (Anafranil®) (1990)

- Resembles imipramine with a chloride group
  - Etymology: C(h)lo(r)+(i)mipramine
- Most serotonergic
  - Combining with 1A2 inhibitor like fluvoxamine gives more of this effect
    - Proceed with extreme caution
- Metabolite is noradrenergic (2/3 activity)
  - Norclomipramine
- Only FDA approved for OCD
- Used off label for MDD and panic disorder
- One of the worse agents for QTc prolongation

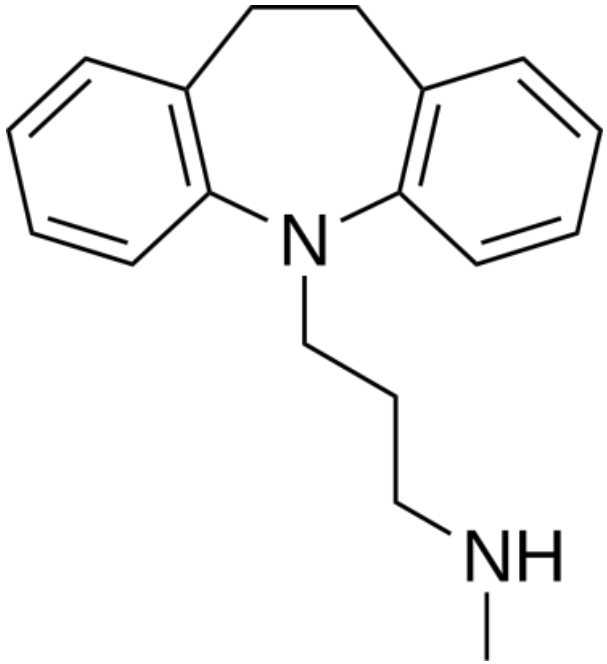


# Secondary Amines



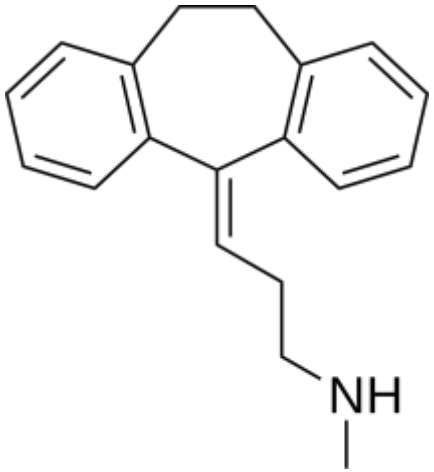
# Desipramine (Norpramin®) (1963)

- Metabolite of imipramine
  - Amine has been demethylated turning it into a secondary amine
  - Etymology: des(methyl)+(im)ipramine
- Approved for MDD
- Off label for neuropathic pain syndromes
- Least of many adverse effects of TCAs
  - Orthostasis
  - Sedation
  - Weight gain
  - ASEs
  - Anticholinergic effects



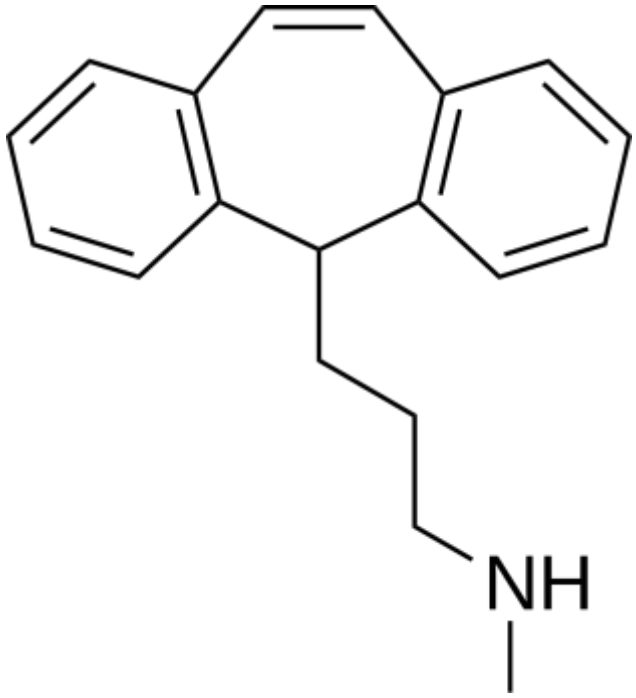
# Nortriptyline (Pamelor®) (1964)

- Metabolite of amitriptyline
  - Amine has been demethylated turning it into a secondary amine
  - Etymology: nor+(ami)triptyline
    - In the case "nor" means normal or the state where the amine is completely demethylated, however the term is also used for a single demethylation as in this case
- Approved for MDD
- Used off label for neuropathic pain syndromes, headaches, and smoking cessation
- Less when compared to tertiary amines
  - Orthostasis
  - Sedation
  - Anticholinergic effects

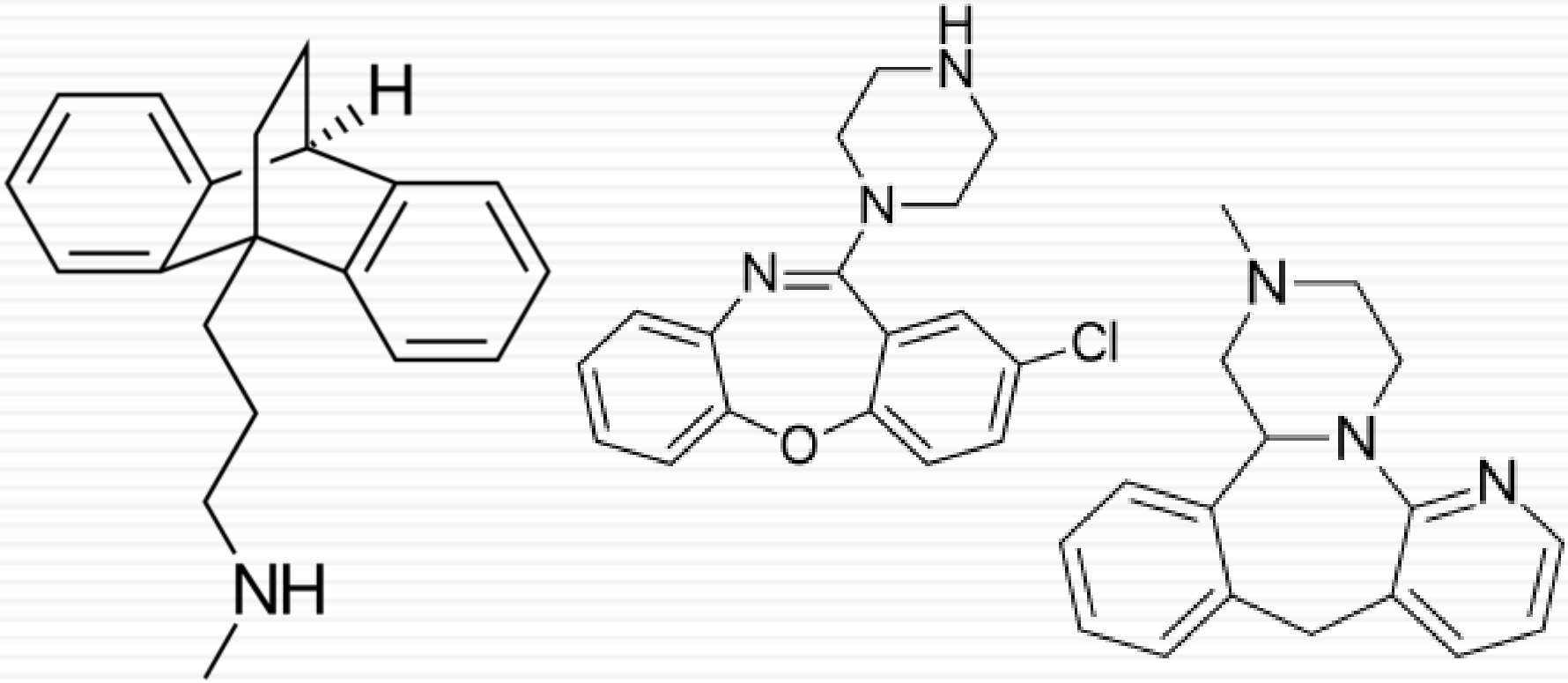


# Protriptyline (Vivactil®) (1966)

- Similar to nortriptyline with double bond moving positions
- Etymology: pro(pyl)+tri+(he)ptyl+ine
  - Has a propyl amine hanging off of the heptyl ring
- More rapid response
- Longer half life (54-92 hrs)
- Most anticholinergic of the secondary amines
- Rarely used



# Tetracyclic Antidepressants



# Tetracyclic Antidepressants

- Maprotiline (Ludiomil®) (1974)
  - Not available in the US since 2021
  - Reports not promising for benefit over other available agents


- Amoxapine (Asenden®) (1992)
  - Metabolite of loxapine
    - Despite being a metabolite of an FGA, it actually has significant 5HT2C blockade similar to an SGA
  - Appoved for MDD
  - Could consider for MDD with psychotic features due to D2 blockade
  - D2 blockade risk factors: EPS, NMS risk
- Mirtazepine (Remeron®)
  - May be considered to be tetracyclic
  - Will review later where it is classed as an atypical antidepressant
    - Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)
- Others with tetracyclic ring structures
  - Mianserin (Tolvon®), Quetiapine, Loxapine

# Receptor Selective ADs

| Medication | MDD | GAD | SAD | OCD | PD | BN | PMDD | BD | PTSD | VMSM | SAD[2] | SC | Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fluoxetine | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | |
| Sertraline | ✓ | | ✓ | ✓ | ✓ | | ✓ | | ✓ | | | | |
| Paroxetine | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | | | |
| Paroxetine CR | ✓ | | ✓ | | ✓ | | ✓ | | | | | | |
| Fluvoxamine | | | | ✓ | | | | | | | | | |
| Citalopram | ✓ | | | | | | | | | | | | |
| Escitalopram | ✓ | ✓ | ✓ | | | | | | | | | | |
| Vilazodone | ✓ | | | | | | | | | | | | |
| Vortioxetine | ✓ | | | | | | | | | | | | |
| Trazodone | ✓ | | | | | | | | | | | | |
| Nefazodone | ✓ | | | | | | | | | | | | |
| Mirtazapine | ✓ | | | | | | | | | | | | |
| Venlafaxine | ✓ | ✓ | ✓ | | ✓ | | | | | | | | |
| Duloxetine | ✓ | ✓ | | | | | | | | | | | ✓* |
| Desvenlafaxine | ✓ | | | | | | | | | | | | |
| Milnacipran | | | | | | | | | | | | | ✓** |
| Levomilnacipran | ✓ | | | | | | | | | | | | |
| Gepirone | ✓ | | | | | | | | | | | | |
| Bupropion | ✓ | | | | | | | | | | ✓ | ✓ | |

MDD=major depressive disorder, GAD=generalized anxiety disorder, SAD=social anxiety disorder, OCD=obsessive-compulsive disorder, PD=panic disorder, BN=bulimia nervosa, PMDD=post-menstrual dysphoric disorder, BD=bipolar depression with a mood stabilizer, PTSD= post-traumatic stress disorder, VMSM=vasomotor symptoms of menopause, $SAD^2$=seasonal affective disorder, SC=smoking cessation

*Fibromyalgia, chronic musculoskeletal pain, neuropathic pain associated with DM, **Fibromyalgia

# Antidepressant off-label uses

- SSRI-induced sexual dysfunction (Bupropion)
- ADHD (Bupropion)
- Chemotherapy-induced peripheral neuropathy (Duloxetine)
- Stress urinary incontinence (Duloxetine)
- Migraine prevention (Venlafaxine)
- Tension headache prevention (Mirtazapine)
- Insomnia (Trazodone, Mirtazapine)
- Binge eating disorder
- Body dysmorphic disorder
- Premature ejaculation (Paroxetine and fluoxetine most used)
- Personality Disorders (SSRIs, SNRIs, NDRI, Mood Stabilizer, AP)
- Inflammation associated with COVID (Fluvoxemine through σ1 agonism)

# QTc Prolongation

# QTc Prolongation

- Measure of ventricular depolarization and repolarization
- Normal
  - Males: <450 ms
  - Females: <460 ms
- Change of QTc from baseline
  - <10 ms: Low concern
  - 10-20 ms: Increasing concern
  - >20 ms: Definite concern
- High risk features on EKG
  - Torsades de pointes
  - Ventricular ectopy
  - T-wave Alternans
  - AV Block
  - Widened QRS

# QTc Prolongation (Risk factors for TdP)

- Non-modifiable
  - Congenital long QT syndromes
  - Elderly (>65 yo)
  - Family hx of sudden cardiac death (<50 yo)
  - Female sex
  - History of arrhythmias
  - Myocardial infarction
  - Structural brain disease
- Drug induced
  - Anti-arrhythmics
  - Antibiotics
  - Antidepressants
  - Antipsychotics
  - Methadone
- Possibly Modifiable
  - Bradycardia (pulse <50 bpm)
  - Electrolyte Disorders
    - Hypokalcemia
    - Hypomagnesemia
    - Hypocalcemia
  - Eating disorders
  - Heart failure
  - Hypoglycemia
  - Hypertension
  - Hypothyroidism
  - Drug interactions that increase levels
  - Acute hepatic failure
  - Alcohol Use
  - Myocardial ischemia

# QTc Prolongation (Medications)

- High risk
  - Anti-arrhythmics
  - Antibiotics
  - Antidepressants
    - TCAs/TeCAs
    - Citalopram
    - Gepirone ER
  - Antipsychotics
    - Perphenazine
    - Chlorpromazine
    - Mesoridazine
    - Thioridazine
    - Pimozide
    - Ziprasidone (SGA)
  - Antivirals
    - Hep C
    - HIV
  - Cisapride
- Moderate risk
  - ADHD agents
    - Amphetamines
    - Atomoxetine
    - Methylphenidate
  - Anti-arrhythmics
  - Anti-biotics
  - Anti-convulsants
  - Anti-neoplastics
  - Antidepressants
    - SSRIs except citalopram
    - Venlafaxine
    - Gepirone
    - Trazodone
    - Nefazodone

# QTc Prolongation (Medications)

- Moderate risk continued
  - Hydroxyzine
  - Anti-hypertensives
    - Beta-blockers
    - Calcium channel blockers
  - Anti-nausea (5-HT3 blockers)
  - Antipsychotics
    - Haloperidol
    - Clozapine
  - Appetite suppressants
    - Phentermine
    - Fenfluramine
  - Lithium
  - Alfuzosin
  - Bronchodilators
  - Phenylephrine
  - Pseudoephedrine
  - Indapamide
  - Octreotide
  - Vardenafil
  - Cimetidine
  - Tacrolimus
  - Tizanidine
  - Methadone
  - Amantidine
  - Chloral hydrate
  - Cocaine
- Low risk
  - Quetiapine
  - Risperidone

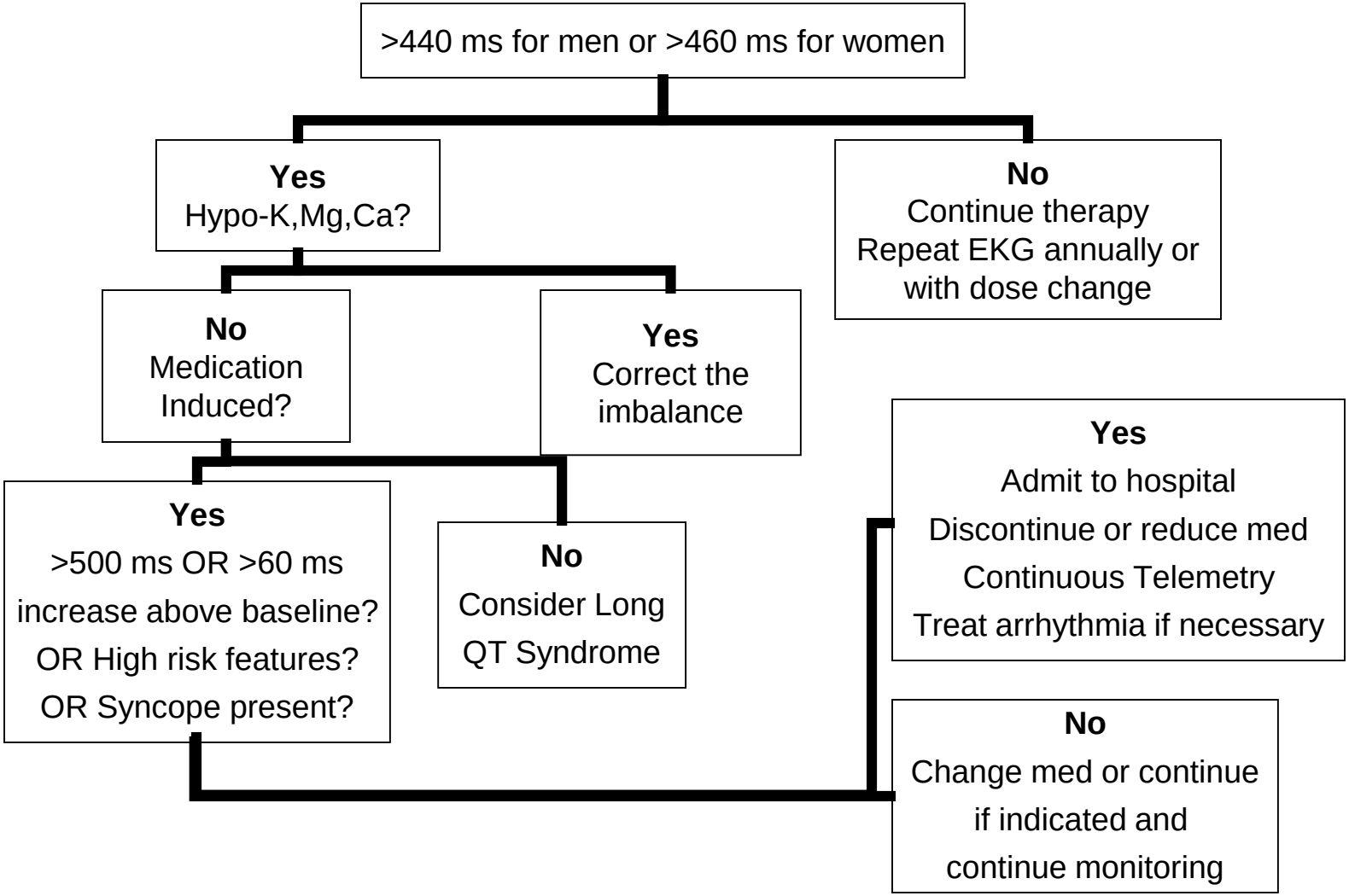
# QTc Prolongation (Guidance when combining agents)

- Healthy adult: Combination of any SSRI with trazodone: No action needed
- > 60 yo: EKG screening before and after
- Determine
  - Other QTc prolonging medication being taken
  - Any pre-existing long QT syndrome
  - Advanced age that may be of concern
- If one of the above is positive
  - Review the medical record to see if an EKG has been performed at the current doses of the QT prolonging drugs
  - If the patient is on a 3rd QT prolonging drug, complete a risk/benefit evaluation and typically suggest cessation of one of the agents and/or routine EKG monitoring
  - If in doubt about the patient's cardiac status, consult cardiology and ask them to comment on liability of the psychotropic medications with QT prolonging risk
  - QTc >500 ms: Cessation of QT prolonging medications should be completed and cardiology consulted
  - QTc >475 ms: Stop one of the agents, no further dose increases of the other agent, and repeat EKG in 1-2 weeks

# When to obtain an EKG

- IV haloperidol or pimozide
- Methadone >=120mg/day
- Antipsychotic, TCA, lithium, methadone, citalopram, stimulant AND
  - Bradycardia
  - Structural heart disease
  - Cardiac arrhythmias
  - Known prolonged QTc
  - Hepatic Dysfunction
  - Hx of syncope
  - Family hx of sudden unexplained deaths
  - Family hx of congenital Long QT Syndrome
  - On other QT prolonging drugs
  - On P450 inhibitors that affect QT prolonging drugs
  - Risk of electrolyte abnormalities (eating disorder, diuretic, etc)
  - Hypokalcemia, hypomagnesemia, hypocalcemia
- Concern for acute ingestion, acute cardiac symptoms, AMS, delirium

# What to do with the EKG



# QTc Prolongation of Antidepressants

| Compound | (ms) |
|---|---|
| Trimipramine | 18.6 |
| Clomipramine | 18.4 |
| Gepirone ER | 18 |
| Maprotiline | 13.9 |
| Doxepin | 12.8 |
| Citalopram | 12.8 |
| Imipramine | 11.8 |
| Amitriptyline | 11.6 |
| Desipramine | 11.4 |
| Nortriptyline | 10.9 |
| Venlafaxine | 10.6 |
| Miratazapine | 8.1 |

| Compound | (ms) |
|---|---|
| Fluoxetine | 4.5 |
| Bupropion | 3.6 |
| Escitalopram | 2.7 |
| Sertraline | 1.7 |
| Paroxetine | 1.7 |
| Fluvoxamine | 1.7 |
| Trazodone | -12.1 |
| Vilazodone | N/A |
| Vortioxetine | N/A |
| Duloxetine | N/A |

# QTc Prolongation of Antipsychotics

| Compound | (ms) |
|---|---|
| Mesoridazine | 39-53 |
| Thioridazine | 33-41 |
| Pimozide | 19 |
| Chlorpromazine | 19 |
| Clozapine | 10 |
| Ziprazidone | 9.7 |
| Iloperidone | 6.93 |
| Asenapine | 5.6 |

| Compound | (ms) |
|---|---|
| Risperidone | 4.77 |
| Olanzapine | 4.29 |
| Quetiapine | 3.43 |
| Haloperidol | 1.69 (higher with IV) |
| Paliperidone | 1.21 |
| Aripiprazole | -0.43 |
| Cariprazine | -1.45 |
| Brexpiprazole | -1.46 |
| Lurasidone | -2.21 |

# Citalopram and QT prolongation

- Dose-dependent QT interval prolongation
- Max daily dose lowered to 40mg/day
  - 20mg/day in patients with hepatic impairment, >60 years of age, CYP 2C19 poor metabolizers, taking concomitant cimetidine
- Use with caution in patients with
  - Congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs
  - Avoid in patients with congenital long QT syndrome
  - Concomitant 2C19 inhibitors (ie omeprazole, esomeprazole)
- Correct hypokalemia and hypomagnesemia before starting citalopram
- Increase EKG monitoring in patients with
  - Congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval
- No dose adjustment for mild or moderate renal impairment
- Educate patients about signs and symptoms of an abnormal heart rate or rhythm while taking citalopram
- Escitalopram risk lower; no dose adjustment warning

# SRI-Induced Sexual Dysfunction

# Adverse Effects: Sexual Dysfunction

- Arousal based on parasympathetic system using acetylcholine
- Orgasm is based on triggering of sympathetic system using norepinephrine
- Increasing serotonin in the spinal cord interferes with both processes (ie 5-HT2A and 5-HT3 receptors)
- Incidence: ~50-70% of patients on serotonergic medications
- Worst with fluoxetine and paroxetine
- Type of sexual dysfunction
  - Delayed ejaculation
  - Anorgasmia or delayed orgasm
  - Impaired libido
  - Erectile dysfunction can occur but less common
  - Vaginal dryness

# Adverse Effects: Sexual Dysfunction

- Switch AD to non-serotonergic antidepressant (ie bupropion, mirtazapine)
- Drug holiday for 2-3 days
  - May have withdrawal, decreased efficacy, worsening of non-compliance
- Testosterone
  - Males: If levels low and with sx of hypogonadism
  - Females: Estratest® for use of sexual dysfunction post menopause
- Serotonin modulation
  - 5-HT1A partial agonism can mediate serotonergic intensity
    - Buspirone 15-60mg daily: Limited evidence (also has a-2 adrenergic antagonism)
    - Vilazodone, vortioxetine, gepirone
  - Antiserotonergic
    - 5-HT2A antagonism (also causes sedation)
      - Cyproheptidine 4-12mg 1-2 hrs prior
      - Mirtazapine
      - Trazodone
      - Flibanserin: Limited evidence (see later slide)
    - 5-HT3 antagonism
      - Granisetron 1mg 1-2 hrs prior: Limited evidence

# Adverse Effects: Sexual Dysfunction

- Cholinergic and adrenergic
  - Bethanechol 30-100mg PRN 1-2 h prior: Limited evidence
  - Neostigmine 50mg PRN 1-2 h prior: Limited evidence
- Noradrenergic stimulation
  - Norepinephrine reuptake inhibition
    - Bupropion (IR may be more useful): Some evidence as adjunct
    - Stimulants (a couple hours prior, avoid at nighttime)
  - a2-adrenergic antagonism -> increase in NE
    - Mirtazapine 30-45mg QHS
  - a1-adrenergic agonism
    - Midodrine 7.5-30mg, 30-120 mins prior
    - Imipramine 25-75mg QHS
    - Ephedrine 15-60mg 1 hr prior
    - Pseudoephedrine 60-120mg 2-3 hrs prior

# Adverse Effects: Sexual Dysfunction

- Dopamine modulation
  - Agonism
    - Pergolide 0.25-2mg daily
    - Pramipexole 0.125-1mg TID
    - Ropinirole 0.5-1.75mg TID
    - Bromocriptine 2.5mg BID-TID
    - Cabergoline 0.5mg twice weekly
  - Presynaptic DA release and inhibition of DA reuptake post-synaptically
    - Amantadine 100-200mg BID 2 days prior: Limited evidence
- Oxytocin 16-24 IU intranasal during or SL prior
  - Actions on peripheral OT or vasopressin receptors
- Topicals
  - Estrogen creams (females only)
  - Lubricants
  - Zestra® or Galaxis® (OTC topicals for women)
  - Eroxon® (OTC topical for men, cooling and warming to stimulate)

# Hypoactive Sexual Desire Disorder in Women

- Flibanserin (Addyi®) (2015)
  - Mechanism of action closely resembles buspirone
    - 5-HT1A agonist, 5-HT2A antagonist
  - Increased the risk of dizziness, somnolence, nausea, and fatigue
  - **BBW**
    - Hypotension and syncope when combined with alcohol, moderate to severe 3A4 inhibitors, and patients with hepatic impairment
    - REMS required (medication guide)
  - Limited evidence
    - One-half additional satisfactory sexual encounter per month

# Hypoactive Sexual Desire Disorder in Women

- Bremelanotide (Vyleesi®) (2019)
  - Non-selective agonist of melanocortin receptors (MC1-MC5)
  - SQ 1.75mg 45 mins prior to activity
  - % of satisfying sexual events increased
  - Decrease in distress related to desire
  - However, 0 additional satisfactory encounters
- Esterified estrogen and methyltestosterone (Estratest®)
  - FDA approved for vasomotor symptoms associated with menopause
    - Off label for hypoactive sexual desire disorder in women
  - In use and available to prescribe since 1964
  - **5 BBWs!**
    - Endometrial cancer, CVD, Breast cancer, Pregnancy, Risk vs Benefit

# Hypoactive Sexual Desire Disorder in Women

- Testosterone
  - Testing levels is not diagnostic
    - Only use for baseline and to ensure patient is not already in high physiologic range
  - Caution against compounded bio-identical hormone therapy (cBHT)
    - Often include topical progesterone that is ineffective that exposes to risk of endometrial cancer
    - Supra-therapeutic doses can cause
      - Permanent facial hair, deepened voice, clitoromegaly, and cardiovascular harm
    - Supraphysiologic dosing required to achieve strength, weight loss, and energy
      - Not worth the risk
  - Low doses can be safely used for hypoactive sexual desire
    - 300-500mcg/day (1/10 of male doses)
    - Make sure estrogen levels are normal first
    - Calculate FAI (total testosterone/SHBH x 100)
      - Treat FAI to 1-5% level
    - Monitor CBC and lipids

# Adverse Effects: Sexual Dysfunction (PDE5i)

| Compound | Brand Name | FDA Approved | Onset of Action | ½-Life | PDE5:PDE1 | PDE5:PDE6 | AEs | With a-blocker | With Food |
|---|---|---|---|---|---|---|---|---|---|
| Sildenafil | Viagra | 1998 | 30-120m (60m) | 4h | 80-8500:1 | 9:1 | **May be worse** | 6 hrs apart | Slowed |
| Alprostadil | Caverject | 2002 | 5-20m | 0.5-10m | | | | | |
| Vardenafil | Levitra | 2003 | 30-120m (60m) | 4-6h | 200-1000:1 | 16:1 | | 6 hrs apart | Less |
| Tadalafil | Cialis | 2003 | 30-120m (60m) | **15-17h** | **1000:1** | **1000:1** | | **Contra-indicated** | **No effect** |
| Avanafil | Stendra | 2012 | **15-45m** | 5h | | | | 6 hrs apart | Slowed |

# Adverse Effects: Sexual Dysfunction (PDE5i)

- PDE1 is found in the brain, heart, and vascular smooth muscle
  - Causes vasodilation, flushing, and tachycardia
- PDE6 is in the eye
  - Can alter color perception (rare)
- Adverse Effects
  - Headaches, Nasal Congestion, Facial flushing, Stomach/back pain, NOT PRIAPISM!
- Combination with alpha blocker
  - Not recommended with tadalafil
  - Given 6 hours apart with others
- Fatty foods can delay absorption except tadalafil
- Do not take within 24 h of a nitrate (tadalafil within 48 h)
- Taladafil can be dosed daily and can be used for LUTS as well
- If ineffective
  - Titrate to max dose
  - Do not take with full stomach or fatty food
  - Takes up to 2 hours to take effect except avanafil
  - Sexual stimulation still required to achieve erection

# Supplements

- *Epimedium*
  - AKA yin yang huo or Horny Goat Weed
  - Active compound: incariin
  - Weak PDE5 inhibitor
  - Limited scientific research
- Saw palmetto extract
  - Contains 5α-reductase inhibitor
  - Very limited evidence of positive effect on LUTS
  - No evidence for benefit in prostate cancer or sexual enhancement
- Yohimbine 5.4mg BID to TID
  - Derived from the bark of the African tree: *Pausinystalia*

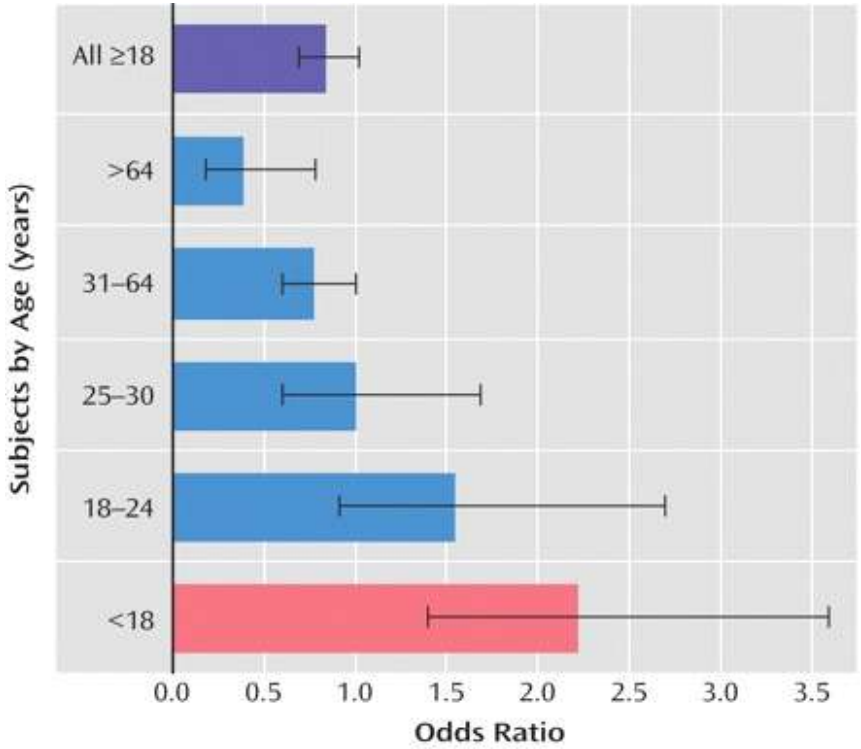
# Supplements

- Ginkgo Biloba 60mg daily to 120mg BID: Limited evidence
  - Increase in nitric oxide
  - Inhibits platelet activating factor: may increase bleeding
- Gensing (Red type most effective?)
  - Increase in nitric oxide, dopamine, and several other chemicals
- Maca AKA Peruvian gensing
  - Mechanism unclear
  - Limited evidence
- "Rhino" pills
  - Sold at convenience stores
  - Deemed unsafe by the FDA
  - Many illegally contain PDE5 inhibitors

# Antidepressants and Suicide Risk

# Suicide Risk with SSRI

- Black box warning for patients <25 years old for increased suicidal thinking/behavior during first 2 months of treatment
- Possible explanation is that neurovegetative effects of depression often respond before mood leading to a more impulsive and motivated suicidal thoughts
- Intent of warning was to get providers to see patients sooner after prescribing
  - Guidance is weekly for 4 weeks
  - Then every other week for 4 weeks
  - Then at 12 weeks
- Result was decrease in prescribing and actual suicide rates went up




Leon, AC. A*m J Psychiatry 2007;164:1786-1789.* doi:10.1176/appi.ajp.2007.07050775
www.fda.gov/cder/drug/antidepressants/default.htm. Accessed December 13, 2013.

# Boxed Warning History

- Boxed warnings were introduced in 1979
- Highest warning assigned by the FDA
- Over 500 medications have boxed warnings
- Typically the warnings are applied to a drug class rather than a specific drug
- OTC medications do not have boxed warnings even if their prescription counterparts do
- 1990: First published report of suicidal preoccupation with fluoxetine
- June 2003: UK issued warning about use of paroxetine in children < 18 yo citing increased suicidality and no benefit
- End of 2003: UK banned all antidepressants except fluoxetine for children and adolescents
- In 2004, FDA warning on all antidepressants based on retrospective reports that showed a very slight increased risk of SI in children and adolescents
- Revised in 2007 to include young adults up to age 24

# Suicide Risk with Antidepressants

- All newly approved antidepressants or agents for treatment of depression must carry warning
- Since then more prospective data has emerged that does not support an association
- There was a very small increased risk of SI and attempts but NO completed suicides in children and adolescents in any of the pediatric trials
- Since warning was issued there has been an increase in the rate of suicides in severely depressed patients associated with decrease in antidepressant prescriptions and doctor visits
- Patients should be informed of and monitored for suicidality
- Warning should not prevent prescribing to depressed patients

Culpepper L et al. Suicidality as a possible side effect of antidepressant treatment. Prim Care Companion J Clin Psych 2004;6(2):79-88 www.fda.gov/cder/drug/antidepressants/default.htm

BMJ

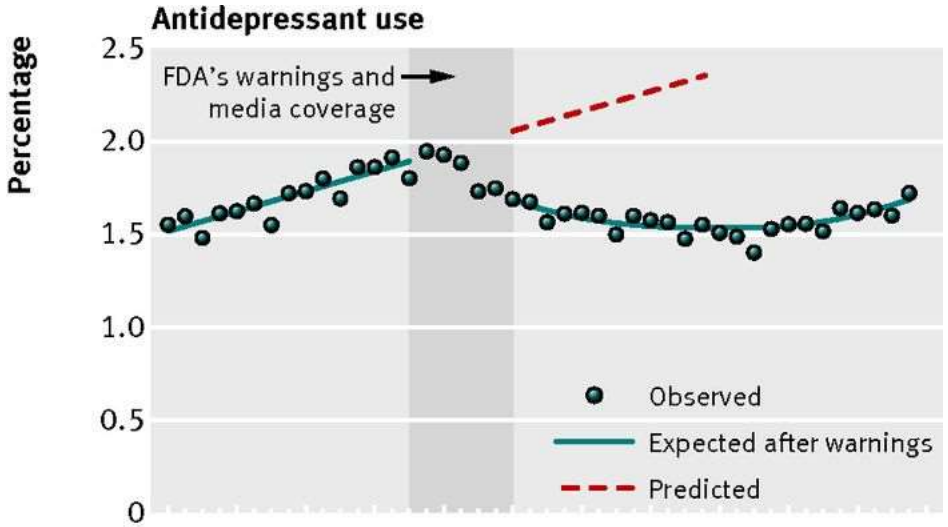
BMJ 2014;348:g3596 doi: 10.1136/bmj.g3596 (Published 18 June 2014)

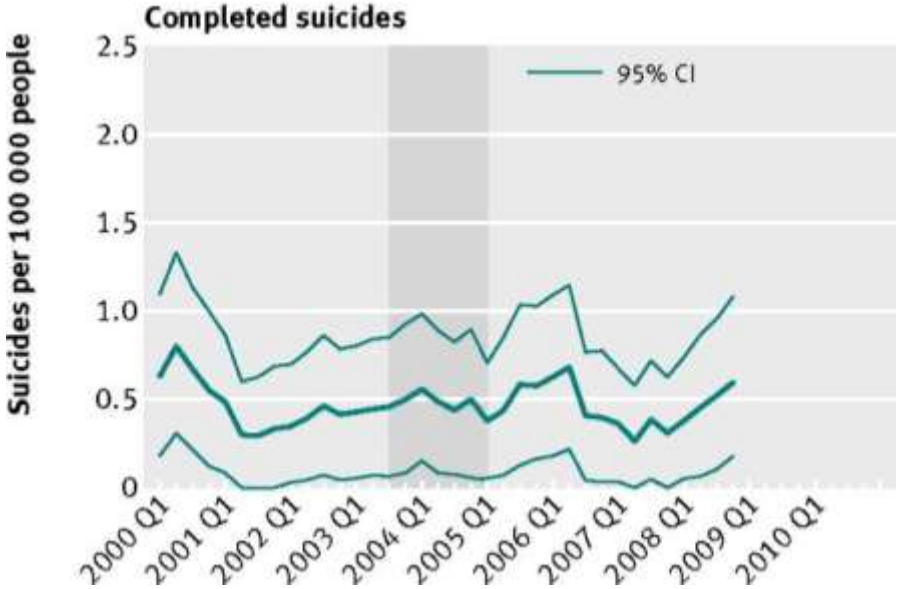


# Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study



Christine Y Lu *instructor*[1], Fang Zhang *assistant professor*[1], Matthew D Lakoma *analyst*[1], Jeanne M Madden *instructor*[1], Donna Rusinak *program manager*[1], Robert B Penfold *assistant investigator; affiliate assistant professor*[2 3], Gregory Simon *senior invstigator; lead investigator*[2 4], Brian K Ahmedani *assistant research scientist*[5], Gregory Clarke *senior investigator*[6], Enid M Hunkeler *senior research*

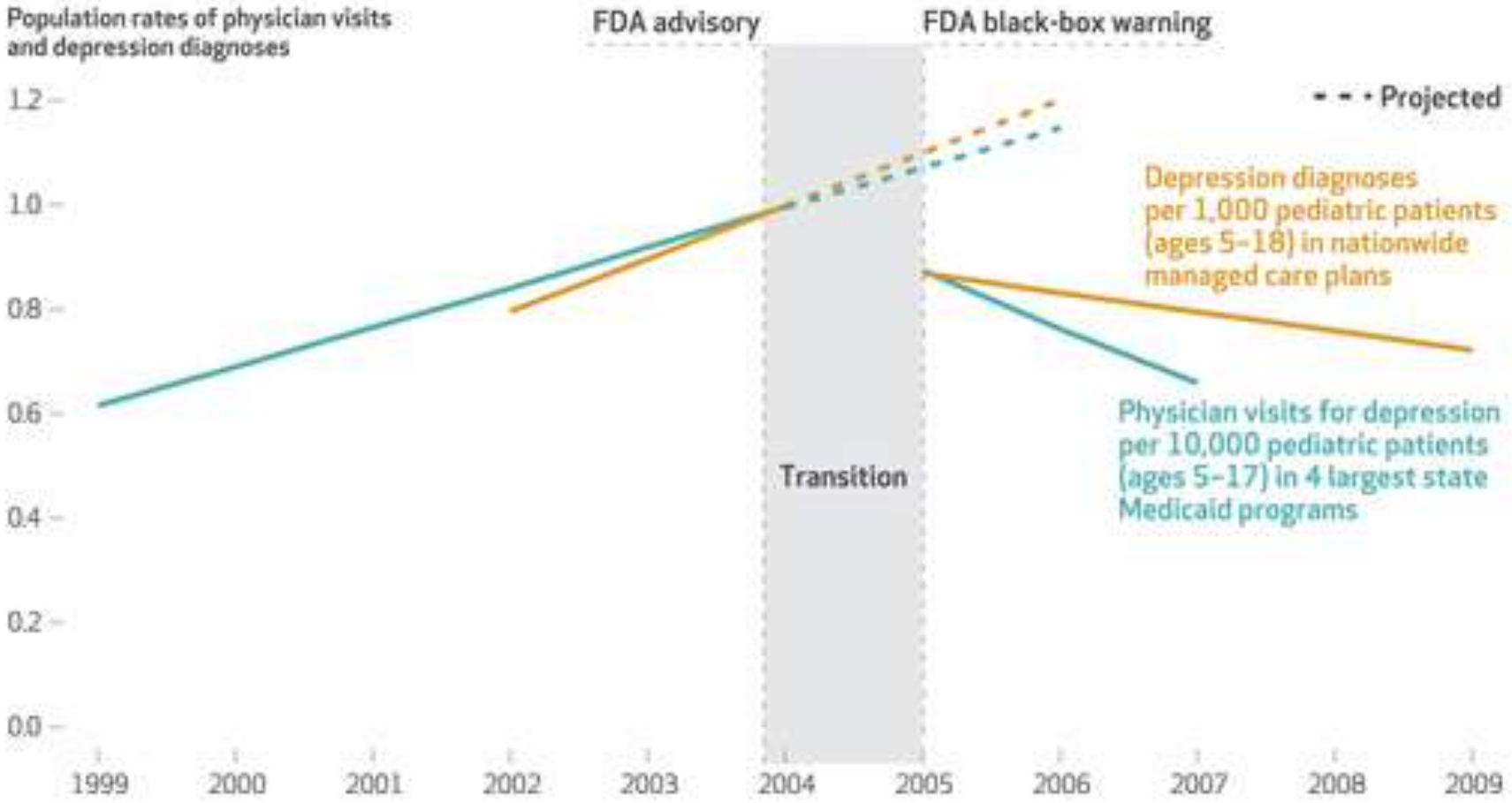


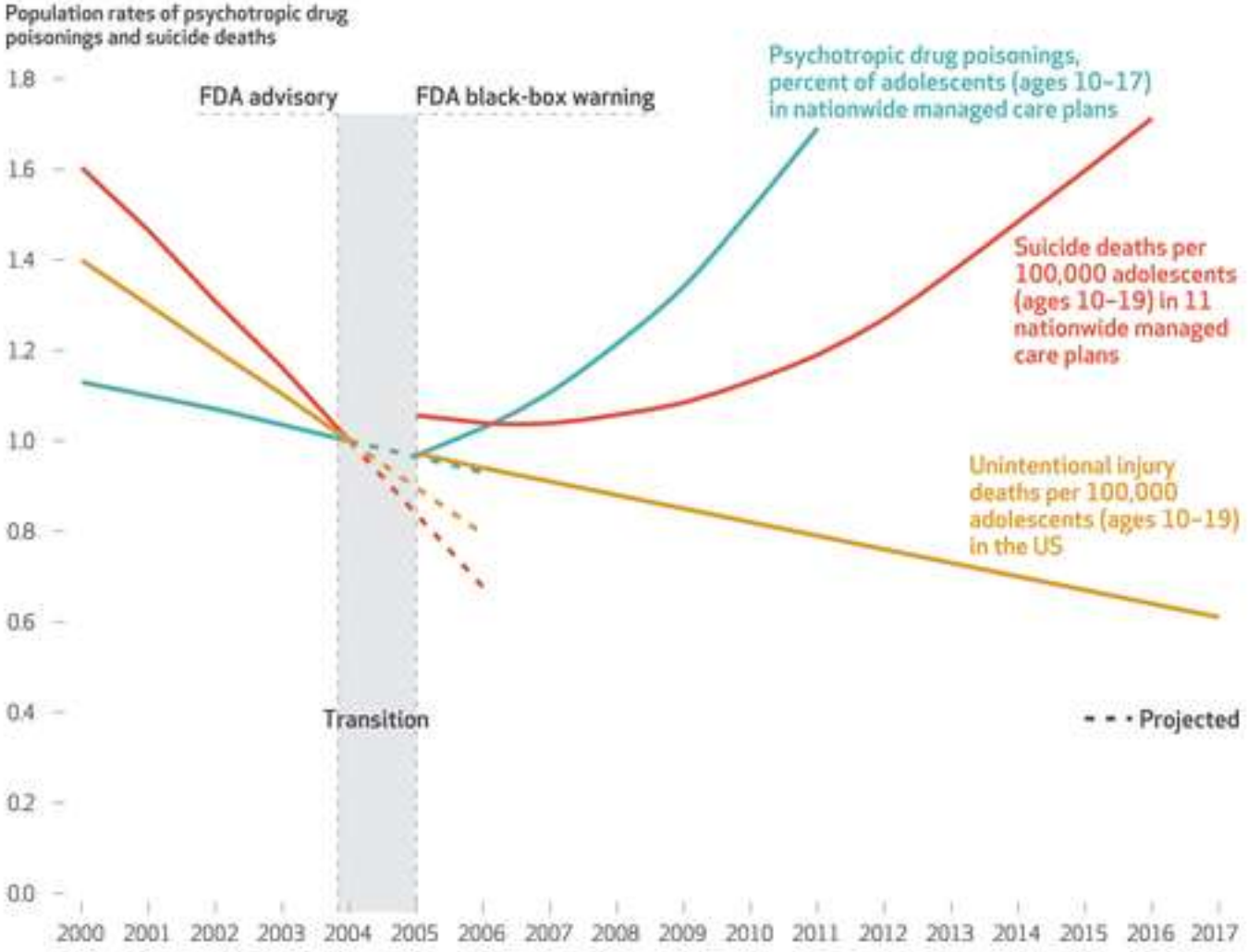



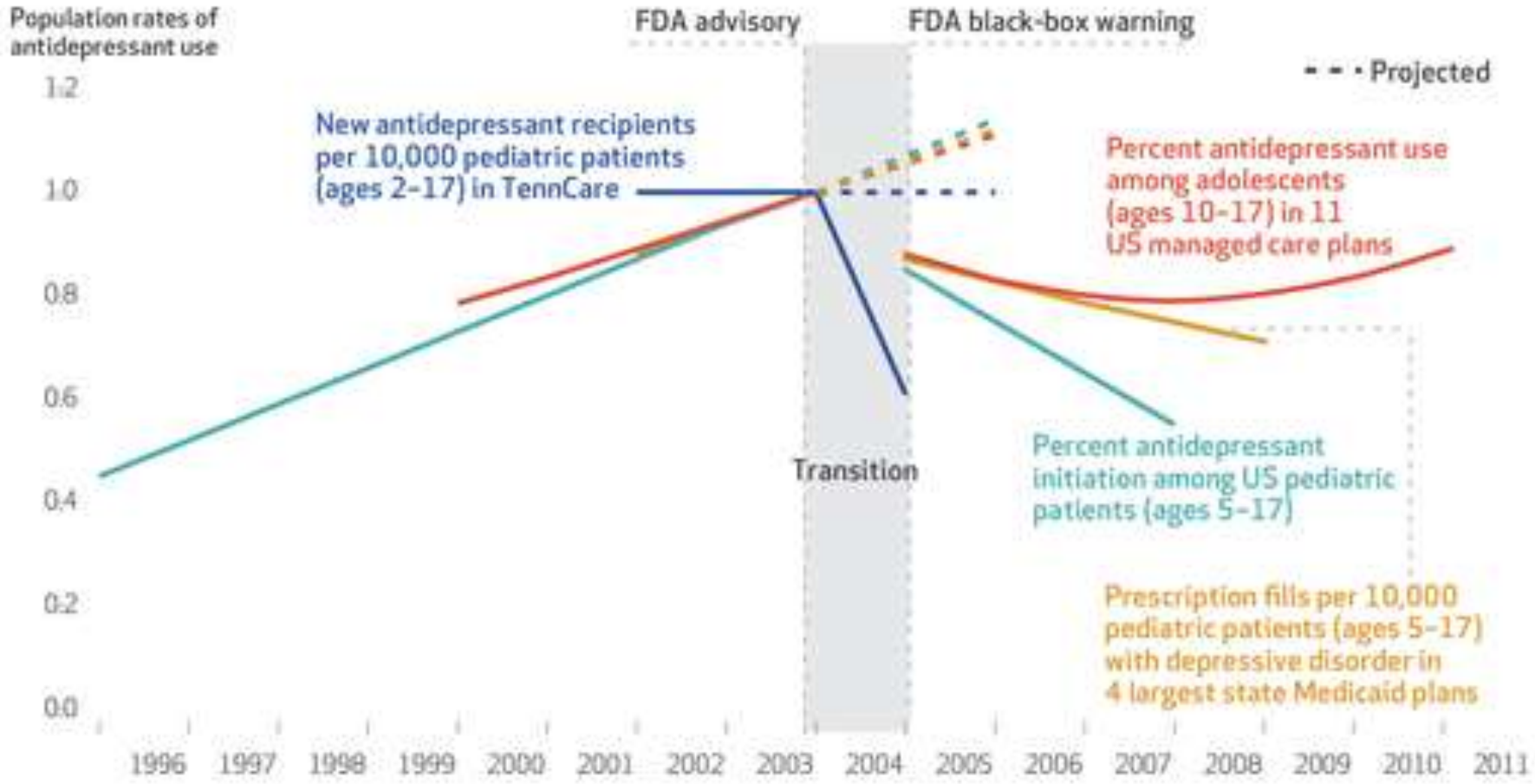
# Suicide Risk with Antidepressants

- Oct 2024 review article from *Health Affairs*
- Eleven studies in the systematic review show that the FDA pediatric antidepressant advisory in 2003 and black-box warning in 2005 were associated with unintended outcomes
  - Reduced physician visits for depression
  - Reduced depression diagnoses
  - Reduced psychotherapy visits
  - Reduced antidepressant treatment and use
  - **Increased** psychotropic drug poisonings and suicide deaths

Soumerai et al. Intended and Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systemic Review. Health Affairs. 43(10). Oct 2024.


Population rates of physician visits and depression diagnoses
FDA advisory
FDA black-box warning
Projected
Depression diagnoses per 1,000 pediatric patients (ages 5–18) in nationwide managed care plans
Physician visits for depression per 10,000 pediatric patients (ages 5–17) in 4 largest state Medicaid programs
Transition
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009


Population rates of psychotropic drug poisonings and suicide deaths
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
FDA advisory
FDA black-box warning
Transition
Psychotropic drug poisonings, percent of adolescents (ages 10–17) in nationwide managed care plans
Suicide deaths per 100,000 adolescents (ages 10–19) in 11 nationwide managed care plans
Unintentional injury deaths per 100,000 adolescents (ages 10–19) in the US
Projected
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017


Population rates of antidepressant use
FDA advisory
FDA black-box warning
Projected
1.2
1.0
0.8
0.6
0.4
0.2
0.0
New antidepressant recipients per 10,000 pediatric patients (ages 2–17) in TennCare
Percent antidepressant use among adolescents (ages 10–17) in 11 US managed care plans
Transition
Percent antidepressant initiation among US pediatric patients (ages 5–17)
Prescription fills per 10,000 pediatric patients (ages 5–17) with depressive disorder in 4 largest state Medicaid plans
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

# Drugs affected

- Antidepressants
  - All MAOis, TCAs, SSRIs, SNRIs, SARIs, NaSSA
    - Including fluvoxamine and milnacipran despite not having FDA approval for depression
  - NDRIs
    - Includes both Wellbutrin® and Zyban®
    - Does not include methylphenidate or amphetamines (not antidepressants)
  - 5-HT1A partial agonists
    - Includes gepirone
    - Excludes buspirone (not an antidepressant)
  - Includes new antidepressants
    - Esketamine and Auvelity® (bupropion + DXM)

# Drugs affected

- Antidepressants
  - Includes antidepressant combinations drugs
    - Symbyax® (fluoxetine/olanzapine)
    - Triavil® (amitriptyline/perphenazine)
    - Limbitrol® (amitriptyline/chlordiazepoxide)
  - Excludes brexanolone and zuranolone (post partum not depression?)
  - Includes maprotiline despite not being available since 2021
  - Antipsychotics approved for depression
    - Quetiapine, aripiprazole, brexpiprazole, cariprazine
- Medications approved for bipolar depression
  - Quetiapine, cariprazine, lurasidone, lumateperone
- ADHD: Atomoxetine

# Serotonin Toxicity

# Serotonin syndrome

- Symptoms
  - **Hyperkinesia**
    - Anxiety, agitated delirium, disorientation, tremor
  - Autonomic instability
    - Diaphoresis, tachycardia, HTN, tachypnea, hyperthermia
  - Other symptoms
    - Vomiting, diarrhea, hyperactive bowel sounds, sialorrhea, mydriasis
  - Neuromusclular
    - Muscle rigidity (LE predominent)
    - **Clonus, hyperreflexia** (unless masked by muscle rigidity)
- Within 6-24 hours of medication change

# Serotonin syndrome

- Hunter Criteria (meets one of the following)
  - Spontaneous clonus
  - Inducible clonus + agitation or diaphoresis
  - Ocular clonus + agitation or diaphoresis
  - Tremor + Hyperreflexia
  - Hypertonia + temp>38C + Ocular clonus or inducible clonus

# Serotonin syndrome

- Likely mediated by **5-HT2A agonism**
- Serotonin metabolism
  - MAOIs including methylene blue, linezolid, Syrian rue
- SRIs
  - SNRIs, SSRIs, tramadol, methadone, meperidine, fentanyl, DXM, chlorpheniramine, brompheniramine, fenfluramine, sibutramine, cocaine, St. John's Wort, metoclopramide, ziprasidone, lumateperone
  - Serotonergic TCAs (Amitriptyline, Imipramine, Clomiprapine)
- SRAs
  - MDMA, fenfluramine, carbamazepine
- Serotonin precursors
  - L-tryptophan, 5-HTP
- 5-HT2A agonists
  - LSD, psilocybin, mescalin (theoretically there should be risk but there are no good case reports of it)

# Serotonin syndrome

- AEDs can affect serotonin
  - Valproic acid, lamotrigine, gabapentin
- Caution with strong CYP inhibitors (All TCAs depend on 2D6)
- Poor association
  - Triptans (5-HT1B/D ag)
  - Antiemetics (-setrons) (5-HT3 ant)
  - Mirtazapine and trazodone (5-HT2A ant)
  - Bupropion (NDRI)
  - Buspirone (5-HT1A ag)
  - Methylphenidate and amphetamine (NDRI)
  - Morphine analogues (not SRIs)
  - Cyclobenzaprine, lithium
- Treatment: Stop offending agents and supportive care
  - Cooling blankets
  - Cyproheptidine (serotonin antagonist)
  - Benzodiazepines (sedation)

# Differential Diagnosis

- Neuroleptic Malignant Syndrome
  - **Bradykinesia, hyperthemia, bradyreflexia, "lead-pipe" rigidity in all muscle groups**
  - Typically seen with dopamine blocking medications
  - Can be seen with serotonergic medications as well
  - Elevated CK >1000
  - Within 10 days of medication change (usually 1-3 days)
- MAOi hypertensive crisis
  - Severe headache, neck stiffness, photophobia
  - **Hypertension**, diaphoresis, nausea, vomiting
  - Lacks hyperkinesia, hyperreflexia, clonus, hypertonia
- Anticholinergic "toxidrome"
  - Mucus membranes are **dry**
  - Hot and dry to the touch
  - Bowel sounds decreased or absent
  - Normal muscular tone and reflexes

# Other Serotonergic Adverse Effects

# Overview

- Most adverse effects appear in 1-2 weeks and gradually subside except sexual dysfunction
- ¾ of patients experience no adverse effects at low starting doses
- 10-15% won't tolerate even a small dose of a particular SSRI
- Most beneficial effects often seen at low doses while adverse effects worsen as drug is increased
- Over 50% of patients who respond poorly to one SSRI will respond favorably to another

# CNS and GI

- CNS Effects
  - Sedation: worst with fluvoxamine, paroxetine
    - Can change to SNRI/NDRI
  - Insomnia: worst with fluoxetine
    - Can add trazodone or other med
  - Headaches
  - Vivid dreams/nightmares
- GI Effects
  - N/V/D: worst with sertraline
    - Giving with food may help
  - Constipation: paroxetine is most anticholinergic
    - Also other anticholinergic effects (ie dry eyes, dry mouth)
    - CR formulation may be better tolerated

# Adverse Effects

- Sweating
  - Treatment is alpha blocker like terazosin
  - Increased risk with short-acting agents (paroxetine, fluvoxamine, venlafaxine)
- Bruxism
  - Buspirone may help
- Weight gain
  - 1/3 of patients
  - TCAs>>Paroxetine>Sertraline/Fluoxetine>Others
- ↓ bone mineral density
  - 4% less BMD in elderly
  - Inhibits osteoblast activity

# Adverse Effects

- Bleeding/anemia
  - All serotonergic drugs have potential
  - Serotonin signals platelet aggregation
  - Bleeding may occur due to serotonin depletion from SRIs
  - Caution in patients with defect in platelet number or function and with chronic NSAID treatment
- Emotional dulling: feel like a "zombie"
- Manic Switch
  - Caution in patients with history of mania, hypomania, or family history of bipolar disorder
  - If patient has this effect, it may be a clue that they have a bipolar spectrum disorder
- EPS

# SIADH

- Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
  - ADH is released from the hypothalamus
    - Increases absorption of water in the renal distal tubules
    - Triggered when ions in the blood are too concentrated (ie sodium)
  - Normal sodium level is 135-145
  - Hyponatremia: Na < 130 may begin to show symptoms, especially < 125
    - Mild (<130): nausea, malaise, headache
    - Moderate (<125): neurological impairment (balance and gait affected, falls)
    - Severe (<120): seizures, coma, respiratory arrest, death
    - Pseudohyponatremia: severe hypertriglyceridemia, DKA, HHS, hyperalbunemia
  - Causes
    - Cancer (~25%): often small cell lung cancer
    - CNS disorders (~10%): subarachnoid hemorrhage, pituitary surgery, tumor, infection, stroke, head trauma
    - Others: pulmonary, hereditary, sarcoidosis, etc

# SIADH

- Causes
  - Drug-induced (~20%)
    - Stimulation of ADH release
      - Opiates, vincristine, platinum-based antineoplastics, MDMA
    - Enhancers of ADH effect
      - NSAIDs
    - ADH analogues
      - Desmopressin, oxytocin
    - Vasopressin receptor 2 activators
      - SSRIs (~33%), carbamazepine, oxcarbazepine, FGAs, cyclophosphamide

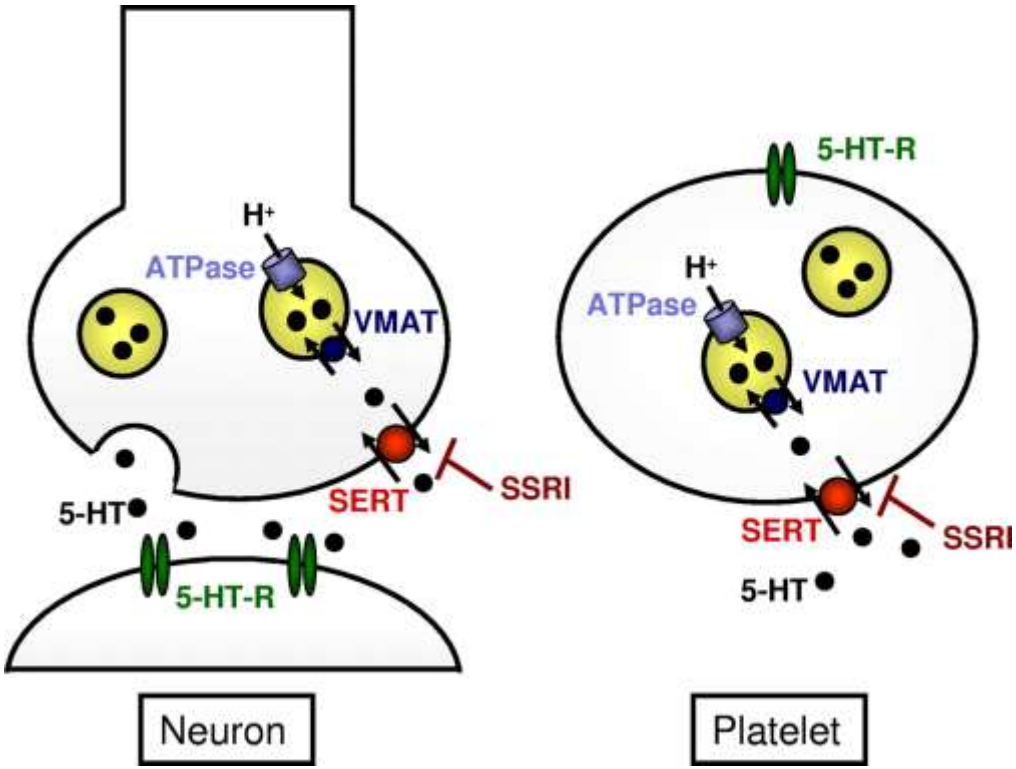
# SSRIs

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- Fluoxetine (Prozac®)
- Sertraline (Zoloft®)
- Paroxetine (Paxil®, Paxil CR®, Pexeva®, Brisdelle®)
  - Pexeva® initially was a cheaper alternative to Paxil® which was not yet generic
  - Pexeva® never produced as generic so now is more expensive
  - Brisdelle® is one of three FDA approved formulations for vasomotor spasms and is formulated at 7.5mg
  - Paxil® is a hydrochloride salt
  - Pexeva® and Brisdelle® are mesylate salts
- Fluvoxamine (Luvox®)
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)

# Mechanism of Action

- Blocks serotonin reuptake pump: All
- Anticholinergic activity: paroxetine
- Blocks dopamine reuptake pump: sertraline (mild)



# Dosing Considerations

- All SSRIs are administered once daily
  - Except fluvoxamine at doses above 100mg daily
- Initial dose can be maintenance dose
- Increase dose q3-6 weeks if tolerated/needed
- Can titrate q1week if returning to previously effective dose

# Drug Interactions

- 1A2 inhibition
  - **Strong: fluvoxamine**
- 2B6 inhibition
  - Mild: fluvoxamine
- 2C9 inhibition
  - Moderate: fluvoxamine
  - Mild: fluoxetine, paroxetine
- 2C19 inhibition
  - **Strong: fluvoxamine**
  - Moderate: fluoxetine
- P-glycoprotein inhibition
  - Sertraline, fluoxetine, paroxetine, (fluphenazine)
  - Substrates: BZDs, TCAs, citalopram, risperidone, paliperidone

# Drug Interactions

- 2D6 inhibition
  - **Strong: fluoxetine, paroxetine**
  - Moderate: sertraline
  - Mild: citalopram, escitalopram
  - Substrates
    - Many beta-blockers are very sensitive
    - Many narcotics require 2D6 to be effective
      - Codeine, oxycodone, tramadol, hydrocodone
    - Tamoxifen requires 2D6 to be effective
- 3A4 inhibition
  - **Moderate: fluvoxamine**
  - Mild: fluoxetine
- No SSRIs are inducers (
  - Except herbal St. John's Wort
    - Strong: 3A4
    - Moderate: 1A2
    - Mild: 2C9, 2C19
    - Also: P-gp

# Drug Interactions

- Neuroleptic malignant syndrome / EPS
  - In combination with MAOIs, antipsychotics/dopamine antagonists
    - Reports with SSRI and SNRI alone
  - SNRIs most common but still very rare
  - Fluoxetine most reported of SSRIs
  - Mechanism may be due to increased potentiation of 5-HT2A due to inhibition of reuptake of serotonin
- Increased risk of bleeds with anticoagulants/antiplatelet agents
- DDIs
  - Tamoxifen, codeine, tramadol (fluoxetine, paroxetine)
  - Fluvoxamine with many medications
    - ie tizanidine, ramelteon

*FDA warning regarding NMS with SSRI/SNRI, February 5, 2009

# Contraindications

- Use of MAOI within past 2 weeks
  - Allow 5 weeks to elapse when starting an MAOI after fluoxetine
- Thioridazine, pimozide → QT prolongation, arrhythmias
- SIADH

# Caution

- Cardiovascular
  - Recent MI/unstable heart disease, long QT
    - QT prolongation (citalopram)
  - Altered platelet function
- Hepatic/renal impairment
- Mania
- Seizure disorder
- Narrow-angle glaucoma (paroxetine)
- Adding new antidepressant (fluoxetine due to long ½ life)
- Diabetes (fluoxetine may lower glucose)
- Uric acid nephropathy (sertraline is uricosuric)

# Serotonin Withdrawal Syndrome

- Due to abrupt discontinuation of meds, especially meds with short ½-lives
  - Antidepressantss with short ½-lives
    - Doxepin, amitriptyline, imipramine, desipramine
    - **Fluvoxamine, venlafaxine, paroxetine**
  - Symptoms
    - Flu-like symptoms, shooting pains in extremities, anxiety, irritability, lethargy, insomnia, cholinergic symptoms, anxiety
  - Not life-threatening
- Onset: ~24-48 hours after last dose
- Duration: 3-7 days

# SSRI Summary

## Advantages

- Safer vs older ADs
  - Lower SE incidence
  - Lower risk toxicities
    - Overdose
    - Serotonin toxicity
    - Malignant hypertension
- May help with
  - Anxiety disorders
  - Severe depression
  - Premature ejaculation
  - Eating disorders
  - Menstrual disorders
  - Post-partum
- Patient familiarity

## Disadvantages

- Short term SEs
  - N/V/D
- Delayed response
- Minimal response in many
  - Mild, moderate symptoms
- Sexual dysfunction
- DDIs
- Increased risk of SI in children/adolescents
- Emotional dulling
- Sedation/insomnia
- Some get significant weight gain

# History of SSRIs

- Zimelidine
  - First SSRI
  - Discovered in 1969


  - Approved for depression outside the US in 1981
  - Pulled from the market in 1983 due to cases of Guillain-Barre
- Indalpine
  - Second SSRI
  - Discovered in 1977


  - Approved for depression outside the US in 1983
  - Pulled from the market in 1985 due to agranulocytosis

# Fluoxetine / Prozac® (1987)

- Advantages
  - Long half-life (for inconsistent patient)
  - Activating
  - Can be given with Zyprexa for treatment-resistant depression
  - Eating disorders except anorexia
  - Safest for pregnancy but not breastfeeding for neonates
  - Mild 5-HT2C antagonism -> may lead to NE and DA increase -> stimulant
    - Agomelatine (approved for depression outside the US): 5-HT2C antagonist
  - Mild NET and DAT reuptake inhibition; very mild mACh blockade
- Disadvantages
  - May want to avoid in agitated insomnias (give in morning due to activation)
  - Headache
  - Long half-life can be problematic with switching medications (ie MAOi)
  - Potent 2D6 inhibitor (Codeine, B-blockers, Strattera, Thioridazine, Pimozide, DXM, **fluoxetine**, decreased efficacy of tamoxifen)
    - Caution non-linear pharmacokinetics due to auto-inhibition
  - May lower glucose

# Sertraline / Zoloft® (1991)

- Advantages
  - May help with fatigue, low energy, cognitive flattering
    - Most DAT action of SSRIs though Ki is 100x higher than SERT
    - Mild NET action as well
  - Safest for cardiovascular risk (QTc)
  - Best overall safety profile for breast feeding and pregnancy of ADs
- Disadvantages
  - Highest GI SE risk
  - Takes longer to titrate to max dose if needed
  - Very mild mACh blockade
  - Mildly uricosuric
    - Decreases serum uric acid by ~7%, unknown clinical significance

# Paroxetine / Paxil® (1992) / Pexeva® (2002) / Brisdelle® (2013)

- Advantages
  - Strongest affinity to SERT may lead to slightly more efficacy
  - Help with insomnia
  - CR formulation may help with SEs
    - Nausea mainly, perhaps sedation, sexual dysfunction, withdrawal
  - 2nd line for breastfeeding
  - Premature ejaculation
  - Some NRI property at higher doses
  - Maybe some DAT activity as well

# Paroxetine / Paxil® (1992) / Pexeva® (2002) / Brisdelle® (2013)

- Disadvantages
  - Anticholinergic effects (ie constipation)
    - Most sedating, fatigue, weight gain of SSRIs
  - Potent 2D6 inhibitor
    - Codeine, B-blockers, Strattera, thioridazine, pimozide, **paroxetine**, decreased efficacy of tamoxifen
      - Caution non-linear pharmacokinetics due to auto-inhibition
  - Despite being the only serotonergic med with FDA approval for vasomotor symptoms of menopause
    - Evidence that other SSRIs are also helpful
      - Have many fewer adverse effects
  - NOS inhibition: worst sexual dysfunction of SSRIs
  - Shorter half-life requires consistently taking at same time daily
    - Withdrawal worse than other SSRIs (akathisia, GI, dizziness, tingling)
  - Only SSRI with D rating for pregnancy

# Fluvoxamine / Luvox® (1994)

- Advantages
  - CR formulation available and may be better tolerated
  - Highly selective SSRI
  - May have more rapid onset of effect
  - Small study shows improvement in COVID outcome thought to be due to anti-inflammatory effects due to σ1 agonism
- Disadvantages
  - Short half-life requires multi-day dosing (only antidepressant like this)
    - Worse than other antidepressants: withdrawal, sedation, sweating, etc.
  - Wide dosing range
  - Only FDA approved SSRI for OCD, however despite reputation is no better at treating anxiety disorders than other antidepressants
  - One of the worst drugs for CYP450 interactions
    - Strong 1A2 inhibitor
    - Mild 2B6 inhibitor
    - Moderate 2C9 inhibitor
    - Strong 2C19 inhibitor
    - Moderate 3A4 inhibitor

# Citalopram / Celexa® (1998)

- Advantages
  - Does not affect CYP450 enzymes (only mild 2D6)
    - Good for elderly and those on a lot of meds
  - SEs more tolerable than other SSRIs
    - Though escitalopram is more tolerable
  - Less sexual SE risk (though not much)
- Disadvantages
  - Escitalopram is similar and typically superior for SEs and interactions
  - QTc prolongation risk
  - R-citalopram has mild H1 blockade: sedation, weight gain
  - Last choice of SSRIs for breastfeeding
  - Lowest effect size of the antidepressants

# Escitalopram / Lexapro® (2002)

- Advantages
  - 10mg may be equivalent to 40mg of citalopram due to R-citalopram interference with S-citalopram binding
  - Most selective SSRI
  - Generally best tolerated SSRI
  - Less sexual SE risk (though not much)
  - Does not affect CYP450 enzymes (only mild 2D6)
    - Good for elderly and those on a lot of meds
  - Lacks dosing restrictions that citalopram has for QTc
  - Most selective of SSRIs
- Disadvantages
  - Last choice of SSRIs for breastfeeding
  - Lowest effect size of the antidepressants

# SNRIs

# Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine (Effexor®, Effexor XR®, Venlafaxine ER)
- Duloxetine (Cymbalta®, Drizalma® (Sprinkle))
- Desvenlafaxine (Pristiq®)
- Milnacipran (Savella®)
- Levomilnacipran (Fetzima®)




# Serotonin Norepinephrine Reuptake Inhibitor (SNRI)

- Mechanism of action
  - Block presynaptic serotonin (5HT) and norepinephrine (NE) reuptake in the brain (mood) and spinal cord (pain)
  - Blocking NET also blocks reuptake of some DA in prefrontal cortex
  - Venlafaxine dose-related effects
    - <150mg/day → primarily 5HT action
    - >150mg/day → dual effects of 5HT and NE
    - >375mg/day → triple effects on 5HT, NET, and DAT
  - Duloxetine increases 5HT and NE at initial doses
  - Levomilnacipran and milnacipran possible dose-related effects
    - Greater NE at low doses, 5HT at high doses

Frazer A. J Clin Psych 2000;61(suppl 10):25-30;Rush AJ, Thase ME. J Clin Psych 1997;58(suppl 13):14-22; Cohen LJ. Advances in pharmacological treatment of depression. ACCP Online Educational Program.

# Serotonin Norepinephrine Reuptake Inhibitor (SNRI)

| Compound | Brand Name | SERT | NET |
|---|---|---|---|
| Venlafaxine | Effexor | 30 | 1 |
| Desvenlafaxine | Pristiq | 10 | 1 |
| Duloxetine | Cymbalta | 10 | 1 |
| Milnacipran | Savella | 1 | 1 |
| Levomilnacipran | Fetzima | 1 | 2 |

# SNRI: FDA Indications

- Venlafaxine
  - Depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder, (possibly OCD)
- Desvenlafaxine
  - Depression
- Duloxetine
  - Depression, GAD, diabetic peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain, (possibly OCD)
- Levomilnacipran
  - Depression
- Milnacipran
  - Pain
  - No FDA approved mental health indications
    - Approved for depression elsewhere in the world

# Adverse Effects

- Serotonergic
  - GI effects (nausea, constipation, diarrhea)
    - XR venlafaxine better tolerated than IR
  - Insomnia/somnolence
  - Sexual dysfunction
  - Suicidal thoughts
- Noradrenergic
  - Dizziness
  - Hypertension, tachycardia
  - Sweating
- Dry mouth
- Duloxetine
  - Hepatitis and cholestatic jaundice (10/17/05)
- Levomilnacipran: mydriasis, urinary retention, seizures

# Drug Interactions

- All SNRIs not recommended with MAOI and other serotonergic agents
  - Due to serotonin syndrome risk
- Neuroleptic malignant syndrome
  - Reported with SSRI and SNRI alone or in combination with MAOIs, antipsychotics/dopamine antagonists
- Venlafaxine
  - No significant inhibition of P450 enzymes
  - Inhibitors of CYP2D6 and 3A4 may ↑ levels (can lead to cardiotoxicity)
- Desvenlafaxine
  - Renal clearance
- Duloxetine
  - Moderate 2D6 inhibitor
  - Inhibitors of 1A2 and 2D6 may increase levels
- Levomilnacipran
  - No significant inhibition of P450 enzymes
  - Inhibitors of 3A4 may increase levels
  - Not recommended for ESRD

# Switching/Discontinuing SNRIs

- These are some of the most difficult antidepressants to change due to withdrawal syndrome
- Venlafaxine is by far the most difficult
- Switching TO SNRI
  - Switch from SSRI typically well tolerated
  - Would consider direct switch without cross taper
  - Could consider cross taper if on max dose of SSRI
    - Be aware that fluoxetine and paroxetine and 2D6 inhibitors which affects duloxetine and venlafaxine
- Switching FROM SNRI
  - Going from NRI action to no NRI action necessitates a cross taper
- Switching BETWEEN SNRIs
  - Direct switch is typically well tolerated
  - Consider cross taper if on max dose
- Discontinuing
  - Very slow taper is recommended
  - If discontinuation symptoms are severe
    - Consider adding fluoxetine during taper and then discontinue fluoxetine
    - Consider 1% reduction, crushing tablet and disolving in 100mL liquid, disposing of 1mL at each step

# SNRI Summary

## Advantages

- Useful for multiple pain disorders and indications (esp. duloxetine)
- Added benefits of NRI
  - Energy
  - Concentration/ADHD
  - Improvement in depression and anxiety
- Less DDIs than SSRIs
- May work if failed SSRI

## Disadvantages

- Serotonergic side effects
- BP/cardiac risk
- All have short ½-lives (withdrawal)
- Do not have the same effect of higher doses helping with treatment-resistant anxiety as SSRIs do
- All have dosage adjustment recommendations for renal impairment

# Venlafaxine (XR) / Effexor® (1993)

- Advantages
  - Can be used in combination with mirtazapine (California Rocket Fuel)
    - For treatment resistant depression (other SNRIs can as well)
  - Works faster if titrated to 150 over 1 week's time (other SNRIs as well)
  - Of the antidepressants only venlafaxine, levomilnacipran, and vilazodone have no known 2D6i
  - At supratherapeutic doses >= 375mg there is dopamine reuptake inhibition
- Disadvantages
  - Withdrawal can be severe (may need to go down extremely slowly)
    - Very difficult to stop even if it was ineffective
  - Worst adverse sexual effects due to strong serotonergicity
  - Higher rate of death from OD than SSRIs, but less than TCAs
  - Does not have NRI properties until doses >= 150mg/day
  - At higher doses no clear advantage over other SNRIs
  - At lower doses no clear advantage over SSRIs
  - Titration can be tedious

# Duloxetine DR / Cymbalta® (2004) / Drizalma® (2019)

- Advantages
  - No titration required
  - Treats urinary incontinence (approved in many countries), and many pain syndromes
  - May have less HTN than venlafaxine (monitor BP)
  - Withdrawal not as bad as venlafaxine
  - Slight edge in effectiveness over other SSRIs and SNRIs
  - Drizalma®: new formulation may help with those that cannot swallow pills
- Disadvantages
  - Avoid with any hepatic impairment
  - Avoid with severe renal impairment (CrCl <30)
  - Moderate 2D6 inhibition (only SNRI with significant P450 system inhibition)
  - Due to effect on urinary incontinence (helping with it) may be bad choice for patients with urologic disorder like BPH where this would be a problem
  - Capsule has unique coating that appears in stool
    - Those with gastroparesis may have difficulty with the coating
    - Those post-bariatric surgery may not absorb properly
  - Transient orthostasis early in treatment

# Desvenlafaxine / Pristiq® (2008)

- Advantages
  - Minimal metabolism should lead to more consistent plasma levels than venlafaxine (active metabolite of venlafaxine)
    - May be good for those with liver impairment (duloxetine contraindicated)
  - Has relatively more effect on NET vs SERT than venlafaxine at comparable doses
  - Avoids drug-drug interactions since it is not metabolized
  - Longer ½-life than venlafaxine
    - Less withdrawal than venlafaxine
- Disadvantages
  - Duloxetine has similar advantages over venlafaxine and may be cheaper
  - Doses other than 50mg do not show increased benefit (maybe?)
    - 100mg dose = blood levels of 75mg TID of venlafaxine
    - Max dose is actually 400mg daily
  - Affected by P-gp
  - Company website doesn't even list advantages; just tells you how to get name brand

# Milnacipran / Savella® (2009)

- Advantages
  - Fibromyalgia
  - Chronic pain syndrome
  - Has greater NRI effect (may not be significant)
- Disadvantages
  - Urologic disorders, prostate disorders
  - Higher incidence of sweating and urinary hesitancy than other SNRIs (can use a1 antagonist for hesitancy)
  - Not FDA approved for mental health conditions in the US

# Levomilnacipran ER / Fetzima® (2013)

- Advantages
  - Stronger NRI than SRI may lead to improvements in pain, concentration, and motivation
  - Least sexual adverse effects due to least serotonergicity
  - No CYP enzyme inhibition
- Disadvantages
  - Stronger NRI than SRI may lead to worse cardiac effects
  - Lower doses recommended with renal impairment (CrCl < 60)
    - Contraindicated in end stage renal disease
  - Company website doesn't even list advantages over other medications even though it still isn't generic

# Atypical Antidepressants

# Atypical Antidepressants

- Agents other than MAOis, TCAs, SSRIs, and SNRIs
- Tricyclic Antidepressant
  - Trimipramine (Surmontil®)
- Serotonin Antagonist and Reuptake Inhibitors
  - Trazodone (Desyrel®), Trazodone XR (Oleptro®, discontinued), Nefazodone (Serzone®)
- Norepinephrine-Dopamine Reuptake Inhibitor
  - Bupropion (Wellbutrin®, Wellbutrin XL®, Aplenzin®, Forfivo®)
- Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)/TeCA
  - Mirtazapine (Remeron®)
- Serotonin Modulators and Stimulators (partially atypical)
  - Vilazodone (Vybriid®)
  - Vortioxetine (Trintellix®, formerly Brintellix®)
- NMDA Antagonists
  - Esketamine (Spravato®)
  - Dextromethorphan-bupropion (Auvelity®)
- 5-HT1A agonist
  - Gepirone (Exxua®)

# SARIs

# Serotonin Antagonist and Reuptake Inhibitors (SARIs)

- Two FDA approved phenylpiperizines
- Trazodone (Desyrel®)
  - FDA approved only for depression
    - Typically used as sedative-hypnotic, not for depression
  - Developed in contrast to TCAs in search of less anticholinergic effects
  - Trazodone XR (Oleptro®) released in 2010 reportedly caused less sedation, however it was discontinued in 2015
  - Despite short ½-life, trazodone is equally effective for depression given all QHS
  - Dose 2-3 hours before bedtime to further lessen adverse daytime effects
- Nefazodone (Serzone®)
  - FDA approved only for depression
  - Developed in contrast to trazodone in search for less sedating effects
  - Lost favor due to risk of hepatotoxicity **(BBW)**
  - Serzone® removed from market by manufacturer but generic still available

# SARI: Mechanism of Action

- Affects the following receptors in roughly this order for both SARIs
- Block postsynaptic 5-HT2A receptor (both): sedation, lack of ASEs
- Block postsynaptic 5-HT2C receptors (both, trazodone less): weight gain
  - Metabolite mCPP agonizes and is has stronger affinity so blockade may be minimal
- Block postsynaptic alpha 1 receptor (both): orthostasis
- Block postsynaptic H1 receptor (both): sedation
- Agonist at 5-HT1A (both): anxiolytic, antidepressant
- Block presynaptic reuptake of serotonin (both, weaker than above): antidepressant
- Block reuptake of NE and DA (nefazodone weakly): antidepressant

# SARI: Mechanism of Action

- Estimated occupancy of receptors by trazodone at different doses
  - 5-HT2A: 50% at 1mg, near complete at 10mg
  - SERT: 75% at 50mg, 86% at 100mg
  - 5-HT1A: 91% at 50mg
  - 5-HT2C: 83% at 50mg
  - a1: 88% at 50mg
  - H1: 84% at 50mg

# SARI: Mechanism of Action

- Metabolites
  - mCPP: metabolite of trazodone and nefazodone
    - Agonist at 5-HT2C: antidepressant, appetite loss, penile erection
    - Agonist at 5-HT1A: anxiolytic, antidepressant
    - Relatively weak agonist at 5-HT3: nausea
    - May lead to positive drug screen for MDMA due to SRA activity
  - Trazodone
    - mCCP: Active metabolite is at 10% the level of trazodone
  - Nefazodone
    - Triazoledione: Active metabolite is at 4-10x the level of nefazodone
      - Effects 5-HT2A and a1 similarly to nefazodone, but stronger at H1; much longer ½ life than nefaz
    - Hydroxynefazodone: Active metabolite is at 40% the level of nefazodsone
      - Effects 5-H12A, a1, and H1 similarly to nefazodone
    - mCCP: Active metabolite is at 7% the level of nefazodone
      - Agonizes 5-HT1A and 5-HT2C which nefazodone has much less effect on and acts as an antagonist
      - Much longer ½ life than nefazodone

# SARI: Adverse Effects

- CNS: Sedation (traz > nefaz), dizziness, confusion
- CV: Orthostasis (traz > nefaz)
- Hepatotoxicity: (nefaz > traz)
  - **BBW** with nefazodone
  - In US, about one case of severe liver damage reported for every 250,000 to 300,000 patient-years
  - Baseline LFTs and monitor periodically throughout therapy, warn patients s/sx of hepatotoxicity
- Priapism: (traz > nefaz)
  - Priapism risk highest: sickle cell anemia, leukemia, hypercoagulable states, cocaine/methamphetamine use; frequent morning erections are a warning sign
  - Erections lasting longer than 2-4 hours mandates a trip to the ED
- Anxiety/panic attacks: due to mCPP metabolite accumulation

# SARI: Drug Interactions

- Nefazodone
  - Potent 3A4 inhibitor
  - DDI for many drugs
    - Cisapride, triazolobenzodiazepines, estrogen, terfenadine
- Trazodone
  - CPY3A4 substrate
- mCPP is CYP2D6 substrate
  - Caution with CYP2D6 inhibitors or 2D6 slow metabolizers
  - Rapid mCPP accumulation can lead to anxiety and dysphoria
- Serotonin syndrome
  - MAO inhibitors contraindicated, however both block 5-HT2A and are relatively weak reuptake inhibitors at lower doses

# SARI Summary

## Advantages

- Compared to TCAs
  - Safer in overdose
  - No anticholinergic effects
- Compared to SRIs
  - Less GI effects
  - Minimal sexual dysfunction
  - Weight neutral
- Those with insomnia
- Inexpensive
- May be good in SSRI non-responders

## Disadvantages

- Daytime sedation
  - Most cannot tolerate sedation at doses needed to treat depression
- Orthostasis
- Dose titration required
- Priapism

# Trazodone (Desyrel®) (1981)

- Advantages
  - Agitation/aggression with dementia
  - Can be used in low doses during the day for anxiety if sedation is tolerated
  - Less likely to have sexual SEs, weight gain, serotonin syndrome
  - Lower risk in inducing mania in bipolar disorder
  - Insomnia, non-addictive
  - May have added antidepressant effect when used for insomnia as adjunct to other antidepressant
- Disadvantages
  - Very often not tolerated for depression due to sedative effects
  - SE of ataxia/intoxicated-like feeling, feeling "groggy"
  - Orthostasis
  - Priapism in 1/6000-8000 men (early indication of slow detumescence when awakening)

# Nefazodone (Serzone®) (1994)

- Advantages
  - Same advantages as trazodone
  - Compared to trazodone:
    - Less sedation, orthostasis, and priapism risk
    - May have some effect on NET and DAT
- Disadvantages
  - Hepatotoxicity
    - Risk is low but likely not worth potential benefit as there are many other antidepressants that work equally well
  - Potent 3A4 inhibitor
  - Not widely available
  - BID dosing

# NDRI

# Bupropion / Wellbutrin® (1985) / Zyban® (1997) / Aplenzin® (2008) / Forfivo XL® (2011)

- Generic renamed from amfebutamone in 2000
- Mechanism of action
  - Blocks reuptake of NE and DA, but much more NE
  - Noncompetitive antagonist of nicotinic receptors
  - Activates proopiomelanocortin (POMC) neurons in the hypothalamus
    - Appetite suppression
  - Anti-inflammatory: reduced TNFa
  - Stabilizes osteoclasts and decreases bone resorption
  - No blockade of alpha-1, M1, H1 receptors or SERT

# Bupropion / Wellbutrin® (1985) / Zyban® (1997) / Aplenzin® (2008) / Forfivo XL® (2011)

- Clinical Uses
  - Depression*, smoking cessation*, seasonal affective disorder*, ADHD, neuropathic pain, weight loss** (FDA approved as combination with naltrexone: Contrave®), treatment of sexual dysfunction**
- Substituted amphetamine
  - Banned in Russia and labeled as a narcotic
  - Only approved for smoking cessation in Australia, France, and the UK

*FDA approved indications **Manufacturer paid $3B fine for false marketing these conditions

# Bupropion Formulations

- Bupropion hydrochloride
  - Immediate release
    - Peaks at 2hrs
    - 100mg BID, 100mg TID, 450mg (divided TID/QID)
  - Sustained release (Wellbutrin SR®, Zyban®) ($10 vs $1 per pill!!)
    - Peaks at 3 hrs
    - 150mg daily, 150mg BID
    - Can be split but swallow whole
  - Extended release (extra long) (Wellbutrin XL®) ($100 vs $1 per pill!!)
    - Peaks at 5hrs
    - 150-450mg qAM
  - Extended release (Forfivo XL®) ($20 per pill!!)
    - 450mg qAM
- Bupropion hydrobromide
  - Aplenzin®: 174mg, 348mg, and 522mg dosage ($100-200 per pil!!)
  - Bromide has anticonvulsant properties so HBr formulation may (not proven) reduce seizure risk

# Bupropion: Adverse Effects

- Adverse Effects
  - **Insomnia**
  - **Agitation**
  - **Jitteriness**
  - Headache
  - Nausea
  - Rash
  - Seizures
  - Weight loss
  - Increased BP

# Bupropion and Seizure Risk

- Mostly with IR form at high doses
  - Recommended dose was IR 400-600mg in 1985
  - Withdrew from the market in 1986, reintroduced in 1989
  - Introduction of fluoxetine and stain of withdrawal resulted in fear of use for years
- With normal BMI, XL dosing, no risk factors: prudent doses have very low risk
  - 5% incidence of seizures at doses >450 daily, otherwise <1%
- If patient is on an AED, Wellbutrin should be tolerated and may help with concentration and energy side effects associated with AEDs
- Active metabolite probably associated with seizures
- Dose-related effect

# Bupropion and Seizure Risk

- Contraindication when combined with other risk factors for seizures
  - AV malformation, head injury, severe stroke, CNS tumor, CNS infection, hypoglycemia, hyponatremia, severe hepatic impairment, hypoxia
- Contraindication with history of anorexia/bulimia
- Contraindication with abrupt discontinuation of EtOH, benzos, barbiturates, anticonvulsants
- Caution in combinations of other drugs that increase seizure risk
  - TCAs, lithium, some antipsychotics (ie phenothiazines, thioxanthenes), theophylline, corticosteroids, stimulants, anorectants, hypoglycemia agents, alcohol, tramadol
- TCAs and even (es)citalopram have a higher risk of seizures

# Bupropion: Drug Interactions

- Drug Interactions
  - Affected by CYP2B6 inhibitors
    - Sertraline, norfluoxetine, clopidogrel, etc
  - Affected by CYP2B6 inducers
    - Carbamazepine, rifampicin, ritonavir, etc
  - Hydroxybupropion is potent inhibitor of CYP2D6
    - Affects fluoxetine, paroxetine, duloxetine, fluvoxamine, risperidone, venlafaxine, desipramine, dextromethorphan, etc
- Active metabolite: hydroxybupropion (elim half-life = 20 hrs)

# Bupropion Advantages

- Lacks SSRI-induced sexual dysfunction, apathy, weight gain
- Contrary to serotonin worsening bone density, bupropion can improve it
- Low likelihood of inducing mania in patients with bipolar disorder
- Partial responders to SSRI (May only need 150mg XL)
- Psychomotor slowing
- Atypical Depression
- Hypersomnia
- Nicotine Dependence (may use in conjunction with nicotine replacement)
- Cognitive slowing
- Well tolerated
- No alpha-1, H1, M1 effects
- Concentration problems
- Can be effective anxiolytic in some, can worsen in others
- Unique MOA
- Fatigue

# "Is Bupropion Your No. 1 Antidepressant Choice?"

- SSRIs
  - Weight gain
  - Sexual dysfunction
  - Long taper
  - Withdrawal
- 3 reasons providers skip bupropion
  - It won't treat co-morbid anxiety and may make it worse
    - 59% vs 64% compared to SSRIs for anxious depression
    - 54% vs 61% compared to SSRIs for anxiety
  - Fear of inducing seizures
    - 0.1% vs 0.08% risk compared to general populations with SR formulation
    - Only 2 case reports of seizures associated with XL
  - Titration
    - Need in the community of 2 separate scripts
    - 150mg for 1 week, then 300mg

# Bupropion Disadvantages

- Irritability, agitation "jittery"
- May increase blood pressure
- Strong 2D6 inhibitor (affects most ADs)
  - Doesn't affect sertraline, (es)citalopram, desvenlafaxine, vilazodone, trazodone
- May worsen anxiety in some
- Over activation (dose in morning)
  - May cause insomnia
- Concern over low weight
- Patients with history of or higher risk for seizures
  - Patients with eating disorder
- May worsen tics
- When used with dopaminergic agents, may precipitate psychosis, delirium, and dyskinesias

# NaSSA/TeCA

# Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

- Mirtazapine (Remeron®)
- Mianserin (Tolvon®)
  - Similar to mirtazepine, slightly different binding profile, not FDA approved
- Mechanism of Action is complex
  - Blocks alpha-2 autoreceptor (causes ↑ NE, 5-HT)
  - Blocks postsynaptic 5-HT2A → sedation, no ASEs
  - Stimulates 5-HT1A receptor (likely through a2)
  - Blocks postsynaptic 5-HT2C receptor → weight gain
  - Blocks postsynaptic 5-HT3 receptor → less GI SEs
  - Blocks H1 receptor → sedation, weight gain
- Adverse Effects
  - Sedation: commonly seen at lower doses
  - Weight gain

# Mirtazapine / Remeron® (1996)

- Drug Interactions
  - Possible decreased antihypertensive effects when combined with clonidine
  - Concomitant sedative agents may decrease motor skills, cognition
  - Avoid combination with ETOH due to sedation
  - Avoid combination with MAOi, however serotonin syndrome unlikely as it blocks 5-HT2A
- Dosing
  - Start at 7.5-15mg
  - Max dose is 45mg
    - Doses higher than 30mg rarely helpful

# Mirtazapine Advantages

- Advantages
  - Can be used as adjunct with other antidepressants
    - Combination with SNRI (California Rocket Fuel) for treatment resistant depression
    - Adjunctive benefit mostly seen in those with anxious depression
  - Low risk of sexual side effects
  - Insomnia
    - Higher doses may be less sedating due to alpha-2 blockade leading to increased NE
  - Low weight patient (7.5-15mg doses)
    - Avoidant restrictive eating disorder
  - May counteract drug-induced insomnia, agitation, anxiety, nausea, diarrhea (IBS), stomach cramps, GI side effects
  - Earlier onset of effect than SSRI
  - No CYP450 interactions
  - May mitigate negative symptoms of schizophrenia
  - May help mitigate amphetamine withdrawal, improving relapse
  - Can help with akathisia

# Mirtazapine Disadvantages

- Disadvantages
  - Weight gain
    - Can use Wellbutrin, stimulant to counter
    - More likely in premenopausal women
  - Patient with low energy
  - Oversedation
    - Less likely with higher doses
  - Some abuse potential
    - Sedation, delirium, hallucinations

# Serotonin Modulators and Stimulators

# Vilazodone / Viibryd® (2012)

- Mechanism of Action
  - 5-HT reuptake inhibitor via SERT (antidepressant effect)
  - 5-HT1A receptor partial agonist
    - Anxiolytic effect (?)
    - Less sexual adverse effect (?)
- Indications: Major depression

# Vilazodone: Pharmacokinetics

- Pharmacokinetics
  - $C_{max}$ reached within 4-5 hrs
  - Food **DOES** affect bioavailability
    - ~72% with food
    - Decreased ~50% without food
  - Highly (96-99%) protein bound
  - Extensively metabolized
    - CYP3A4
    - CYP2C19
    - CYP2D6
  - Terminal half-life: 25 hrs

# Vilazodone: Adverse Effects

- Adverse Effects
  - Nausea, diarrhea, headache, other serotonergic side effects
- Pregnancy: Information limited
- Drug Interactions
  - Strong inhibitors of CYP2D6 can increase vilazodone
    - ie bupropion
  - Strong inducers of CYP enzymes can decrease vilazodone
    - ie carbamazepine, phenytoin
  - Contraindicated with concurrent use of MAOI
  - No significant protein binding interactions noted
    - ie aspirin, warfarin
  - CYP inhibition
    - None: one of few antidepressants that has no inhibition of CYP2D6

# Vilazodone: Dosing

- Dosing
  - Recommended dose is 40 mg daily, 20mg with strong 3A4 inhibitor
  - Initially 10mg for 7 days, 20mg 7 days, then 40mg
  - Should be taken with food
    - Without food can lower levels by ~50%
    - Administration without food can result in inadequate drug concentrations and may diminish effectiveness
  - When discontinuing treatment, reduce the dose gradually

# Vilazodone

- Advantages
  - 5HT1A partial agonism
    - May have lower sexual side effect risk
      - Bupropion and vortioxetine are better
    - May have lower weight gain risk
    - Potential benefit for anxiety
      - Though effect size is lower than SSRIs in general
    - This "benefit" could be done with buspirone instead
  - No CYP inhibition
  - Patent expired June 2022 so it has become much cheaper
    - Consider if desiring to prescribe SSRI with buspirone
- Disadvantages
  - **Must** be taken with food for effectiveness
  - May be slightly worse with GI adverse effects than other SSRIs
  - No good evidence for improved efficacy or tolerability over other antidepressants
  - Sensitive to 3A4 inhibitors/inducers

# Vortioxetine /Trintellix® (2013)

- Originally called Brintellix®
  - Changed to Trintellix®
- Mechanism of Action
  - 5-HT reuptake inhibitor via SERT (antidepressant effect)
  - 5-HT1A receptor agonist (anxiolytic effect, ?less adverse sexual effects)
  - 5-HT1B receptor partial agonist (?antidepressant effect)
    - Sumatriptan is an agonist and does not improve depression
  - 5-HT1D receptor antagonist (?antidepressant effect)
    - Sumatriptan is an agonist, so might this med worsen migraines?
  - 5-HT3 receptor antagonist (Lower GI AEs)
    - May be the only benefit of all these extra effects
  - 5-HT7 receptor antagonist (antidepressant, sleep/wake modulation)
    - May benefit depression and cognition
- Indications: Major depression

# Vortioxetine: Pharmacokinetics

- Pharmacokinetics
  - $C_{max}$ reached within 7-11 hrs
  - Food does not affect bioavailability (~75%)
  - Highly (98%) protein bound
  - Extensively metabolized
    - CYP3A4/5
    - CYP2C9/19
    - CYP2D6
      - Produces carboxylic acid metabolite
  - Terminal half-life: **66 hrs**

# Vortioxetine: Adverse Effects

- Adverse Effects
  - Nausea, vomiting, constipation, other serotonergic side effects
- Pregnancy Category C
- Drug Interactions
  - Strong inhibitors of CYP2D6 can increase vortioxetine
    - ie bupropion
  - Strong inducers of CYP enzymes can decrease vortioxetine
    - ie carbamazepine, phenytoin
  - Contraindicated with concurrent use of MAOI
    - As well as for **3 weeks** after stopping vortioxetine
  - No significant protein binding interactions noted
    - ie aspirin, warfarin

# Vortioxetine

- Advantages
  - Claims of improved cognitive ability, weight, sexual dysfunction (?)
    - Fluoxetine originally reported as 1.8% ASEs so this may be inaccurate as well
  - Does not affect CYP enzymes
  - Is metabolized by multiple CYP enzymes so is less affected by inhibitors and inducers except bupropion which increases levels 128%
  - Best tolerated: has lowest drop-out rate of antidepressants (?)
  - Long ½-life good for compliance and withdrawal
  - 5HT-3 blockade may help with nausea (?)
- Disadvantages
  - Essentially just another SSRI
  - Above listed advantages are from trials only
    - Not widely used; trials almost all limited to those done for approval
  - Effect size is on the low end at 0.28
  - Expensive: on patent until 2031

# NMDA Receptor Antagonists

# Ketamine IV

- NMDA receptor antagonist
- FDA approved as dissociative anesthetic (1970)
- Schedule III controlled substance
- Off-label for suicidality since early 2000s
- Has similar effects on the brain as ECT
  - Likely increases levels of BDNF and ultimately increases activity of mTOR
    - mTOR increases protein synthesis at synapses; this in turn increases synaptogenesis, especially in the prefrontal cortex
  - Turns on rapid response genes that activate structural genes in the limbic system neurons and start replacing receptors and transport systems within the cells
- 50:50 racemic mixture of esketamine and arketamine
  - Both are metabolized to hydroxynorketamine
- 40 minute infusion (antidepressant effects in less than 24 hours)
- Dose at 0.5-1mg/kg over 30-40 minutes 2-3 times per week for 2-3 wks
- Hold sedatives and stimulants during treatment
- 100% bioavailability

# Esketamine (Spravato®) (2019)

- FDA indications
  - Treatment-resistant depression
  - MDD with suicidality
- Intranasal given in clinic twice weekly changing to weekly at week 5
- 30-50% bioavailability
- Schedule III controlled substance
- REMS required
  - Requires extensive healthcare setting processes to include having on-site prescriber, registration of site, registration of patient, training of staff, etc.
  - Patient counseling
  - Patient monitoring for 2 hours
  - Extensive record keeping

# Esketamine

- Almost as effective as ketamine for acute depression and SI
  - Requires more treatments for effect
  - Cost vs Ketamine is ~$32.4K vs $2.5K per year
  - 27-50% response rate for treatment-resistant depression
  - 2023 study showed no difference from antidepressant alone after 6 weeks
    - Chen X et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Plus a Newly Initiated Oral Antidepressant in Adult Patients with Treatment-Resistant Depression: A Randomized, Double-Blind, Multicenter, Active-Controlled Study Conducted in China and USA. Neuropsychiatr Dis Treat. 2023 Mar 31;19:693-707.
- SL formulation being investigated for home use
- Effect Size for AD augmentation similar to AP at meager 0.15-0.23

# Esketamine: Adverse Effects

- 5 BBWs
  - Sedation
  - Dissociation (41-48%)
  - Respiratory Depression
  - Abuse and misuse
  - Suicidal thoughts and behaviors (generic antidepressant BBW)
- Increased BP (10-15%)
- Altered taste (19-20%)
- Nausea (27-28%)
- Vomiting (9-10%)
- Anxiety (13-15%)
- Dizziness (29-45%)
- Headache (20%)
- Decreased sensations (13-18%)
- Sedation (23-29%)

# Esketamine

- Advantages
  - Offers new mechanism of action
  - Reports of higher effect size
  - One of the few FDA approved treatments for treatment-resistant depression
  - Home use version may become available
- Disadvantages
  - Conflicting evidence for improved efficacy over standard antidepressants (inferior to ketamine)
  - REMS requirement is onerous (none for ketamine)
    - Requirement to give it frequently in the clinic is onerous for prescriber and patient
  - 5 BBWs (none for ketamine) and many adverse effects
  - Schedule III controlled substance
  - Cost: Generic eligible in 2024 but isn't (ketamine much cheaper)

# DXM+Bupropion (Auvelity®) (2022)

- FDA approved for MDD
- Mechanism of Action
  - Dextromethorphan (DXM)
    - NMDAR antagonist
    - σ1 agonism
      - Altered trafficking of AMPA
      - Increased synthesis of BDNF
      - Interferes with pro-inflammatory compounds
    - SSRI
  - Bupropion
    - 2D6 inhibitor
      - Extends ½-life of DXM, DXM peak levels increased 40x, AUC by 60x
      - Other AD 2D6 inhibitors can contribute to serotonin syndrome with DXM such as fluoxetine
      - Similar tactic used with Nuedexta which combines DXM with quinidine
    - NDRI

# Dextromethorphan+Bupropion

- Positive Effects
  - More rapid onset of symptom relief (1 week)
  - 46.5% vs 16.2% bupropion alone achieved remission in 6 week trial
    - An unpublished trial showed no difference
- Adverse Effects
  - Somnolence, nausea, dizziness, headache, dry mouth, hypertension
  - No cases of psychosis, serotonin syndrome, dissociation, addictive behaviors

# Dextromethorphan+Bupropion

- Dosing
  - 45mg DXM / 105mg bupropion SR daily for 3 days
  - 45mg DXM / 105mg bupropion SR BID
  - 2D6 poor metabolizers: do not increase dose at day 3
- Can dose separately as generics for ~$50 vs $1200/month
  - Bupropion XL better tolerated qAM and DXM QHS
  - Bupropion does not need to be BID to inhibit 2D6
  - Also allows flexibility in dosage of each used
  - Doses of DXM as high as 60mg BID have been tested
  - “BupropiDex” is a DXM product that does not contain bupropion

# Dextromethorphan+Bupropion

- Advantages
  - May work more quickly than other antidepressants
  - May be more effective but evidence is mixed
  - Offers unique mechanism of action as NMDAR antagonist in oral form
- Disadvantages
  - Cost: ineligible to be generic until 2034
  - Potential for abuse
  - May not be more effective than other options
  - 2D6 inhibition

# 5-HT1A Partial Agonist

# Gepirone ER / Exxua® (2023)

- Azapirone similar to buspirone
  - Two others available in Japan
    - Tandospirone for depression and anxiety
    - Perospirone for psychosis (Also blocks D2 and 5HT2A
- Mechanism of Action
  - 5-HT1A receptor partial agonist
    - Similar to buspirone
  - Metabolite (1-PP) is same as buspirone
    - a-2A antagonist
      - Similar to mirtazapine, leads to increase in NE and 5HT
      - Reportedly more significant for gepirone than buspirone
      - Dizziness, nausea, headache
- Indications: Major depression

# Gepirone ER: Pharmacokinetics

- Pharmacokinetics
  - $C_{max}$ reached within 6 hrs
    - With low fat meal (~200 kcal): 27% higher
    - With medium fat meal (~500 kcal): 55% higher
    - With high fat meal (~850 kcal): 62% higher
    - Instruction to be taken with food unlike buspirone
  - Bioavailability: 14-17%
  - Moderate (72%) protein binding
  - Extensively metabolized via CYP3A4 similar to buspirone
  - Terminal half-life: **~5 hours** (longer than buspirone)

# Gepirone ER: Adverse Effects

- Adverse Effects
  - Nausea (35%), dizziness (49%), fatigue (15%), headache (31%), insomnia (14%)
  - These adverse effects are much higher than buspirone
- Warning of induction of mania is likely zero to minimal
- Generic antidepressant black box warning for suicide risk in those <25
  - Warning is not on buspirone
  - Company website reports that this risk does not exist
- Pregnancy Category: not yet determined

# Gepirone ER: Drug Interactions

- Strong inhibitors/inducers of CYP3A4 have X rating
  - Inhibitors increase levels 5x
  - Inducers decrease by **20-29x!**
  - Do not combine
- Moderate inhibitors/inducers of CYP3A4 have D rating (increase 2.5x)
  - Decrease gepirone dose by 50%
- Contraindicated with concurrent use and 14 days after stopping MAOI
  - This risk is likely zero to minimal
- Possible decreased antihypertensive effects when combined with clonidine
- Caution with use with other QT prolongating agents

# Gepirone ER: QTc Prolongation

- Label instructs
  - Measure QTc at initiation, dose adjustments, and periodically
  - Correct electrolyte abnormalities prior to initiation
  - Do not initiate if QTc is >450
- Even thioridazine with a black box warning does not have such strict guidelines
  - Avoid combination with other QTc prolongating drugs, patients with Long QT Syndrome, and hx of cardiac arrhythmias
- Ziprasidone also known to prolong QTc does not require an EKG
- 2-times max dose of gepirone led to 18msec prolongation

# Gepirone ER

- Advantages
  - Potentially similar efficacy as other antidepressants without serotonergic adverse effects
    - Sexual dysfunction and may enhance sexual functioning
    - Weight neutral
    - Not sedating
  - Once daily dosing vs BID/TID with buspirone
  - Does not affect CYP enzymes

# Gepirone ER

- Disadvantages
  - **QT prolongation risk appears to be extremely significant**
    - Frequent EKG and electrolyte testing makes prescribing very onerous
  - Drug was developed in 1986 and FDA declined approval at least 4 times due to lack of efficacy prior to company finally getting 2 positive trials after 30 years leading the way to FDA approval
  - Necessity to take with food
  - Dizziness, nausea, headaches are relatively significant
  - Extremely vulnerable to 3A4 inhibition/induction
    - Interactions are D/**X** ratings
  - Very short ½-life (is daily dosing adequate?)
  - High cost relative to buspirone, but generic eligible in 2025
  - Manufacturer does not appear to be putting effort into marketing (why?)
  - The worst antidepressant? Use buspirone instead

# Antidepressant Dosing

# Optimal Daily Dose Ranges for Receptor Selective ADs

| Compound | Optimal Dose for Depression (mg) | Max Approved Dose in Depression (mg) (may be needed for anxiety) | Max Possible Dose (mg) |
|---|---|---|---|
| Bupropion | 150-300 | 450 | 450 |
| Citalopram | 20-40 | 40 | 40 |
| Desvenlafaxine | 50 | 100 | 400 |
| Duloxetine | 40-60 | 120 | 120 |
| Escitalopram | 10-20 | 20 | 40 |
| Fluoxetine | 20-40 | 80 | 120 |
| Fluvoxamine | 100-150 | 300 (in OCD) | 300 |
| Mirtazapine | 15-30 | 45 | 90 |
| Paroxetine | 20-30 | 50 | 75 |
| Sertraline | 50-100 | 200 | 400 |
| Trazodone | 150-300 | 600 | 600 |
| Venlafaxine | 75-150 | 225 | 600 |

- 5% of patients fall outside of the bell curve and may require higher or lower doses

From the Article: "Antidepressants: When Dosage Matters" by Rehan Aziz, MD, *The Carlat Psychiatry Report*, Volume 20, Number 4, April 2022

# CYP450 Enzyme Phenotypes

| Enzyme | Phenotype | Asian (%) | Black (%) | White (%) |
|---|---|---|---|---|
| 2C9 | Poor | 0.4 | 0 | 1 |
| | Intermediate | 3.5 | 13 | 33 |
| | Ultrarapid | | | |
| 2C19 | Poor | **18-23**[1] | 1.2-5.3 | 2-5 |
| | Intermediate | 30 | 29 | 18 |
| | Ultrarapid | | | |
| 2D6 | Poor | 1-4.8 | 1.9-7.3 | **7-10** |
| | Intermediate | **51** | **30** | 1-2 |
| | Ultrarapid | **0.9-21** | 4.9 | 1-5 |

[1] Japanese: 20.3, Chinese: 13.6, Korean: 13.7

# Hepatic/Renal Dosing

- Hepatic dosing
  - No adjustment necessary
    - Desvenlafaxine, milnacipran, levomilnacipran, vilazodone, vortioxetine
  - Contraindicated with any impairment
    - Duloxetine, isocarboxazid
  - Dose adjustment recommended
    - All SSRIs, venlafaxine, bupropion, gepirone ER, doxepin, selegeline, phenelzine
  - No recommendations made but caution advised
    - All others
- Renal dosing
  - All SNRIs
  - Gepirone ER
  - Paroxetine

# Investigational ADs

# Investigational Antidepressants

- Neurosteroids (ie brexanolone, zuranolone)
- Glutamate activity (ie esketamine, hydroxyketamine, ALTO-202)
- 5-HT2A agonists (ie Psilocybin, LSD, MDMA)
- Sestrin modulators (mTOR) (ie NV-5131)
- BDNF modulators (ie ALTO-100)
- H3 inverse agonists (ie ALTO-203)
- MT1/2 agonists (ie agomelatine)
- TrkB agonists (ie LM22A-4)
  - BDNF binds this receptor
- κ-opioid receptor antagonists (ie buprenorphine)
- Histone deacetylase (HDAC) inhibitors (HDIs)
  - Valproic acid
- Fatty acid amide hydrolase (FAAH) inhibitors
  - FAAH breaks down anandamide (endogenous cannabinoid)

# Neurosteroids

- Pregnanolone is a precursor of allopregnanolone and is available over the counter through mostly herbalists and may be prescribed by alternative medicine practitioners
- Pregnanolone levels fall post-partum and is thought to contribute to depression
- Brexanolone and zuranolone are synthetic allopregnanolone
- Affects $GABA_A$ receptors that are not sensitive to benzodiazepines
  - Act as positive allosteric modulator of $GABA_A$
  - At low and high doses stimulates the $GABA_A$ receptor
  - At medium doses inhibit $GABA_A$
  - These same levels are seen during the luteal phase
  - Not known to be habit forming

# Glutamate Activity: Investigational

- REL-1017 (esmethadone, dextromethadone, S-(+)-methadone)
  - Antagonizes NMDA receptors
  - 20 times lower affinity for opioid receptors than levomethadone
  - Low risk for respiratory depression and abuse
  - Phase 2 trials showed rapid antidepressant effects
  - Phase 3 trials (Dec 2024) have been disappointing; future is unclear
- (2R,6R)-hydroxynorketamine (RR-HNK)
  - Activates AMPA glutamate ion channel with downstream effects increasing BDNF and mTOR
    - Does not bind the NMDA glutamate receptor
  - Demonstrated rapid antidepressant activity in animal models
  - Phase 1 trial (2024) demonstrated lack of dissociation and abuse potential
- ALTO-202
  - GluN2B subunit-containing NMDA receptor negative allosteric modulator
  - Phase 2 top line results expected in 2025

# 5-HT2A Agonists (Schedule I Substances)

- Being Researched for psychodelic-assisted therapy
- Many centers for use opening up around the US, UK, and Australia
- Growing interest by psychiatrists (>50% report wanting to incorporate)
- Psilocybin
  - Recently legalized for use in Australia
  - Decriminalized in several cities in the US
  - Legal use in Oregon and Colorado
    - Colorado also legalized DMT, ibogaine, and mescaline
- LSD
  - FDA recently granted break through status for GAD
  - Also research showing benefit for depression and substance abuse
- MDMA
  - FDA granted breakthrough status for PTSD
  - Also research for social anxiety in autism, alcohol use disorder, and MDD
  - Approved in Australia in 2023
  - FDA voted against approval in 2024

# Sestrin Modulator (NV-5138)

- The protein kinase mammalian target of rapamycin (mTOR) forms part of a protein complex that is responsible for many functions, including cell growth and synaptogenesis
- Researchers have hypothesized that several antidepressants, including esketamine/ketamine, increase neuronal levels of mTOR as one of the final actions in a molecular cascade to treat depression
- The amino acid leucine activates mTOR Complex 1 (mTORC1) by binding to the upstream regulator sestrin
- NV-5138 is a selective small molecule modulator of sestrin, which readily crosses the blood-brain barrier and putatively facilitates sestrin's activation of the mTORC1, ultimately providing a rapid antidepressant effect through synaptogenesis in the medial prefrontal cortex (mPFC)
- In theory, NV-5138 would bypass much of the molecular cascade that is currently necessary to increase brain derived neurotropic factor (BDNF) and ultimately activate mTORC1, hence providing a more direct path to synaptogenesis
- This might result in a targeted response with less adverse effects
- A single dose of NV-5138, in the required presence of BDNF, resulted in a rapid and long-lasting antidepressant effect in rats by putatively increasing synaptogenesis in the mPFC
- Currently in Phase 2 trials

# BDNF Modulators

- ALTO-100
  - Mechanism is currently unknown
    - Indirectly **modulates BDNF**, which is enhanced by a number of things to include healthy diet, exercise, psychotherapy
    - Has been shown to enhace hippocampal neuroplasticity and neurogenesis
  - Studied since 2010 for MDD, bipolar disorder, and PTSD
  - MDD trials
    - Phase 2a results in 2023 were positive
    - Phase 2b results in 2024 were not better than placebo
  - Bipolar disorder Phase 2b trial initiated in 2024
    - Results expected 2026

# H3 Inverse Agonism

- ALTO-203
  - Mechanism of action
    - H3 receptor inverse agonist
      - Stimulant pitolisant is a H3 antagonist
      - Leads to dopamine release in the reward system
  - Currently in Phase 2 trials for MDD with anhedonia
    - Top line results expected in 2025

# MT1/2 Agonism

- ALTO-300 (agomelatine)
  - Mechanism of action
    - MT1/2 receptor agonist (like remelteon)
    - 5-HT2C antagonist (like mirtazapine)
  - Approved in the EU (2009) and Australia (2010) by Servier
  - Sold to Norvartis
  - Development discontinued in the US in 2011after lackluster trial results
  - Sold to Alto
    - Phase 2a trials were positive
    - Phase 2b results expected in 2025

# TrkB Agonist (LM22A-4)

- Tropomyosin receptor kinase B
- Agonists
  - BDNF
  - Amitriptyline
  - LM22A-4
    - Has produced neurogenic and neuroprotective effects in animal models
- Positive allosteric modulators
  - NMDAR antagonists (ketamine, hydroxynorketamine)
  - Several antidepressants (ie fluoxetine, imipramine)
  - Serotonin psychodelics (ie LSD, psilocin)
- Target of drugs in development for Alzheimer's Disease, Parkinson's Disease, and other neurodegenerative and psychiatric disorders

# K-opioid receptor antagonists

- Buprenorphine/samidorphan (ALKS-5461)
  - Buprenorphine: mu-opioid partial agonist, k-opioid antagonist
  - Samidorphan: mu-opioid antagonist
    - May reduce abuse potential of buprenorphine
  - Under development as add on to antidepressant in treatment-resistant depression
  - Has had several failed trails and denials from the FDA

# Medication Selection

# Selecting an Antidepressant

- Patient preference
- Previous response or familial response
- Side effect profile
- Interactions
- Indication
- Severity and type of depression and symptoms
- Financial consideration / availability
- Half-life
- Suicidal ideation or risk of overdose
- Co-morbidities
  - Medical/psychiatric disorders, substance abuse history
- Age
- Pregnancy, breastfeeding
- Based on symptoms

# Tips for Selecting an Antidepressant

- Select based on adverse effects
  - Patients who experience sexual dysfunction
    - Bupropion
    - Mirtazapine
    - SSRIs are worst (especially paroxetine and fluoxetine)
  - Patients who are concerned about weight gain
    - Bupropion
    - **Avoid** paroxetine and mirtazapine
- Inflammation: high CRP has indicated better response to
  - TCAs
  - Dopaminergics (bupropion, pramipexole)
  - Diet changes
  - Omega-3 FAs (may need up to 4000mg/day)
  - Lower response to
    - SSRIs

# Tips for Selecting an Antidepressant

- Select based on predominating symptoms (less important than ASEs)
  - Patients with primarily low energy and anhedonia
    - Antidepressant with NE effects
      - SNRI (duloxetine, venlafaxine)
      - Bupropion
      - Stimulants
    - Fluoxetine
    - Theoretically may help
      - Vortioxetine, cariprazine, pramipexole
    - **Avoid**
      - Meds that are sedating (paroxetine, mirtazapine, trazodone, etc.)
  - Patients who are anxious and irritable
    - Antidepressant with serotonergic activity
      - SSRIs

# Tips for Selecting an Antidepressant

- Select based on medical condition
  - Hypertension, cerebrovascular disease
    - Avoid venlafaxine, duloxetine, TCAs, MAOIs
    - SSRIs may be preferred
  - Diabetes
    - Avoid paroxetine, MAOIs, TCA, mirtazapine (weight gain)
    - CYP3A4 inhibitors (DDI sulfonylurea)
  - Parkinson's
    - Bupropion preferred (↑ DA)
    - Avoid amoxapine and antipsychotics
  - HIV/AIDS
    - Avoid nefazodone, fluvoxamine (or other CYP3A4 inhibitors)
  - Seizures
    - Avoid bupropion and TCAs

# Depression Treatment Algorithm

- 1st: SSRI/Bupropion
- 2nd: Bupropion/SSRI/different SSRI/SNRI
- 3rd: One from step 2 not tried
- 4th: MAOi/ECT/TCA
- 5th: One from step 4 not tried
- Augmenting agents can also be tried at each step

# Antidepressant Tier List

- S Tier
  - Lifestyle modifications and psychotherapy, ECT, TMS
- A Tier
  - Bupropion, duloxetine, escitalopram
- B Tier
  - Sertraline, fluoxetine, mirtazapine, DXM+bupropion
- C Tier
  - MAOi (tranylcypromine), TCAs (desipramine, nortriptyline), trazodone, citalopram, desvenlafaxine, ketamine
- D Tier
  - Paroxetine, fluvoxamine, other MAOis, other TCAs, levomilnacipran, esketamine, vortioxetine
- E Tier
  - Nefazodone, vilazodone, venlafaxine
- F Tier
  - Gepirone ER

# American Psychiatric Association Practice Guidelines (2010)

- **Level I Recommendations**
  - SSRIs, SNRIs, bupropion, TCAs, and MAOIs are comparable in effectiveness
  - SSRI, SNRIs, mirtazapine and bupropion are optimal for most patients
  - MAOIs reserved for treatment-resistance and atypical depression
    - Atypical depression
      - Hypersomnia
      - Hyperphagia
      - Leaden paralysis
      - Interpersonal rejection sensitivity

# AD Effectiveness

# Effect Sizes

- 0-0.25: No to small effect
- 0.25-0.5: Mild benefit
- 0.5-1.0: Moderate to large benefit
- >1.0: Huge benefit

- >0.5: Clinically meaningful benefit

# Effect Size of Antidepressants

| Compound | Effect Size |
|---|---|
| *ECT* | 2.1 |
| *rTMS* | 1.3 |
| Ketamine | 0.9 |
| Esketamine | 0.7/~0.2 |
| Amitriptyline | 0.62 |
| Fluvoxamine | 0.44 |
| Duloxetine | 0.38 |
| Trazodone | 0.38 |
| Mirtazapine | 0.37 |
| Venlafaxine | 0.34 |
| Clomipramine | 0.33 |
| Nefazodone | 0.31 |
| Vortioxetine | 0.31 |

| Compound | Effect Size |
|---|---|
| Paroxetine | 0.3 |
| Fluoxetine | 0.3 |
| Milnacipran | 0.3 |
| Sertraline | 0.28 |
| Levomilnacipran | 0.27 |
| Vilazodone | 0.26 |
| *Agomelatine* | 0.25 |
| Desvenlafaxine | 0.24 |
| Bupropion | 0.22 |
| Citalopram | 0.21 |
| Escitalopram | 0.21 |
| Antipsychotics | 0.2 |
| *Reboxetine* | 0.19 |

Cipriani et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. 2018.

# AD Ineffectiveness Explanations

- Placebo response is very robust
  - Antidepressant and placebo response likely overlap
  - Research techniques do not mimic real world practice
    - Likely amplify placebo response due to intensity of interventions
- Diagnosis
  - More severe symptoms have more robust response
  - Accuracy of diagnosis plays a big role
    - Worse outcomes with bipolar disorder
    - Poor response with adjustment disorder, PD, ADHD
    - Less response with PTSD
    - Type of depression has better response to different medications
- STAR*D revealed 2/3 of patients with remission
- Patients are often not optimized on medications properly
  - Kept on ineffective med too long
  - Medications with all the different MOAs often not tried

# AD Ineffectiveness Explanations

- Heterogeneity
  - Average hides effectiveness
  - Patients do not respond uniformly
    - Many do much better, many little to no response, many much worse
  - Large response: 25% vs 10% placebo
  - Minimal response:12% vs 22% placebo
- Rating scale used by research mixes many symptoms giving less weight to most significant symptoms
  - Difficulty in assessing and equilibrating depressive symptoms
  - Symptoms are very heterogeneous among patients
    - Different patients more affected by different symptoms
    - Assessment is completely qualitative and mostly subjective
  - Effect size: 0.27 with whole scale vs 0.4 for just depressed mood sxs
- Similar effect size as therapy and many other medical treatments

# Antidepressant Effectiveness

- 12% of Americans are on antidepressants
  - Women over 40: 25%
- 80% of psychiatric meds are given by primary care
  - Given after a very short appointment
  - Often symptoms are due to a transient situation
  - Positive effect from med may actually just be due to time
    - May stay on medication for indefinite period of time
- Little to no benefit beyond placebo for mild to moderate depression, adjustment disorder, PD, etc
  - Time, exercise, and therapy more effective
- Most effective for severe depression

# Antidepressant Effectiveness

- Placebo effects: ~75-80% of antidepressant effect is placebo
  - These are real effects but have nothing to do with the MOA
    - Often a placebo after a first visit with new provider then wanes after months
    - Often a placebo upon stopping treatment; depression returns after a few months
      - Includes medication, lifestyle changes, and therapy
    - Often a placebo with any kind of change, but may not be sustained
  - Effect size of placebo is ~1.59 for antidepressants for MDD and GAD
    - Higher for milder symptoms, lower for treatment resistance
    - Highest after first visit
- How you talk about the medications affects how they help or harm
  - Optimistic attitude towards medications
    - Drug-naïve patients -> improved outcomes with enthusiasm
    - Patients that have failed numerous meds -> worse outcomes
      - Maintain realistic humility about limits of medications
      - Remind patient that medication is less likely to work if they don't commit to the plan
  - Education of possible adverse effects
    - Patient more likely to get the adverse effects (nocebo)
    - Patient also more likely to continue treatment if they get the effects

# Antidepressant Effectiveness

- Characteristics of the pill affect its effectiveness
  - Gold>Silver>Colored>White
    - Red, angular shape=activating
    - Blue, curved shape=calming
  - Angular shape>curved shape
  - More frequent dosing>less frequent
  - Higher dose>lower dose
  - Brand name>generic
  - More expensive>cheaper
  - Worse taste>better taste
  - More painful treatments>less painful
  - Capsule>tablet
  - Route of administration: Surgery>IV/IM>PO

# Improving Effectiveness of ADs

# Using Dynamics to Improve Response

- Addressing psychological and interpersonal dynamics can help to resolve symptoms
  - Avoiding the mind-body split
    - The delusion that we know exactly how our medications work
    - The division of mind and body between therapist and prescriber
    - Patient focused vs illness centered (biologic) focus
    - Medications support therapy and therapy addresses issues with medications
  - Knowing who the patient is
  - Focusing on the alliance
  - Attending to ambivalence
  - Being aware of counter-therapeutic uses of medications
  - Addressing counter-transference enactments in prescribing

# Dynamics: Know the Patient

- Neuroticism has less AD response
- Attachment style (secure attachment vs dismissive attachment)
  - Securely attached patients respond and adhere better to meds
- Defensive style
  - Those with immature defense mechanisms have less AD response
- Locus of Control
  - Those with external locus of control vs internal have less response
- Sociotropy vs autonomy
  - Those anxiously connected/responsive to their social environment have less response than more autonomous patients (75% vs 33%)
- Expectations of treatment
  - Those with high vs low expectation of response (90% vs 33%)
  - Those with negative vs positive expectations have more adverse effects

# Dynamics: Know the Patient

- Theory of illness
  - Those who view their symptoms as psychological vs biological have better response to medication (mild-moderate depression)
- Developmental history
  - Social disadvantage
  - Attachment style
  - Early trauma
  - Characteristic relational patterns are repeated with medications
- Explore relationship with medication

# Dynamics: Focus on Alliance

- Equally important in therapy and med management
- Good therapeutic alliance beats active drug
  - Effectiveness has more to do with WHO is giving treatment than WHAT they are giving
    - Top 1/3 of psychiatrists giving placebo had better results than bottom 1/3 of psychiatrists giving active drug
      - Top 1/3 may have more psychological vs biological view of depression
      - "The doctor is the drug." – Dr. Michael Balint, 1958

# Dynamics: Focus on Alliance

- Negative transferences
  - Patients with past harm by caregivers or authority systems may expect harm
  - Medications can re-activate these schemas
    - Experiences of rejection
      - Take this and get out of my office
    - Sexual abuse
      - Touching through care on physical exam can elicit
      - Taking medication orally or parenterally may elicit
    - Physical or psychological abuse
      - Patient concern of being "turned into a zombie": control issues
    - Systemic oppression
      - Generational medical neglect/abuse
  - Manifestations
    - Efforts to control
      - Struggling around dose, med, compliance, etc
      - Stopping medication after it starts working
    - Nocebo responses

# Dynamics: Focus on Alliance

- Improving alliance
  - Warmth, presence, empathy
    - Tone of voice (can improve by 162%)
    - Any technology use during appointment -> worse result
      - Can reduce likelihood of returning from 77% to 25%
    - Treating the patient as a person instead of a biological substance that interacts with medications
  - Shared decision making
    - Any banal option given improves outcome (ie QD vs TID)
    - Respect for treatment preferences (med vs therapy vs both)
    - Agreement about targets
  - Good communication
  - More frequent appointments

# Dynamics: Ambivalence

- Resistance **TO** medications
  - Concern of harm
    - Worry about adverse effects and becoming dependent
    - Not wanting to take medications
    - About getting better
      - Secondary gain (sick role)
      - What will you lose if you get better?
    - About the provider
  - Leads to non-adherence, non-response, or strong nocebo effects
  - 2-3% signal ambivalence but 23-36% will reveal if asked
  - Important to attend to non-verbal communication
  - Have conversation about ambivalence
  - Readiness for change
    - Medications only work when patient is ready
    - Patients with panic disorder improved more when ready to change and placebo drug than with benzo and precontemplative

# Dynamics: Counter-therapeutic Uses

- Patient surrenders authority to the doctor
- Takes passive position in treatment
- Resistance **FROM** medications
  - Attach to biological explanation of symptoms (medication is a defense)
    - Bipolar vs cluster B
    - The good part is me, the bad part is my diagnosis
    - Not feeling responsible for their behavior
  - Like and want medications
    - Medications undercut their agency and development to heal
      - Use medication to dull appropriate emotions
    - May misuse the medications
    - Medication replaces people and defenses
      - Vicious cycle of more rejection, disappointment, and withdrawal
  - Report feeling better but don't appear better
    - Initial improvement followed by getting worse
  - Leads to chronic condition that doesn't improve

# Dynamics: Counter-transference

- Be aware of counter-transference
  - Avoid prescribing to "deal" with patient
    - Giving in to what patient is asking for
    - Polypharmacy
      - Several symptom-treating medications
      - Sedatives, stimulants, etc
      - Frequent medication changes
    - Remember for many conditions such as adjustment disorder, PD, mild to moderate depression, etc medications are mostly ineffective
      - May get some benefit from placebo of medications but if not, then excessive adjustments are not likely to help the patient
      - Addressing these psychodynamic issues are more likely to lead to benefit, but this is NOT easy

# Psychogenomic Testing

# Psychogenomic/Pharmacogenetic Testing

- Recommended tests
  - CYP2D6, CYP2C19: How fast or slow they metabolize
  - Increased risk of SJS with certain HLAB variants
    - Carbamazepine, lamotrigine, phenytoin, allopurinol, antibiotics, NSAIDs, Tylenol
  - MTHFR: L-methylfolate
- Insufficient evidence for testing benefit
  - COMT gene: COMT metabolizes neurotransmitters
  - Tests that recommend medications
  - SLC6A4 (Serotonin transporter polymorphism) gene
    - Those with hx of major stressors and short allele gene (SL or SS) vs long allele gene (LL) are more vulnerable to depression
    - Those with LL type have more SERT pumps
    - Previously thought that gene type might predict response to medication, however current evidence suggests no relevance
      - SL/LL may respond better to higher doses of SSRIs
      - SS may not respond well to SSRI

# Psychogenomic/Pharmacogenetic Testing

- P-glycoprotein (P-gp) transporter gene
  - Transports protein at BBB that removes unwanted chemicals (also medications) out of the CNS
  - Some patients make less P-gp
  - Study showed that patients given test: 72% vs 28% remission
  - Test may suggest higher doses for some medications
    - Desvenlafaxine (dose up to 200mg), citalopram
    - Risperidone and paliperidone are significantly affected
  - Unaffected antidepressants
    - Bupropion, duloxetine, fluoxetine, mirtazapine
- P-gp inhibitors
  - Fluoxetine, sertraline, paroxetine, fluphenazine

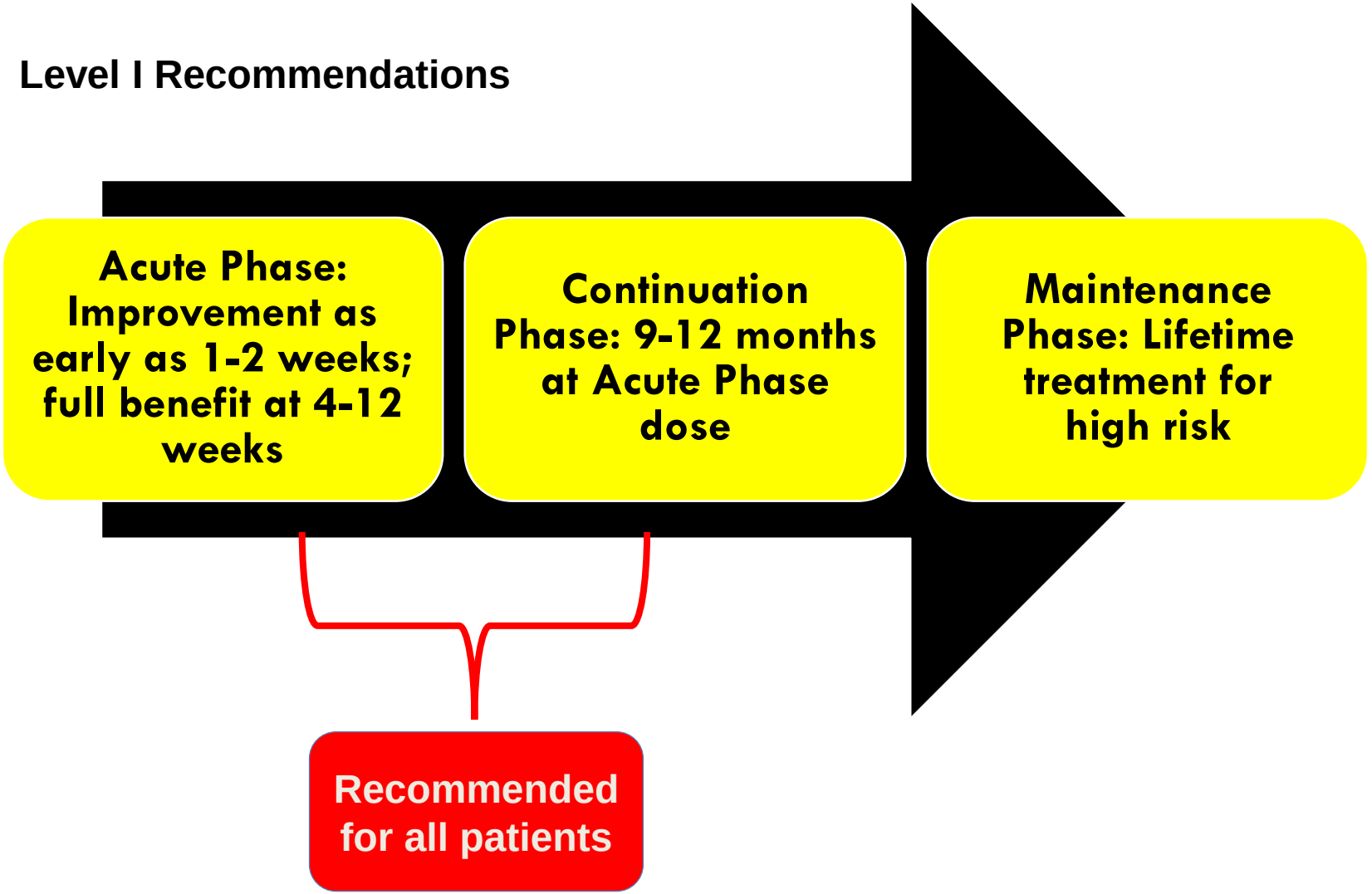
# CYP450 Enzyme Phenotypes

| Enzyme | Phenotype | Asian (%) | Black (%) | White (%) |
|---|---|---|---|---|
| 2C9 | Poor | 0.4 | 0 | 1 |
| | Intermediate | 3.5 | 13 | 33 |
| | Ultrarapid | | | |
| 2C19 | Poor | **18-23**[1] | 1.2-5.3 | 2-5 |
| | Intermediate | 30 | 29 | 18 |
| | Ultrarapid | | | |
| 2D6 | Poor | 1-4.8 | 1.9-7.3 | **7-10** |
| | Intermediate | **51** | **30** | 1-2 |
| | Ultrarapid | **0.9-21** | 4.9 | 1-5 |

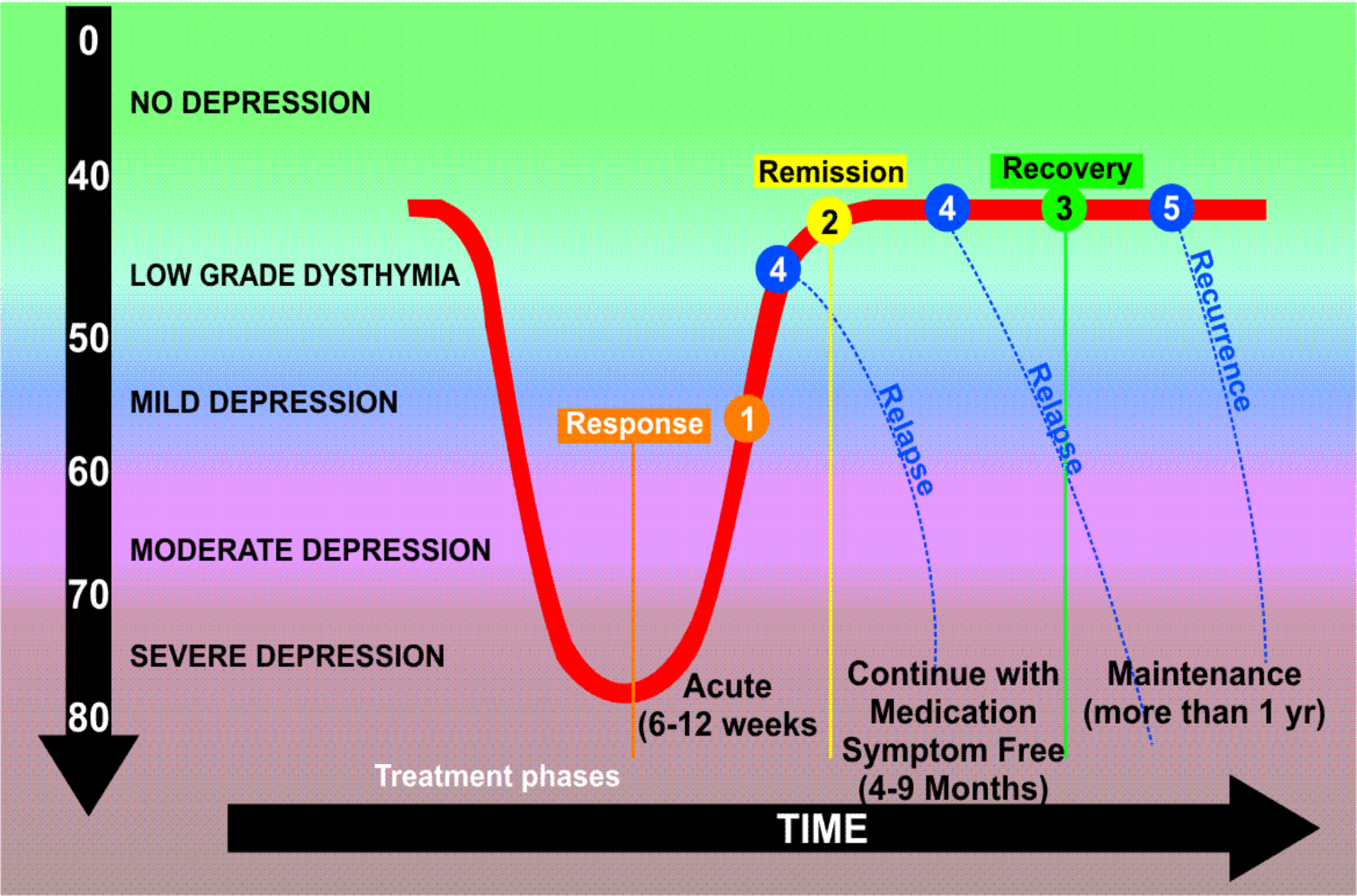
[1] Japanese: 20.3, Chinese: 13.6, Korean: 13.7

# Medication Treatment Course

# American Psychiatric Association Practice Guidelines: Duration of Treatment of Antidepressant



# INDICATION HOW LONG MEDICATION SHOULD BE TAKEN



# STAR*D Cumulative Remission (QIDS-SR≤5; ITT)

**Level 1**

- Citalopram: (n=2876)
- 32.9% remission on QIDS-SR
- 47% response rate

**Cumulative remission rate after Level 4: 67%***

**Level 2**

- Switch to Bupropion-SR, CBT, sertraline or venlafaxine XR: 25.6% (n=727)
- *OR* Augment with Bupropion-SR or buspirone or CBT: 35.8% (n=565)

**Level 3**

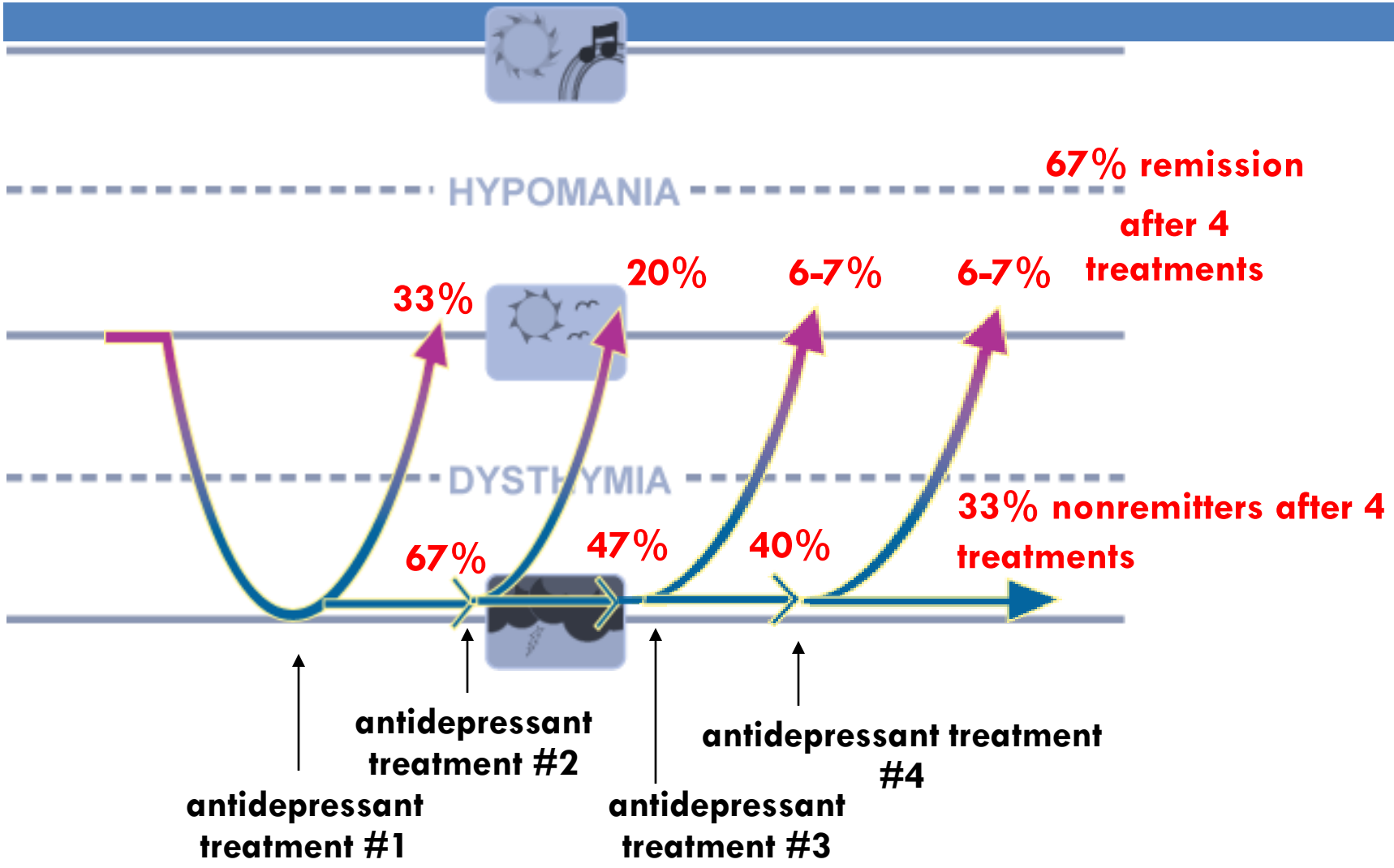
- Switch to Mirtazapine or nortriptyline: 10.2% (n=235)
- *OR* Augment with: Lithium or triiodothyronine: 20.4% (n=142)

**Level 4**

- Switch to: tranylcypromine: 13.8% (n=58)
- Switch to: mirtazapine combined with venlafaxine-XR: 15.7% (n=51)

STAR*D=Sequenced Treatment Alternatives to Relieve Depression; CBT=cognitive behavioral therapy

# What Proportion of MDD Remits?



# American Psychiatric Association Practice Guidelines 2010

- Therapeutic trial = 4 to 6 weeks (adequate dose)
- If no response to monotherapy → switch
  - Within or between pharmacological class
- If partial response to monotherapy
  - Augmentation with psychotherapy
  - Augmentation with non-MAOI antidepressant or non-antidepressant medication

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373:746-58.

# Discontinuation of Therapy

- Patients should be treated for at least 9-12 months before considering taper
  - Risk of relapse is higher if discontinuing sooner or previous relapse
- All ADs should be gradually titrated down
  - Over weeks and perhaps longer
  - The longer a patient has been taking, the longer the taper
  - Fluoxetine's metabolite has a ½-life up to 2 weeks so may take over a month before completely metabolized, so faster taper can be considered
- Warn patients of signs and symptoms of withdrawal
  - Especially venlafaxine, paroxetine, and fluvoxamine
- Long term therapy may not be necessary

# Discontinuation of Therapy

- Patients should be treated for at least 9-12 months before considering taper
  - Long-term use is not needed for most
    - Especially those with mild-moderate symptoms or single episode
  - Adverse effects can be bothersome long term
    - Emotional numbing, fatigue, weight gain, sexual effects (sometimes doesn't go away after discontinuation of medication), risk of falls in the elderly
  - Deprescribing of antidepressants is often not brought up with patients and they continue for years

# Discontinuation of Therapy

- All ADs should be gradually titrated down
  - Factors to select speed of taper
    - Type of antidepressant
      - SNRIs, paroxetine, mirtazepine most difficult
      - Vortioxetine, bupropion least difficult
    - Duration of therapy
      - The longer they have taken the longer it will take to stop
    - Dose
      - Higher doses require slower taper
    - Past experience with withdrawal
      - Those who have previously experienced worse withdrawal will need slower tapers
- RELEASE has algorithm to help select speed of taper

# Discontinuation of Therapy

- RELEASE: Redressing Long-tErm Antidepressant uSE
  - University of Queensland
  - Funded by National Health and Medical Research Council
  - Designed for general practitioners
  - Royal Australian College of General Practitioner endorsed
  - www.racgp.org.au/clinical-resources/clinical-guidelines/guidelines-by-topic/view-all-guidelines-by-topic/preventive-health/release-resources

# Discontinuation of Therapy

- Tapers for 15 meds are given on website (4 not used in US)
  - Includes most SSRIs, SNRIs, mirtazapine, and vortioxetine
- Example taper for sertraline
  - Fast taper: every 2-4 weeks
    - 100mg, 50mg, 25mg 12.5mg, 9mg, 6mg, 4mg, 2mg, 1mg
      - 1-9mg uses liquid
  - Slower taper: every 2-4 weeks
    - 100, 75, 50, 37.5, 30, 25, 20, 15, 12.5, 10, 8, 6, 5, 4, 3, 2.5, 2, 1.5, 1, 0.5
      - Combinations of pills and liquids are used
  - Slowest taper: every 2-4 weeks
    - Has 39 steps

# Withdrawal vs Relapse

- Distinguishing withdrawal from relapse when stopping medication is critical
- Withdrawal is common: ~20%
  - Prolonged withdrawal is not uncommon and can last years
- Time of Onset and Time to relief upon restarting
  - Withdrawal: Starts soon after stopping (within days)
  - Relapse: Typically takes longer (weeks to months)
- Distinguishing Symptoms
  - Withdrawal: dizziness, lightheadedness, vertigo, headaches, brain fog, "brain zaps," electric shock sensations, photophobia, phonophobia, nausea, sweating, tremors, vivid dreams, muscle aches, agitation, akathisia
  - Relapse
    - Physical symptoms such as those above are not part of relapse
    - Resumption of symptoms that occurred prior to starting medication

# Relapse Rates

- After remission
  - 25% relapse within the first 6 months
  - 30-50% in 2 years
  - 50-75% in 5 years
- The risk of relapse during early remission can be reduced significantly by maintaining patients on antidepressants for 9 months after remission
  - 90% continued to respond while on medication
  - 50% will relapse if medication stopped after a year
  - Number of episodes positively correlated to probability of relapse

# Medication Switching

# Switching Antidepressants: MDD Disease Medication Management Guideline

Switch drug with washout period

Direct switch with no washout period

Cross-taper with taper and titration periods

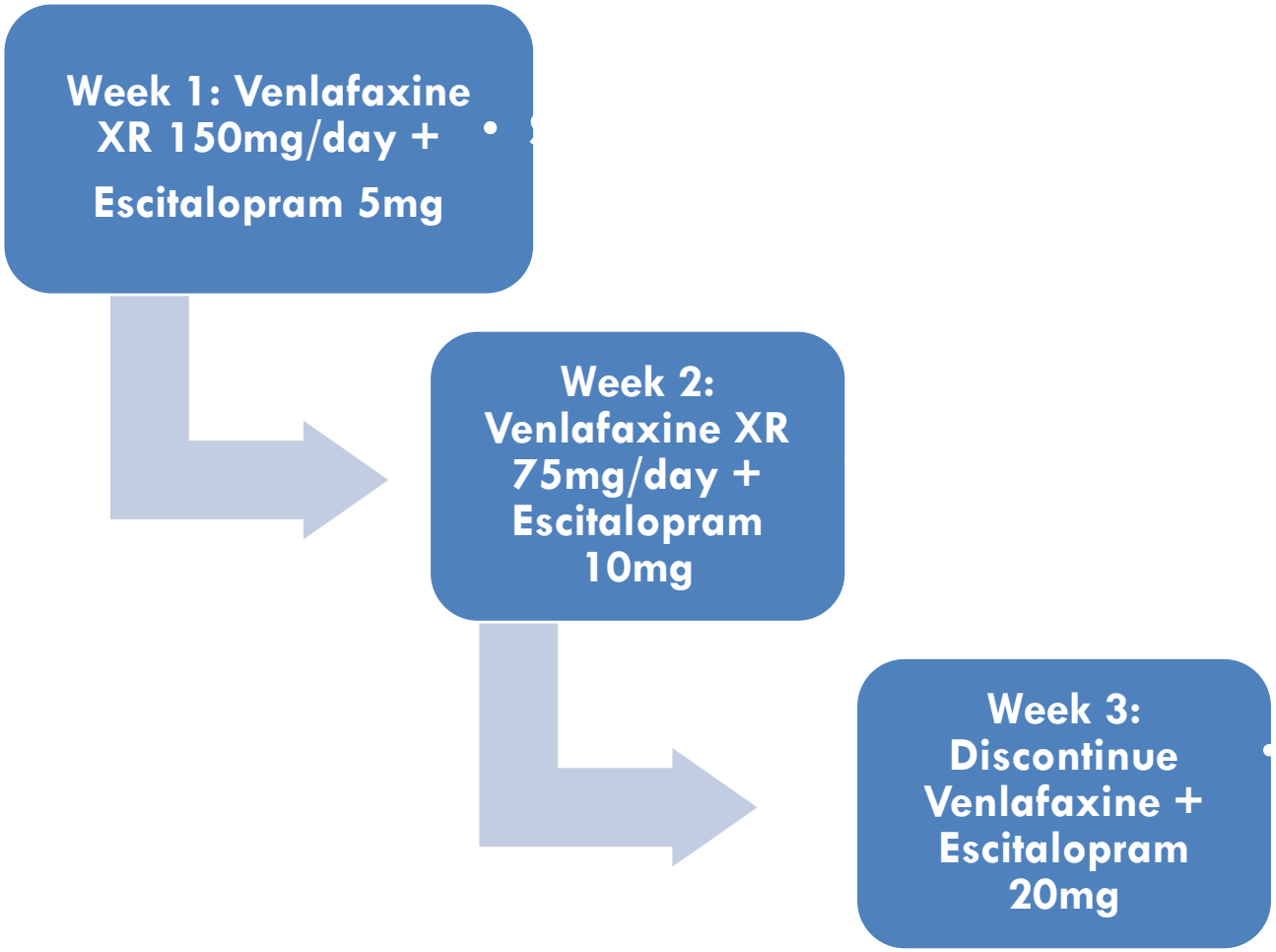
# Switching Antidepressants: MDD Disease Medication Management Guideline

- Three strategies for antidepressant switch
  - Stop first drug with washout period; start new drug
    - For drugs that can potentially interact (ie MAOIs), a wash-out period between antidepressants is necessary
      - 2 week wash-out when going from/to an MAOi
      - 5 week wash-out from fluoxetine, 3 week from vortioxetine to MAOi
  - Direct switch
    - SSRI to SSRI can be done by direct switch
    - Low to moderate dose SSRI to SNRI
    - Consider waiting 4-7 days when switching from fluoxetine, then starting a low dose of another SSRI

# Switching Antidepressants: MDD Disease Medication Management Guideline

- Three strategies for antidepressant switch
  - Cross-taper
    - Often used when switching to an antidepressant with a different mechanism of action
      - SNRI to SSRI
    - Consider if switching from max dose of any antidepressant
    - When switching from fluoxetine or paroxetine to a medication that is metabolized by 26D, consider starting new med at lower dose due to 2D6 inhibition
      - Longer ½-life of fluoxetine may necessitate slower cross-taper
    - Avoid cross-taper with clomipramine due to high serotonergic capacity

# Example: Cross-Tapering Strategy



# Augmentation Strategies

# Augmentation Strategies

- Lithium
  - Best evidence for augmentation
- Bupropion, mirtazapine
  - May be combined with SSRI/SNRI (caution BP with SNRI)
- Trazodone
- Pindolol
  - $5HT_{1A}$ antagonist ($\uparrow$5HT)
  - May accelerate response (but inconclusive studies)
  - Dose = 2.5mg TID
- Pramipexole
  - D3 agonist
  - Dose = 1-5mg daily

# Augmentation Strategies

- CNS stimulants
  - Methylphenidate and dextroamphetamine
  - Modafinil
    - Useful for patients with low energy in addition to depressive sxs
    - Should not be used alone for depression
- Buspirone
  - No advantage over placebo
  - May have some effect for anxiety
- Supplements
  - SAMe, L-methylfolate, magnesium, rhodiola rosea, zinc, NAC, Kanna

# Augmentation Strategies

- Antipsychotics (Effect sizes are meager at around 0.2)
  - Depression w/psychotic features and adjunctive treatment of MDD
    - 5 FDA-approved agents
      - Olanzapine/fluoxetine (6-18mg of olanzapine, 25-50mg fluoxetine)
      - Aripiprazole (2-5mg/day, range 2-15mg/day)
      - Quetiapine XR (50mg/D x 2 days, then 150mg/D, target 150-300mg/D)
      - Brexpiprazole (0.5 or 1 mg/day, target 2-3mg/day)
      - Cariprazine (1.5mg/day, range 1.5-3 (4.5)mg/day)
    - Non-FDA-approved which have some evidence
      - Risperidone 0.5-3mg/day
      - Lurasidone 20-60mg/day
      - Lumateperone 42mg/day
    - Ineffective: Pimavanserin, ziprasidone, and the rest
    - Poor evidence for chronic treatment; consider taper

# Augmentation Strategies

- NMDAR antagonists
  - Ketamine
    - Effect size close to 0.9
    - May work through the opioid system
  - Esketamine (Spravato®)
  - Minocycline
    - Also anti-inflammatory
    - Small studies showing 0.7 effect size
    - For depressed patients developing acne, particularly lithium-induced, favor over doxycycline
    - 200mg daily
    - May want to take with probiotic to counteract altering of gut microbiome

# Augmentation Strategies

- NMDAR antagonists
  - D-cycloserine
    - Has been researched to aid in learning, facilitate exposure therapy for PTSD and anxiety, and for treatment-resistant schizophrenia
    - Affects NMDAR at 1000mg daily
  - Lamotrigine
  - Dextromethorphan-bupropion (Auvelity®)
  - Amantadine
- Thyroid supplementation
  - Most evidence with T3 augmentation of TCA (not SSRI)
  - Cytomel 25-50mcg/day
  - May be helpful in patients with even low-normal levels of TSH
  - Meta-analysis → accelerate response to TCA in non-refractory depression*

*Altshuler et al. Am J Psych 2001;158(10):1617-22.

# Augmentation Strategies

- Benzodiazepines
  - Originally used as antidepressants after they supplanted barbiturates
  - After antidepressants became wide spread, benzodiazepines continued to be used as augmentation to relieve symptoms prior to antidepressant beginning to work over 1-2 months; this is still practiced
    - 1 in 10 receive a benzo with antidepressant
    - 1 in 8 remain on the benzo a year later
  - Studies show that it accelerates response to antidepressants but does not enhance past 30 days
  - Despite risks, may be the only med that helps some patients
  - May help patients to remain in treatment and tolerate adverse effects of antidepressants
  - May help with anxious depression

# Depression Sub-Types

# Sub-types

- Treatment-resistant depression (TRD)
- Psychotic depression
- Depression with mixed features
- Depression with anxious distress
- Melancholic depression
- Atypical depression
- Seasonal pattern (SAD)
- Catatonia (will discuss with antipsychotics)
- Peripartum onset (will discuss with reproductive psychiatry)

# Treatment-resistant depression (TRD)

- Four unsuccessful trials of medication of adequate dosage and duration
- At least 30% of those diagnosed with MDD
- Exponential increase since 1980
- Make up a large proportion of psychiatry panel
  - PCMs typically have already effectively treated less severe cases
- Six D's
  - Diagnosis: make sure it's correct
  - Dose: maximize it
  - Duration: treatment is adequate duration
  - Drug mechanism: try drugs with different mechanisms
  - Different treatment: try different classes of meds or ECT
  - Dynamics

# TRD Treatments

- FDA-approved treatments
  - Aripiprazole
  - Brexpiprazole
  - Olanzapine
  - Quetiapine
  - Esketamine (only medication approved for monotherapy)
  - ECT
  - rTMS
- Off-label treatments
  - Lithium
  - MAOis
  - TCAs
  - Pramipexole
  - Vagus nerve stimulation
  - Deep brain stimulation

# Psychotic Depression

- MDE accompanied by psychotic sxs (hallucinations or delusions)
- Psychosis is present in 15-20% of patients with MDD
- Psychotic symptoms can occur secondary to many other conditions
  - Bipolar disorder
  - PTSD
  - Anxiety
  - Personality Disorders
  - Medical Disorders
  - Depression
    - Can occur with mild, moderate, and severe types
  - In the healthy population without any disorder

# Psychotic Depression

- Antidepressant
- SNRI preferred over SSRI
- If ineffective augment with
  - 1st line: Antipsychotic (next slide)
  - 2nd line: ECT
    - 95% remission (83% for non-psychotic depression); can be a first line option
    - Despite its effectiveness, ECT is often not practical
  - 3rd line: Bupropion (males)
  - 4th line: Lithium
  - 5th line: Ketamine

# Psychotic Depression

- 1st line: AP w/ or w/o AD (All APs have similar efficacy so choose based on tolerability)
  - 2010 APA guidelines recommend AP+AD as first line however there is very little evidence to support this
    - Only one small (n=18) placebo-lacking study supported conclusions
    - 2nd had large p value
    - 3rd concluded that AP monotherapy was not helpful
  - Since 2010, 2 larger RCTs showed benefit for AP+AD
    - Sertraline + OLZ over AD alone
    - Venlafaxine + quetiapine over AD alone
    - Also evidence for OLZ + fluoxetine
  - Use of APs can impair recovery to pre-morbid functioning
    - Can impair frontal lobe symptoms
      - Apathy, slowing, difficulty solving problems, dealing with interpersonal relations, multi-tasking, taking initiative
    - Become dependent, passive, and quiet, and lose insight into it

# Psychotic Depression

- 1st line: AP w/ or w/o AD (All APs have similar efficacy so choose based on tolerability)
  - Another better designed study showed that amitriptyline worked as well alone as it did with perphenazine
    - Venlafaxine trial above showed no difference between imipramine, another TCA, and OLZ + venlafaxine
  - AP monotherapy not well studied
    - All studies done do not show a benefit for AP monotherapy over AP + AD
  - If AP is used then relapse is worse if it is stopped sooner than 6 months or withdrawn too quickly
  - If using antipsychotic, use AP dose, not AD dose

# Depression with Mixed Features

- MDD mixed with symptoms of mania or hypomania
  - At least 3 sxs of mania/hypomania nearly every day during last 2 wks of MDE
- Treatments
  - 1st line: Lurasidone
  - 2nd line: Quetiapine
  - Other medications may be effective but have not been studied
    - Lithium?
    - Lamotrigine?

# Depression with Anxious Features (Anxious Depression)

- At least 2 GAD symptoms with MDD
- Prevalence as high as 50-75% of those with MDD
- Difficult to discern from anxiety disorder that triggers depression
- May respond less well to
  - Medications studied in STAR*D, however still try these first
    - SSRI
    - Buspirone
    - Bupropion
- May be helpful
  - Benzodiazepines (most evidence for alprazolam)
    - Alprazolam has 5HT-1A activity and TCA-like molecular structure
  - Eszopiclone
  - Phenylzine
  - Atypical Antipsychotics
    - Quetiapine
    - Aripiprazole

# Melancholic Depression

- Features
  - More severe depressive symptoms than typical MDD
  - **Anhedonia OR Lack of reactivity to positive news and events**
  - At least 3 of the following
    - Excessive guilt
    - Psychomotor retardation
    - Deep despair and worthlessness
    - Interrupted sleep (early morning awakenings)
    - Significant loss of appetite
    - Diurnal variation (mood and energy worse in the morning)
- Differences in medication response for severe inpatients
  - 1st line is TCA
  - 2nd line is SNRI or mirtazapine
  - 3rd line is TCA with Lithium, T3, or ECT
- Responds less well to therapy

# Atypical Depression

- Symptoms
  - Mood reactivity
  - At least 2 of the following
    - Hypersomnia
    - Hyperphagia
    - Leaden paralysis
    - Interpersonal rejection sensitivity
- Treatment choice
  - MAOi
  - Bupropion

# Seasonal Affective Disorder

- Recurrent episodes of major depression, mania, or hypomania with seasonal onset and remission
- Treatments
  - Bupropion is only FDA approved treatment (other ADs also indicated)
  - Bright light therapy
    - 10,000 lux for 30 minutes in the morning (light box)
      - Bright day: 100,000 lux
      - Cloudy day: 25,000 lux
      - Very overcast: 10,000 lux
  - Dawn stimulation: Gradual room light brightening in the morning around 250 lux
  - ECT
  - Summer type: Use of A/C and limit light exposure to <13hrs/day (ie black out curtains)
  - Others: Sleep hygiene, walks outside, exercise, indoor lighting

# Pediatrics

# Pediatrics

- Presentation similar to adults after age 9
  - Many diagnoses in children can look like ADHD
- Increased risk of suicidal ideations (**BBW**)
- Liquid/sprinkle formulations
  - All SSRIs except fluvoxamine as liquids
  - Duloxetine as sprinkles
- Dosing is different so check package inserts

# Pediatrics: FDA-Approved Medications

- Fluoxetine
  - MDD
    - 8-12 yo: 5-10mg daily, usual dose 10mg, max 40mg daily
    - 12-18 yo: 10-20mg daily, usual dose 20-40mg, max 60mg daily
  - OCD: >=7 yo
- Escitalopram
  - MDD
    - 12-18: 10mg daily, 20mg max
  - **GAD/SAD: >= 7 yo (2023)**
- Sertraline: OCD, >= 6 yo
- Duloxetine: GAD, >= 7 yo
- Fluoxetine/olanzapine: depression associated with bipolar I, >=10 yo
- Lurasidone: bipolar disorder, depressive episode, >=10 yo
- Nortriptyline: Depression, >=13 yo
  - TCAs associated with **increased** diastolic BP; baseline EKG recommended
- NeuroStar® TMS: >=15 yo

# Geriatrics

# Elderly

- Presentation different from adults
  - More likely to focus on somatic complaints
- Incidence same as general population
- Increased risk of suicide
- Higher likelihood of relapse
- Choice of antidepressant dependent on comorbidities, drug interactions
  - Dementia – caution with anticholinergic drugs

# Elderly: BEERS Criteria

- Increased risk of CVA/death **(BBW)**
  - Antipsychotics
- Anticholinergic properties
  - Tertiary TCAs
  - Certain APs
  - Paroxetine
- Exacerbate SIADH or hyponatremia
  - ADs (mirtazepine, SSRIs, SNRIs, TCAs)
  - AEDs (caramazepine, oxcarbazepine)
  - APs
- Increased risk of bleeding
  - Warfarin with SSRI

# Elderly: BEERS Criteria

- Syncope
  - APs that affect a1
  - AChEIs
  - Alpha-1 blockers
  - Tertiary TCAs
- Delirium
  - APs, Anticholinergics, Benzos, Sedative hypnotics
- Dementia
  - Anticholinergics, Benzos, Z-drugs, APs
- Falls
  - AEDs, APs, Benzos, Z-drugs, ADs, Opioids
    - Any combination of any >=3 CNS-active drugs

# Elderly: STOPP START Criteria

- START
  - SSRIs
    - Non-TCA antidepressant for depression
    - For severe anxiety that impacts independent functioning and quality of life
- STOPP
  - SSRIs
    - Bleeding risk when combined with
      - Vit K antagonist, direct thrombin inhibitor, or factor Xa inhibitor with previous history of major hemorrhage
      - Current or recent significant bleeding
    - Risk of hyponatremia
      - With Na+ <130
    - May impair sensorium
      - Recurrent falls

# Elderly: STOPP START Criteria

- STOPP
  - TCA
    - Risk of worsening conditions
      - Dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, chronic constipation, recent falls, prior history of urinary retention or orthostatic hypotension
    - Avoid use as 1st line due to increased risk
  - SNRIs
    - Worsening hypertension
      - With severe hypertension

# Elderly: STOPP START Criteria

- STOPP
  - Antipsychotics
    - Risk of urinary retention
      - Those with moderate antichlolinergic activity and patients with LUTS
    - Risk of EPS, CVA, worsening cognition
      - >3 months use for behavioral and psychological symptoms of dementia
    - Risk of EPS
      - Dementia with Lewy Bodies or Parkinsons (except quetiapine, clozapine)
    - Risk of confusion, hypotension, EPS, falls
      - Use as hypnotic
    - Risk of aspiration pneumonia
      - With dysphagia
    - Risk of parkinsonism
      - Recurrent falls

# Elderly: Medication Considerations

- Best choices (fewest DDIs)
  - Escitalopram, citalopram, sertraline
- Worst choices (Most DDIs)
  - Paroxetine (Anticholinergic), fluoxetine
- Other options
  - Mirtazapine: help with appetite and sleep
  - Venlafaxine, duloxetine, nortriptyline
  - Bupropion
  - ECT

# Elderly: Medication Considerations

- Worsened Risk of SIADH
  - Serotonergic medications
  - HCTZ, dehydration, “tea and toast” diet
- Weight Loss Differential
  - Failure to thrive
  - Hypoactive delirium
  - Apathy from dementia
  - Depression
  - Thyroid
  - Malignancy
  - Dysphagia

# Reproductive Psychiatry

# Reproductive Psychiatry

- Premenstrual Dysphoric Disorder (PMDD)
- Peri-menopausal Depression/Anxiety
- Vasomotor Syndromes of Menopause
- Pregnancy
- Post-partum
- Breastfeeding

# Premenstrual Dysphoric Disorder (PMDD)

- OCP
  - 3 cycles on then 4 days off
  - Contraindications
    - Trying to conceive
    - Personal/family risk factors for clots (ie >35 yo, smoker, hx of thrombosis, migraines with aura, hypertension, certain liver/gall bladder diseases, with some medications)
    - Hx of breast cancer
  - Med choice
    - Androgen OCPs can worsen symptoms (ie Norethindrone, norgestrel)
    - OCPs that do not contain drospirenone metabolite not likely to help
    - Choose drospirenone (ie Yasmin, Nextstellis)
  - Effectiveness: 80-90%

# PMDD

- Antidepressant
  - Unlike in primary depressive disorders, PMDD is thought to be caused by disruption in the way serotonin is metabolized, so patients respond to medications/changes quickly
    - Bupropion and other non-serotonergic meds are not effective
  - Can take just during symptoms
  - If already taking an AD, take increased dose just during symptoms
  - Effectiveness: 70-80%
  - FDA Approved
    - Fluoxetine (Serafem® 2000-2024)
    - Sertraline
    - Paroxetine CR


- GnRH antagonist: Last resort if others ineffective
- Non-medications treatments not very effective

# PMDD: What to do if you miss contraceptive pill

- COC
  - Missed by 24-48 hours
    - Take the late pill ASAP
    - Continue pills normally (even if you take 2 on one day)
    - No additional protection needed
    - EC usually not necessary unless missed early or late in cycle
  - >48 hours
    - Take one late pill ASAP
    - Discard other missed pills
    - Continue pills normally (even if you take 2 on one day)
    - Use back-up contraception until 7 days of hormonal pills
  - If pills missed were in the last week of hormonal pills
    - Skip hormone free pills
    - Start fresh pack after finishing last pck
    - Use backup pack contraception until 7 days of hormonal pills
    - Use EC if unprotected sex in last 5 days and missed pill in 1st week

# PMDD: What to do if you miss contraceptive pill

- POP
  - Missed by >3 hours
    - Take 1 pill ASAP
    - Continue pills normally (one per day)
    - Use back-up contraception for 2 days
    - Use EC if unprotected sex in last 5 days

# Peri-menopausal Depression/Anxiety

- Increased risk for MH disorders with prior hx of MH disorder
- SNRI (more evidence for efficacy; also may be more helpful for VMS)
- SSRI
- Estradiol (oral, patch, cream, insert, ring, vaginal tablet)
  - <60 and within 10 years of menopause are lowest risk
  - Not helpful after menopause
  - Hx of breast cancer (Use Gail risk score)
    - No risk associated with oral premarin
  - Use with progestin if they have a uterus to decrease risk of uterine cancer
    - Can use IUD for this
    - Increased risk of breast cancer after 5 years
  - Consider tapering after 5 years (up to 10 years if not on progestin)
    - Waning efficacy, increasing risk
  - Caution with CV risk
    - ASCVD >10%, CAC >100
    - There may be some risk reduction in women <60 (not a reason to use)
  - Caution with hx of thrombosis, stroke, other CVE
    - Highest caution with oral: goes through liver, can increase clotting factors
    - Low dose vaginal preparations are not systemically absorbed
    - Patch is preferred for most (0.025-0.1mg weekly)

# Peri-menopausal Depression/Anxiety

- Testosterone
  - No formulations exist for women
    - Must use those for males at 1/10 the dose (300-500mcg/day)
  - Use estrogen first; make sure vasomotor symptoms are controlled
  - Calculate Free Androgen Index (FAI)
    - Total testosterone/SHBG x 100 and if in lowest quartile (<1%) consider trial
  - Follow FAI; keep it <5%
- Tamoxifen
  - Used by many women to reduce risk of breast cancer or to treat breast, ovarian, and endometrial cancers
  - Endoxifen is active metabolite
  - 2D6 inhitibtors (paroxetine, fluoxetine, duloxetine, bupropion) inhibit metabolism of tamoxifen into endoxifen
- Raloxifene (being researched)

# Vasomotor Symptoms of Menopause (VMS)

- Can have these symptoms for years before menstruation stops
- Lifestyle
  - Weight loss, cooling techniques, hypnosis, CBT
- FDA approved treatments
  - Paroxetine
    - Other SSRIs are likely equally effective
  - Bazedoxifene/estrogen (Duavee®) (2013)
    - FDA approved for osteoporosis prevention and VMS
    - **4 BBWs:** Endometrial cancer, CVD, dementia, Risk vs benefit
    - Used in women with a uterus
      - Bazedoxifene guards against hyperplasia
      - May benefit those that cannot tolerate progestins
    - Reduces hot flashes, pain with intercourse, and vaginal dryness

# VMS

- FDA approved treatments
  - Neurokinin 3 receptor (NK3R) antagonist
    - Estrogen inhibits the NK3 receptor
      - During menopause this inhibition fluctuates
    - Fezolinetant (Veozah®) (2023)
      - Caution liver/renal impairment
        - Check LFTs at 0, 3, 6, and 9 months
        - Avoid use with 1A2 inhibitors
      - Headaches
    - Elinzanetant is in development
- Estradiol (oral, **topical**, ring)
  - Give with progestin if patient has a uterus
    - Oral, micronized vaginal, IUD
- SNRI, Gabapentin, Clonidine, Oxybutynin
- Black cohosh likely no more effective than placebo

# Peri-Partum Depression (PPD)

- High prevalence during & after pregnancy
  - Highest peri-partum complication: 17%
  - If first episode of depression, 3x increased risk of bipolar vs non-PPD
    - 15% vs 5%
- Depression risks in pregnancy
  - Pre-term delivery, low birth weight, meeting developmental milestones
  - Less likely to care for themselves
    - Poor nutrition, substance/alcohol abuse, non-adherence with prenatal care
- Depression risks post-partum
  - Difficulty breastfeeding
  - Changes quality of breast milk
    - More salty, less palatable
- Increased risk of subsequent bipolar disorder or MDD

# PDD: Treatment

- Patients with severe depression, acute suicidality, psychosis, bipolar disorder should receive psych referral
- www.MotherToBaby.org (866) 626-6847
- Severe depression
  - Antidepressant
  - ECT
  - Post-partum psychosis
    - Lithium (most effective) +/- antipsychotic
    - Antipsychotic
    - ECT
    - May be bipolar disorder (meaning chronic)

# PPD: Considering Medication

- Consider medication
  - Severe past episode of depression
  - Hx of suicidality, psychosis, hospitalization
  - Multiple depressive episodes
  - Hx of peri-partum depression
- Weigh risk vs benefit of medication
  - Mixed results suggesting premature birth and lower birth weight
  - Likely linked to depression rather than antidepressant use
  - Studies looking at long-term development suggest some risk with untreated depression and none from antidepressant use of the mother
  - Risk of untreated mental health conditions during pregnancy likely more harmful than the low risk of harm to developing fetus from medications
- Risk of relapse (depression) ↑ 5x among women who discontinue antidepressants during pregnancy*

*Lee Cohen. JAMA 2006, February 1; *Moses-Kolko E et al. JAMA 2005;293(19):2372-2383)
**http://ctr.gsk.co.uk/summary /paroxetine/epip083.pdf; Yonkers KA et al. General Hospital Psychiatry 31 (2009) 403–413

# PPD: Antidepressant Risks

- Most antidepressants are category C
  - Birth defects very unlikely
  - Exceptions
    - ↑ cardiovascular malformations: paroxetine (D), lithium (D), TCAs
    - Neural tube defects: VPA (D), CBZ (D)
    - Increased risk of miscarriage and post-partum hemorrhage: SNRI (1.6-1.9)
    - Increased risk of pre-eclampsia: SNRI, TCA
    - Risk of hypertension when used with tocolytics (MAOi)
    - Brain developement: esketamine (Do not use)
  - Older SSRIs preferred
    - Fluoxetine (however not preferred for breastfeeding (neonates only))
    - Sertraline
    - Others: escitalopram, citalopram, bupropion
- CYP enzyme activity can increase during pregnancy
  - May need to increase dose towards the end of pregnancy

# PPD: Antidepressant Risks

- Some risk of withdrawal in newborn known as poor neonatal adaptation syndrome (PNAS)
  - Irritability, crying, jitteriness, increased muscle tone, dyspnea, altered sleep patterns, tremors, trouble eating, diarrhea
  - Most cases are mild and go away within days with no treatment
  - Most babies are not affected
- Persistent pulmonary hypertension in newborns of mothers who took SSRIs in second half of pregnancy* (2/1000 baseline risk)
  - 4-33% risk of death in newborn from this condition
  - Absolute risk with SSRI use after 20$^{th}$ wk of pregnancy is 1.3-2.9/1000
  - FDA requested labeling changes for all SSRIs but FDA does not recommend altering "current clinical practice"

*Chambers CD et al. NEJM 2006;354:579-87; FDA warning, 12/14/11.

# PPD: Post-partum

- Prevalence of post-partum depression: 10-22% (within 4 wks)
  - Postpartum blues: ~50% (1st few days)
  - Rule out low iron and thyroid
  - 25-50% with depression presentation may be bipolar (often 1st presentation)
- Post-partum OCD: ~15%
- Post-partum PTSD: 3-6%
- Significant drop in hormones post-partum
  - Neurosteroid replacement with medications such as brexanolone and zuranolone
- 20% drop in serotonin binding to 5-HT1A receptors
  - Particularly in the anterior cingulate gyrus
    - Important for maternal bonding
  - Also in the amygdala and hippocampus
  - Breastfeeding can improve binding potential
  - Responsive to use of serotonergic medications

# PPD: Post-partum

- Alternative treatments for PPD (particularly for mild to moderate symptoms)
  - Psychotherapy
  - Good social support to help with newborn
  - Ergonomic infant carrier has helped with prevention
  - Lifestyle: brisk walking, mediterranean (or other healthy) diet
  - Celecoxib 200mg BID
    - Increases BDNF
    - Decreases inflammation
    - Some evidence for positive effect in PPD
  - Circadian rhythm therapy
    - Morning light therapy (ie sun or light box)
    - Evening darkness
    - Use of blue light blocking glasses for night time feedings
  - Use of esketamine for pain control has shown decreased incidence of depression when used for pain control after C-section

# Neurosteroids

- Pregnanolone is a precursor of allopregnanolone and is available over the counter through mostly herbalists and may be prescribed by alternative medicine practitioners
- Pregnanolone levels fall post-partum and is thought to contribute to depression
- Brexanolone and zuranolone are synthetic allopregnanolone
- Affects $GABA_A$ receptors that are not sensitive to benzodiazepines
  - Act as positive allosteric modulator of $GABA_A$
  - At low and high doses stimulates the $GABA_A$ receptor
  - At medium doses inhibit $GABA_A$
  - These same levels are seen during the luteal phase
  - Not known to be habit forming

# Brexanolone (Zulresso®) (2019-2025)


- FDA approved for post-partum depression but no longer available
  - Phase I: 4 women, all had remission, HAMD: 28 to 1.6
  - Phase II: 7 out of 10 had remission, 1 of 11 on placebo had remission
  - Phase III: 2 studies included
    - Study 1: 51% remission vs 16% placebo; held 30 days later
    - Study 2: 61% remission vs 38% placebo; held 30 days later
- Effect size: 1.2
- 60 hour IV infusion due to risk of loss of consciousness
- Cost: $34K for the drug alone
- **BBW**: Excessive sedation and sudden loss of consciousness
- Breastfeeding is acceptable
- Schedule IV
- REMS requirements
- Best candidate: severe depression, onset with a month post-partum (must be within 6 months), not acutely suicidal (not studied)

# Zuranolone (Zurzuvae®) (2023)

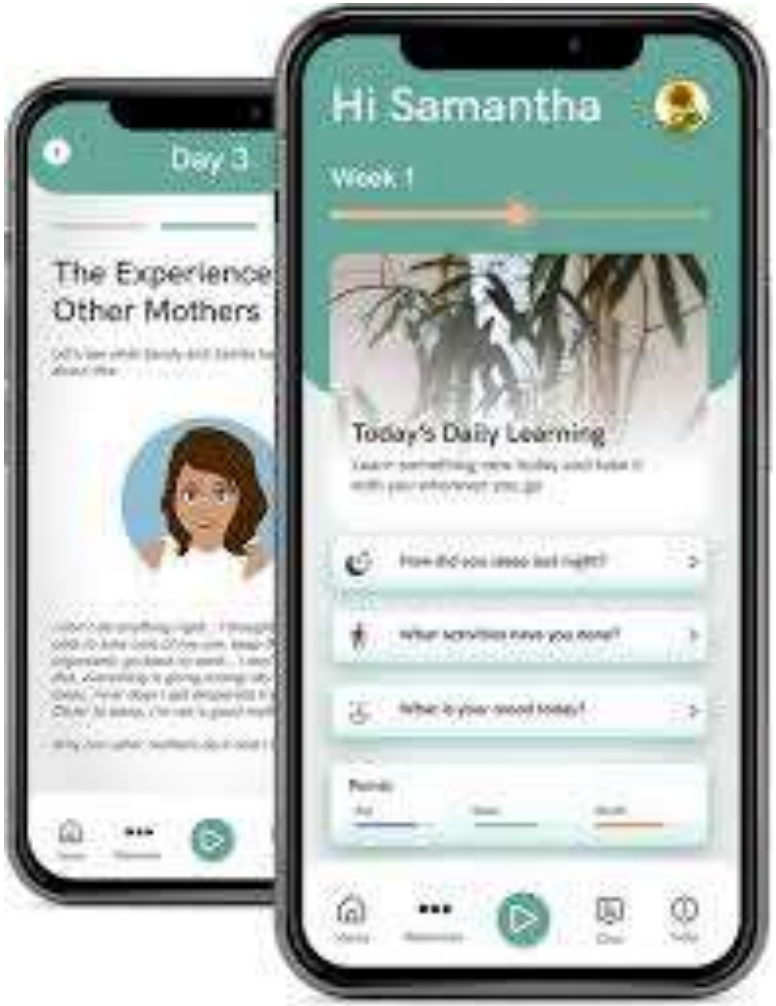
- Higher bioavailability than brexanolone, so can be taken orally
- Phase III trials failed for MDD
  - Short-term relief seen but not long-term
- FDA approved in 2023 for post-partum depression
  - Response seen at day 3
  - 14 day treatment course; improvement seen throughout
  - Improvement decreased after a month; no studies beyond a month have been done
  - Phase III: 45% remission vs 23% placebo; held 45 days later
- Effect size: 0.5 vs 1.2 for brexanolone
- Currently under investigation for PTSD, insomnia, Parkinsons, GAD, and bipolar disorder
- Was only effective in depression for 3 days so will not be approved
- Requires a fatty meal for absorption (400-1000 kcal, 25-50% fat)

# Zuranolone (Zurzuvae®) (2023)

- **BBW:** Avoid driving or other potentially hazardous activities for 12hrs after taking
- Schedule IV
- Breastfeeding is acceptable
- Very unlikely to trigger mania in the case that PPD is actually new onset bipolar disorder
- Adverse effects: drowsiness, diarrhea, dizziness
- 50mg QHS for 14 days, may lower to 40mg based on tolerability
- 30mg QHS for Child-Pugh Class C liver impairment
- 30mg QHS for eGFR (15-59 mL/min/1.73m2)
- Drug dose adjustments may be needed with 3A4 inducers/inhibitors
- Cost is ~$19K for a 2 week course of treatment

# MamaLift Plus® (2024)

- First FDA cleared prescription digital therapeutic for PPD
- Neurobehavioral intervention adjunct to outpatient care
- >=22 years old



# Breastfeeding: Infant Outcomes

| Outcome | % Lower Risk |
|---|---|
| SIDS | 40-64 |
| Infant mortality | 19-40 |
| Lower respiratory infection | 19 |
| Severe or persistent diarrhea | 30 |
| Otitis media | 33-43 |
| Asthma | 10-22 |
| Eczema | 26 |
| Crohn's disease | 29-80 |
| Childhood obesity | 10-22 |
| Childhood and adult obesity | 23-31 |
| DMI | 57 |
| DMII | 33 |
| Celiac disease | 52 |
| Leukemia | 11-19 |

# Breastfeeding: Maternal Outcomes

- Decreased postpartum blood loss
- More rapid involution of the uterus
- Increased child spacing secondary to lactational amenorrhea
- Weight 1.38kg less in those that breastfed
- Exclusive breastfeeding recommended to 6 months
  - Encouraged up to a year; 2 years and beyond is ok

| Outcome | % Lower Risk |
|---|---|
| DMII | 32 |
| Rheumatoid arthritis | 20-50 |
| Hypertension, CVD, HLD | 8-12 |
| Breast cancer | 13-28 |
| Ovarian cancer | 17-37 |
| Endometrial cancer | 11 |
| Thyroid cancer | 9 |

# Breastfeeding: Mental Health

- Adjusted outcomes of intelligence scores and teacher's ratings are significantly greater in breastfed infants
- Increase in postpartum depression in mothers who do not breastfeed or wean early
- Decrease rate of abuse/neglect of newborn
- Drug and alcohol use (breastfeeding safe?)
  - Supervised methadone maintenance: yes
  - PCP, cocaine, cannabis: no
  - Alcohol: limit of 1 drink daily, at least 2 hours prior to breastfeeding
  - Tobacco Use
    - Decreases milk supply and lactation period
    - Increased SIDS, asthma, and respiratory illness with physical exposure
    - Exposure through breast milk is not known to be harmful
    - Minimize smoking/vaping, do not do while breastfeeding, not in home/car
    - Nicotine cessation products are safe

# Breastfeeding: Resources

- Drugs and Lactation Database (LactMed) from the NIH
- Dr. Thomas Hale's Medications and Mother's Milk (www.infantrisk.com)
- MotherToBaby fact sheets
- AAP Clinical report: The transfer of drugs and therapeutics into human breast milk
  - Pediatrics.aappublications.org/content/132/3/e796

# Breastfeeding

- Most antidepressants are considered compatible with breastfeeding
- There are reports of irritability, vomiting, diarrhea, less sleep
- There is a small risk of less weight gain which would likely only be concerning if weight gain were already a concern
- Order of preference
  - Sertraline: least presence in milk
  - Paroxetine (not during pregnancy)
  - Mirtazapine, Duloxetine (not preferred during pregnancy)
  - Escitalopram, citalopram
  - Fluoxetine
    - Long half life and more case reports of sedation and colic
    - Safe for older infants
- If the patient did well in the past with or is already taking and doing well with another antidepressant they should not be switched to sertraline or paroxetine
- Generally older medications have more safety data
- Newer medications should be avoided for lactating mothers due to lack of data unless they are already taking

# Breastfeeding

- L2 (Safer, risk of harm is remote, limited studies)
  - TCAs
    - Imipramine, Amitriptyline, Clomipramine, Desipramine, Nortriptyline, Amoxapine
  - Other Antidepressants
    - Sertraline, Fluoxetine, Paroxetine, Fluvoxamine, Trazodone, Citalopram, Escitalopram, Venlafaxine, Brexanolone, Zuranolone
  - Anxiolytics
    - Quazepam, Oxazepam, Midazolam, Buspirone, Hydroxyzine, Gabapentin
  - Mood Stabilizers
    - Carbamazepine, Lamotrigine
  - APs
    - Olanzapine, Risperidone, Quetiapine, Ziprasidone
  - Stimulants
    - Methylphenidate
  - Hypnotics
    - Zaleplon, Zopiclone

# Breastfeeding

- L3 (Moderately safe, no studies or minimal risk)
  - Vortioxetine, Mirtazapine, Maprotiline, Duloxetine, Desvenlafaxine, Milnacipran, Levomilnacipran, Vilazodone, Esketamine, Gepirone
  - Bupropion (small seizure risk, OK to use if no other risk of seizures), Prazosin
  - Benzodiazepines not listed under L2, Zolpidem, Melatonin, Ramelteon, Suvorexant
  - Aripiprazole, Clozapine, Paliperidone, Asenapine, Iloperidone, Lurasidone, Brexpiprazole, Chlorpromazine, Fluphenazine, Perphenazine, Haloperidol
  - Dextroamphetamine, Lisdexamfetamine, Dexmethylphenidate, (Ar)Modafinil
- L4 (Possibly hazardous, evidence of risk, may use if safer drug not available)
  - Nefazodone, DXM+bupropion
  - Lithium, Valproic acid
  - Loxapine, Pimozide, Thioridazine, Thiothixene, Trifluoperazine, Cariprazine
  - Atomoxetine, Phentermine
- L5 (Contraindicated, risk of use outweighs benefit)
  - Doxepin
    - Excessive accumulation in the newborn, poor suckling, vomiting, hypotonia
  - Kava Kava

# Hypogonadism

# Hypogonadism

- Comparison of non-specific signs of hypogonadism with MDD

| Non-specific signs of Hypogonadism | MDD |
|---|---|
| Sadness | Depressed mood |
| Poor morning erection | Markedly diminished interest or pleasure in activities |
| **Low sexual desire** | |
| Erectile dysfunction | |
| Decreased motivation | |
| Decreased confidence | Feelings of worthlessness |
| Decreased energy | Fatigue or loss of energy |
| Decreased work or physical performance | |
| Sleep disturbances | Insomnia or hypersomnia |
| Poor concentration | Diminished ability to think or concentrate |
| Memory disturbances | |
| | Psychomotor agitation or retardation |
| | Significant weight loss or weight gain |
| | Recurrent thoughts of death |

# Hypogonadism: Causes of Low T

| | |
|---|---|
| Aging | Decrease of germinal epithelium |
| | Increase in connective tissue |
| | Decrease in Sertoli and Leydig cells |
| | Increased concentration of SHBG* |
| Medical conditions | Obesity: can cause decreased SHBG (weight loss likely resolves BMI <40) |
| | Diabetes/metabolic syndrome: can decrease SHBG |
| | **Mental health: anorexia nervosa, alcohol use disorder** |
| | Chronic Systemic Illness: Renal/hepatic failure, COPD, AIDS, hemochromotosis |
| | Hyperprolactinemia |
| | Damage to gonadotroph cells or testes (ie tumor, trauma, cysts, infection) |
| | OSA |
| | Isolated Hypogonadotropic Hypogonadism (Kallman Syndrome if anosmia) |
| | Congenital: Klinefelters (XXY, XXXY), XY/XO mosaic, microdeletions of Y |
| Medication | **Opioids*** |
| | Chronic glucocorticoid, steroid, GnRH agonist use |
| | Chemotherapy, ketoconazole (inhibits testosterone synthesis) |
| | **SSRIs*** |

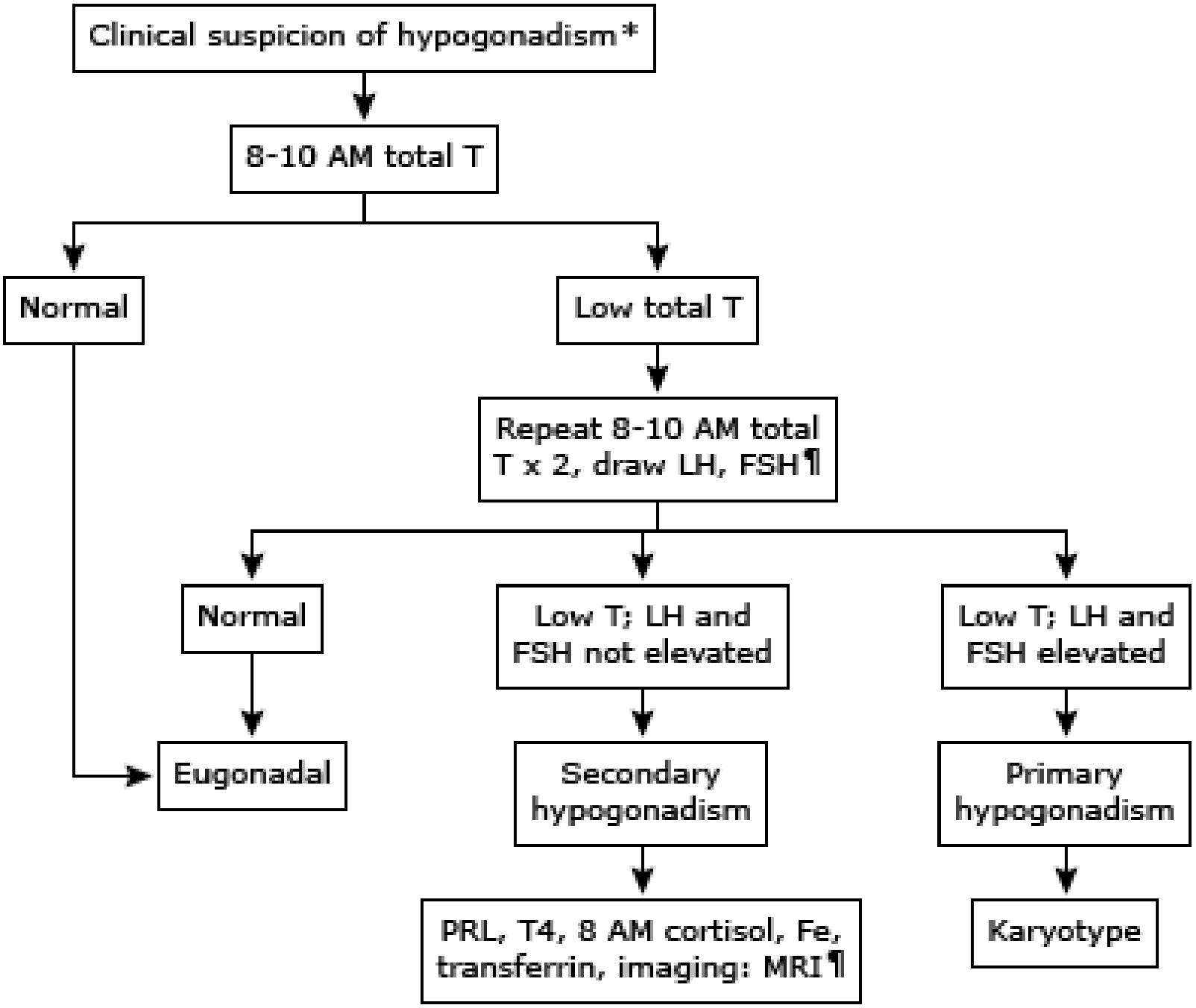
*details on next slide

# Hypogonadism: Causes of Low T

- Increased concentration of SHBG
  - Testosterone is largely protein bound to SHBG and albumin, leaving a small fraction (0.5-3%) as the biologically active form
  - The concentration of SHBG tends to increase with aging; therefore, in aging men the proportion of free testosterone decreases even further than the decrease of total T
  - Hyperthyroidism, high estrogen concentration, liver disease, HIV, antiseizure meds
  - Long-standing primary hypogonadism leads to elevated LH which causes T to aromatize to estrogen, increasing SHBG and causing gynecomastia
- Opioids
  - Rubinstein et al reported in a retrospective cohort study of 81 men 26 to 79 years old that 53% of men on daily opioids had a total testosterone level lower than 250 ng/dL
  - The opioid buprenorphine, which is a partial m-opioid agonist, could be the exception
- SSRIs
  - In a 2017 study by Hansen et al, in vitro administration of these antidepressants to an adrenocortical cell line resulted in decreased testosterone production, ranging from 30% to 80% depending on the drug, through interactions with several different enzymes in the steroidogenesis pathway
  - In addition, there was a relative increase in the ratio of estrogen to androgen, likely due to stimulation of the aromatase enzyme by the SSRIs

# Hypogonadism: When to Test

- Clinical suspicion of hypogonadism
  - 3 sexual symptoms
  - Men with acute or subacute illness should not be assessed for hypogonadism, as they will have a transient functional secondary hypogonadism
  - Other signs
    - Decreased muscle mass
    - Decreased body hair
    - Gynecomastia (primary hypogonadism: due to increased FSH)
    - Infertility
  - Who to test
    - Sexual symptoms (acutely decreased libido is the most specific!)
    - Osteoporosis-associated fractures
    - HIV-associated weight loss
    - Small testes
    - SR opioids or high dose glucocorticoids for prolonged periods of time
- Testosterone measured should be fasting (at least 6 hours)
  - Food decreases testosterone level
- Measure free T vs total T if high or low SHBG is suspected


Clinical suspicion of hypogonadism*
8-10 AM total T
Normal
Low total T
Repeat 8-10 AM total T x 2, draw LH, FSH¶
Normal
Low T; LH and FSH not elevated
Low T; LH and FSH elevated
Eugonadal
Secondary hypogonadism
Primary hypogonadism
PRL, T4, 8 AM cortisol, Fe, transferrin, imaging: MRI¶
Karyotype

# Hypogonadism: Assessment

- Borderline low T with normal or slightly low FSH/LH suggests
  - Obesity: weight loss recommended
  - Diabetes
  - OSA: treat with CPAP before considering testosterone therapy
  - Less responsive to testosterone therapy
- When an MRI should be performed depends upon several factors
  - <40 years with a serum T <250 ng/dL (8.7 nmol/L)
  - >60 years with a serum T <150 ng/dL (5.2 nmol/L)
  - Non-elevated FSH/LH and even slightly elevated prolactin
  - Undetectable FSH/LH
  - Other pituitary hormones are abnormal (ie prolactin is elevated or if serum T4 and/or early morning cortisol are below normal)
- Total testosterone < 317 ng/dl and free testosterone < 220 pmol/L is considered low

# Hypogonadism: Treatment

- Treat underlying reversible cause first
- Topical (preferred)
  - **BBW**: Secondary exposure in women and children can cause adverse effects
  - Monitoring: 4-6 hours after application
- PO/SQ: (not preferred)
  - **BBW**: Increased BP
- IM (may be preferred)
  - May be painful
  - Higher risk of increased Hct
  - Slightly more effective: testosterone levels will be higher
  - Weekly dosing may be preferred
  - Monitoring: after dose change or annually; check half way between injections
  - **BBW**: Pulmonary oil microembolism (POME) reactions
- Nasal gel (not preferred: uncomfortable)
  - **No BBWs**
- Interactions: Protein-bound drugs such as warfarin

# Hypogonadism: Treatment

- hCG (SQ)
  - May help boost testosterone and help infertility and sperm production
  - FSH can be added if insufficient
- Clomiphene
  - Selective estrogen receptor modulator (SERM) boosts LH/FSH
  - May also help with infertility in men and indirectly boosts testosterone
  - Reports of central retinal vein thrombosis exist but cause/effect not established
  - Works best: young, normal, healthy men with secondary hypogonadism
  - Does not work: older men, undetectable LH/FSH, primary hypogonadism, Klinefelters
  - Inferior to hCG
- Women: Combination pill with estrogen is available (Estratest®) for helping with sexual dysfunction in post-menopausal women
  - It does not contain progestin so may need to add if patient has intact uterus

# Hypogonadism

- Labs
  - Monitor lipids/BP (PO/SQ): little-no increased risk for CVE, but increased for pulmonary emboli
  - CBC: (Hct>54): Stop treatment and evaluate (observe for increased RBC)
    - Initially high Hct (48-52) or shortly after beginning treatment suggests OSA
    - Check initally, 3-6 months later, and annually
  - PSA annually: (>4): Stop treatment and evaluate
- Improvement
  - Symptoms most likely to improve are fatigue and libido
  - Patients with low testosterone, low Hct, and primary hypogonadism are most likely to respond
  - Discontinue treatment if there is no improvement
- Risks of TRT
  - Chronic treatment with reversible cause likely leads to decreased response/dependence on TRT
  - Polycythemia: thrombotic and ischemic risks
    - Avoid with recent heart attack or stroke
  - Those with hx of prostate/breast cancer: testosterone can stimulate these cancers
  - Can suppress sperm production and decrease fertility
  - Potential risk of VTE
  - **BBWs**: hypertension with PO/SQ, pulmonary oil embolism with IM, secondary exposure with topical

# Complementary Therapies

# Complemetary Therapies

- Herbals
  - St. John's Wort
  - Rhodiola rosea
  - Kanna
- Vitamins
  - B Vitamins
    - L-Methylfolate
    - SAMe
  - Vitamin D
- Minerals
  - Magnesium
  - Zinc
- Omega-3 Fatty Acid
- NAC
- Essential oils
- Acupuncture
- Ineffective therapies

# Herbals

# St. John's Wort (Hypericum perforatum)

# St John's Wort (SJW)


- Mechanism of Action
  - Reuptake inhibition in order of: NE, DA, GABA, 5-HT
  - Reduction of corticotropin releasing hormone (CRH) secretion through suppression of interleukin-6 release
  - Anti-inflammatory activity may be related to inhibited release of arachidonic acid from membrane phospholipids
- Active Ingredient for depression thought to be hypericin and hyperforin
  - These compounds are used for standardization at 0.3%

# NIH Study on SJW

- 340 moderately to severely depressed patients
- Randomized to 900-1500mg SJW extract, 50-100mg sertraline, or placebo over 8 weeks
- Responders continued for another 18 weeks
- Full response occurred in
  - 31.9% placebo
  - 23.9% SJW
  - 24.8% sertraline

JAMA. 2002 Apr 10;287(14):1807-14.**Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial.**Hypericum Depression Trial Study Group.

# St. John's Wort in Major Depression

- SJW vs. Placebo in MD
  - Ineffective
- SJW vs. Paroxetine in MD
  - SJW at least as effective 16 week f/u P=SJW
- SJW vs. Fluoxetine in MD
  - 12 week DBRCT: SJW 'significantly' more effective than fluoxetine and showed trend towards superiority over placebo
- SJW (600mg/1200mg) vs. Placebo in MD
  - Both doses more effective than placebo[1]

[1]Kasper S et al. *BMC Med* 2006 June, 23; 4:14-19.

# Cochrane Review

- 2000
  - There is evidence that extracts of hypericum are more effective than placebo for the short-term treatment of mild to moderately severe depressive disorders
  - **The current evidence is inadequate** to establish whether hypericum is as effective as other antidepressants
- 2005
  - **Current evidence is inconsistent and confusing**
  - In patients who meet criteria for major depression, several recent placebo-controlled trials suggest that Hypericum has minimal beneficial effects, while other trials suggest that Hypericum and standard antidepressants have similar beneficial effects.

Linde K, The Cochrane Library 2000, 2005

# Cochrane Review

- 2008
  - The available evidence suggests that Hypericum extracts included in the trials
    - Are superior to placebo in patients with major depression
    - Are similarly effective as standard antidepressants
    - And have fewer side effects than standard antidepressants
  - The association of country of origin and precision with effects sizes complicates the interpretation
  - Dropout rates of a review of 35 DBRCT's, 35,562 patients similar to placebo

Linde K, The Cochrane Library 2008

# St. John's Wort in Major Depression

- A meta-analysis on the efficacy and safety of St. John's Wort extract in depression therapy in comparison with selective serotonin reuptake inhibitors in adults
  - 27 studies, (n=3126)
  - SJW was not different from SSRIs in response, remission, and mean reduction in HAM-D
  - SJW had significantly lower rate of adverse events compared to SSRIs (RR 0.77)
  - SJW had fewer withdrawals due to adverse events
  - Limitation: no studies in severe depression (mild-to-moderate only)

Cui Y. A meta-analysis on the efficacy and safety of St John's wort extract in depression therapy in comparison with selective serotonin reuptake inhibitors in adults. Neuropsychiatr Dis Treat. 2016;12:1715-1723.

# St John's Wort

- Dosage
  - 900mg-1800mg/day total, BID dosing best (cost $8–20 per month)
  - May get expensive and giving low dose SSRI might have similar results
    - SJW may have fewer side effects
- Adverse Effects
  - Headache, rashes, GI upset, agitation, insomnia, vivid dreams, mania
  - Safety in pregnancy/breast-feeding unknown
  - **Photosensitivity**: risk is small, may be only at high doses
- Drug Interaction
  - **Potent inducer (3A4), moderate (1A2), mild (2C9, 2C19)**
  - Avoid combination with SSRI and serotonergic agents → serotonin syndrome
  - Alters blood levels of medications
    - **Oral contraceptives**, certain antibiotics, warfarin, digoxin, cyclosporine, theophylline, protease inhibitors, and many antiretrovirals

# St John's Wort: The Verdict

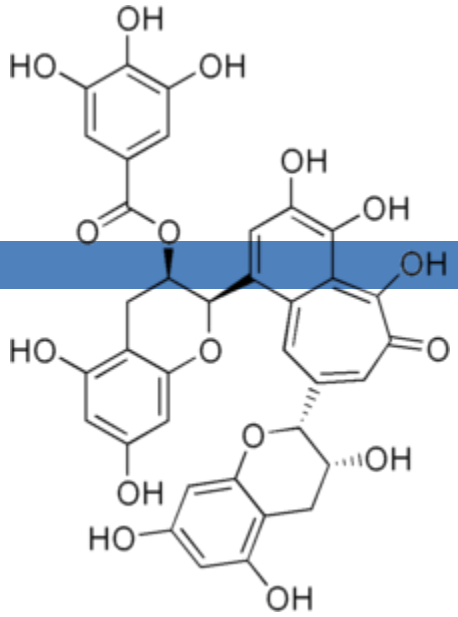
- Safe, effective treatment for **mild-moderate** depression
  - Likely equally effective as antidepressants for mild-moderate depression
    - Though both aren't much better than placebo if at all
  - Adverse effects are better tolerated than antidepressants
  - Possible option in major depression, but may require higher doses (1,500mg daily or more)
  - Caution CYP450 induction interactions
  - Caution photosensativity
  - No studies in severe depression, so unclear if it would be effective
- Patient selection
  - Good history of positive response to low dose SSRI, but intolerant AEs
  - Patient unwilling to take pharmaceutical
  - Patient interested in "natural" and "holistic" treatment

# Rhodiola rosea

## Arctic Root, Golden Root

- Grows in cold regions of the world and has been used to help the body adapt
- Used in traditional medicines of Scandinavia and Russia
- Classified as 'Adaptogen' - compound able to reduce the biochemical effects of stress
- Medicinal properties described in 1749 in Linnaeus Materia Medica

# Rhodiola rosea




- Suspected active ingredients are 'polyphenols'
  - Rhodioniside, Rosavin, rosarin, rosin and salidroside
  - Components often inactive alone, but show synergistic effects when a fixed combination is used
- *Rhodiola rosea* extracts are standardised 3% rosavins and 1% salidrosides
- Standardization
  - Swedish Herbal Institute, Vastra Frolunda was principle product used in clinical trials
  - Natures Way purple top standardized to 250mg per tablet
  - Growing scarcity and lack of regulations has led to environmental degradation, illegal harvesting, and adulteration

# Rhodiola rosea

- Exact mechanism of action unknown
  - HPA axis interactions (cortisol reduction)
  - Action on defense mechanism proteins (heat shock proteins Hsp 70 and FoxO/DAF-16).
  - Improve cerebral circulation (nitric oxide?)
  - Inhibitor of MAO A/B
  - Increase the permeability of the BBB to precursors of DA and 5HT

# Rhodiola rosea

- Some support for use in mood, cognition, and fatigue
  - A DBRPCT, 6 weeks, 88 patients showed significant effect for a Rhodiola extract in doses of 340–680 mg per day in male and female patients from 18 to 70 years old with mild to moderate depression (HAM D 21-31) (Darbinyan 2007)
  - Rhodiola significantly reduced symptoms of fatigue, and improved attention (especially to visuospatial stimulus) after four weeks of repeated administration
    - Also found to reduce cortisol levels (Olsson et al., 2009)

*Darbinyan V, et al Nord J Psychiatry **61** (5): 343–8. 2007 Olsson, E.M.G.,et al 2009. Planta medica 75,105-112 2009*

# Rhodiola clinical use

- Energizing and mild stimulating effect
- May help with sexual side effects
- More common side effects
  - Nausea, irritability, dry mouth and dizziness
- Dosing for mild to moderate depression
  - Start with 150-250mg/day for 1-2 weeks and increase
  - Adjunctive treatment 200-400mg daily
  - Monotherapy may need up to 750mg daily (clinical trial 200-680mg daily (340-500mg++ for antidepressant)
- Claims for use in raynaud syndrome, altitude sickness, and cancer have poor data for recommendation

# Rhodiola: The Verdict

- Likely slightly less effective for mild-moderate depressive sxs compared to antidepressants
  - 2015 head-to-head with sertraline and placebo showed no statistical difference from placebo for sertraline or rhodiola with sertraline having a slightly more reduced HAM-D score
  - 2020 study showed statistically significant improvement in HAM-D with sertraline + 2 doses of rhodiola vs sertraline + 2 doses of placebo and sertraline + placebo + rhodiola indicating rhodiola may have some benefit when combined with sertraline
  - Better adverse effect profile than antidepressants
- Insufficient data for use in severe depression
- FDA has made several warnings to manufacturers for false claims about safety and efficacy
- European Medicines Agency states that trials have considerable deficiencies in quality, therefore use cannot be accepted

# Kanna

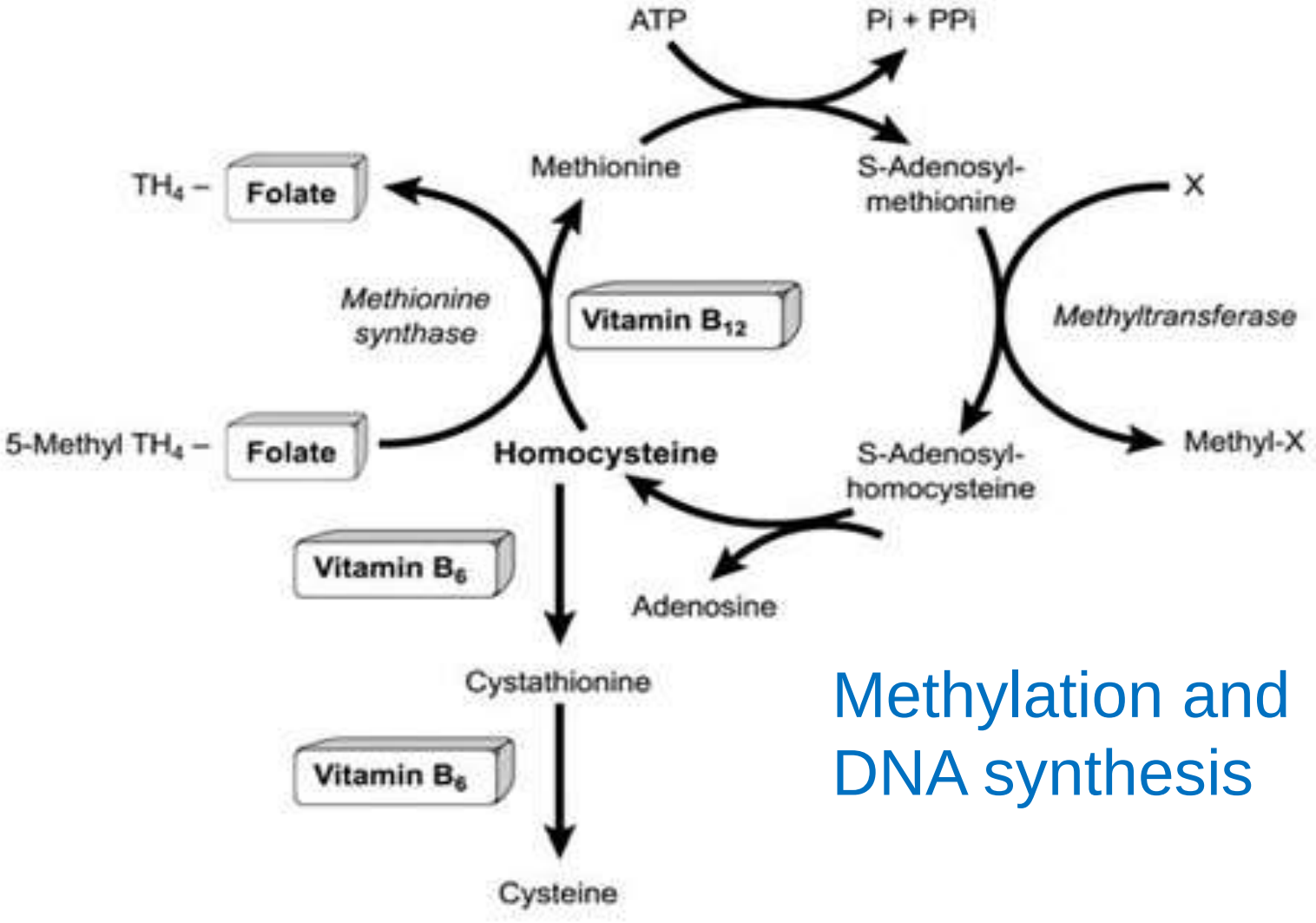
- Sceletium tortuosum
  - Contains many alkaloids, mesembrine likely the most active
- Succulant plant from southern Africa
- Mechanism of Action
  - VMAT2 upregulation (may act like an SRA, also NRA/DRA)
  - SSRI (Ki ~1)
  - PDE4i (weak, Ki ~7000, may also help with mood)
  - Mild inhibition of acetylcholinesterase and MAO-A
- May help with mood, anxiety, focus, sleep
- Adverse effects
  - GI upset
  - No reported ASEs though it is unclear why
    - Even shows up on lists of herbs that help sexual function

# Vitamins

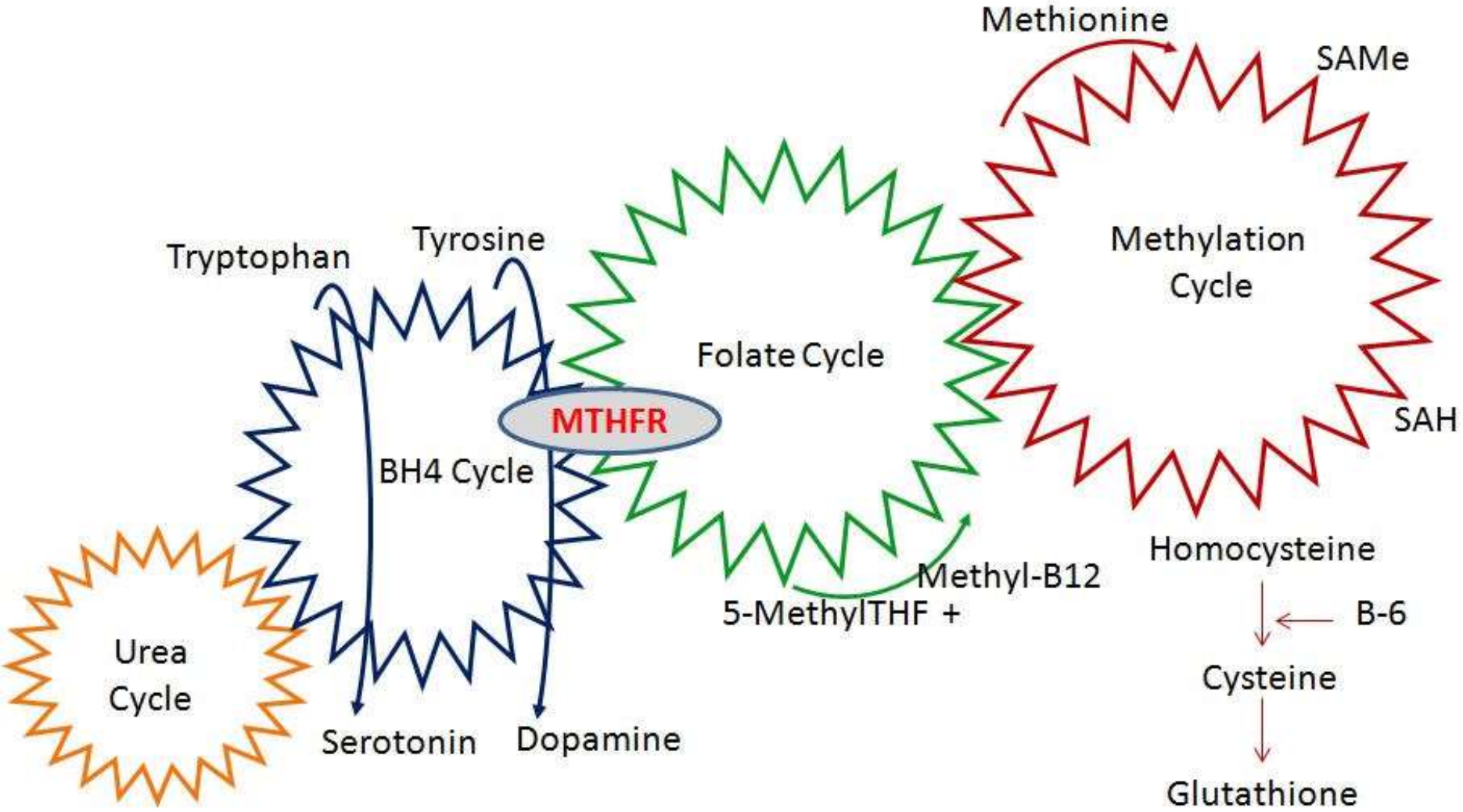
# Vitamins

- Essential organic compounds that cannot be synthesized by the body
  - The "Vit"al "amin"es
  - A, B, C, D(1-5), E, K(1-2)
  - B vitamins are essential water-soluble coenzymes for neuronal health and formation of neurotransmitters; ***bold most important for mental health**
    - B1 (thiamine)
    - B2 (riboflavin)
    - B3 (niacin)
    - B5 (pantothenic acid)
    - **B6 (pyridoxine)**
    - B7 (biotin)
    - **B9 (folate)**
    - **B12 (cobalamin)**
  - "Missing" letters and numbers were either reclassified, determined not to be essential, or were found to be made in the body

# The Folate and Methionine Cycle




Methylation and DNA synthesis


Methionine
SAMe
Tryptophan
Tyrosine
Methylation Cycle
Folate Cycle
MTHFR
BH4 Cycle
SAH
Homocysteine
Methyl-B12
5-MethylTHF +
B-6
Urea Cycle
Cysteine
Serotonin
Dopamine
Glutathione

# B12 Deficiency and Sources

- B12 deficiency is fairly common (6% of adults)
  - Malabsorption
    - Celiac disease, IBD, chronic pancreatitis, bariatric surgery
    - Intrinsic factor deficiency: pernicious anemia
    - Medications: antacids, metformin
  - Vegan and vegetarian diets
  - Alcohol use disorder
    - Malabsorption, liver damage, intrinsic factor disruption, poor nutrition
  - Age related factors (elderly)
- Found in shellfish, fish, liver, beef, lamb, cheese, eggs, fortified foods, nutritional yeast
  - Uniquely can be stored in the liver unlike all other water-soluble vitamins
    - Deficiency can take 3-5 years to develop

# B12 and Psychiatry

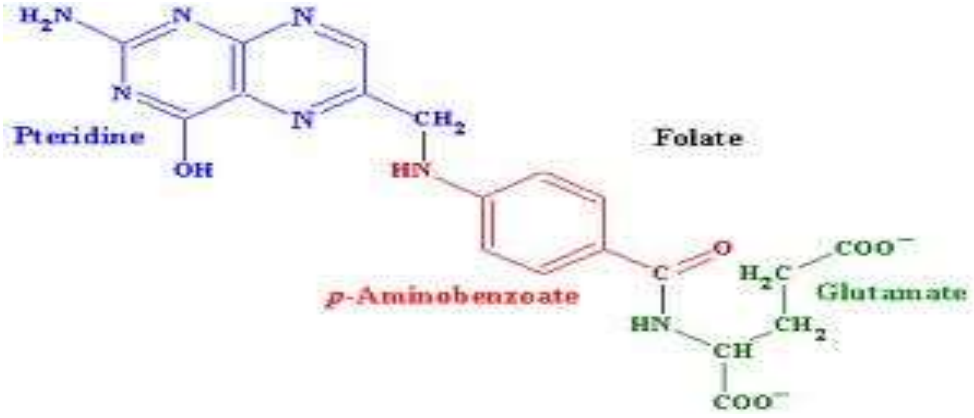
- B12 is a cofactor in many enzymatic reactions to make monoamine neurotransmitters and maintaining mylein sheaths
  - Subacute combined degeneration of the spinal cord
  - Psychiatric symptoms can precede all the more obvious medical findings
- Psychiatric manifestations of B12 deficiency
  - Depression, apathy, mania, confusion, and psychosis
- Physical manifestations
  - Fatigue, weakness, paleness, SOB, headaches, dizziness, loss of appetite, GI upset, numbness, tingling, coordination problems, cognitive changes

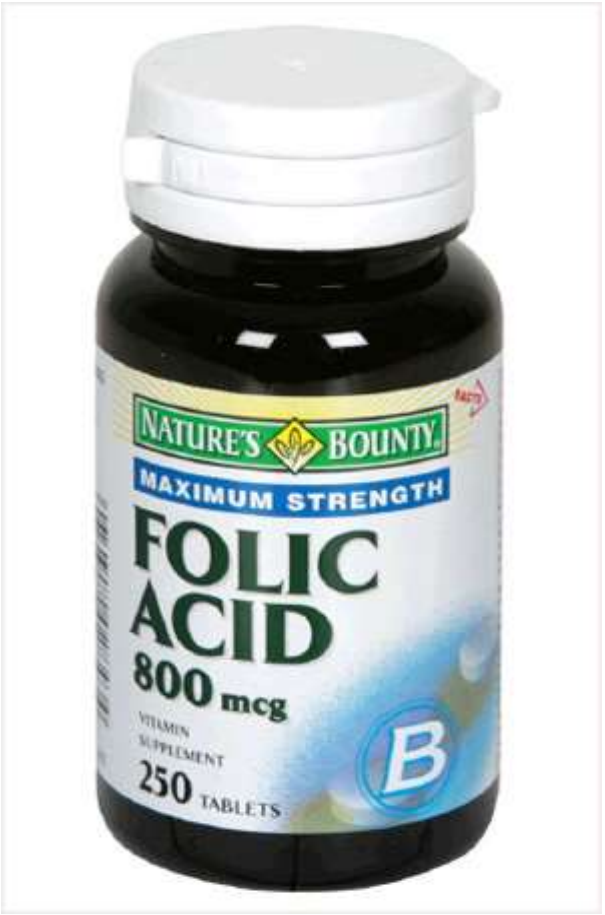
# B12 and Psychiatry

- When to test B12 and folate
  - Underlying condition or diet associated with deficiency
  - Macrocytic anemia with low retic count
  - Mild pancytopenia
  - Hypersegmented neutrophils
  - Unexplained neuropsychiatric abnormalities
    - No apparent cause for symptoms or treatment resistance
- Higher B12 levels associated with more favorable outcome in treating depression

# B12 and Psychiatry

- Most labs will suggest 200 to 1200 is normal
  - 200- 350 is likely too low
- If both Folate and B12 levels are borderline
  - Check MMA and homocysteine
    - Both increased confirms B12 deficiency
    - Only homocysteine increased confirms folate deficiency
- Supplementation
  - Cyanocobalamin most common
  - Oral or injectable
  - 1000mcg a day
  - Methyl or hydroxy may be better utilized
    - Not much evidence for additional cost unless MTHFR mutation





## 12 Foods Rich in Folate

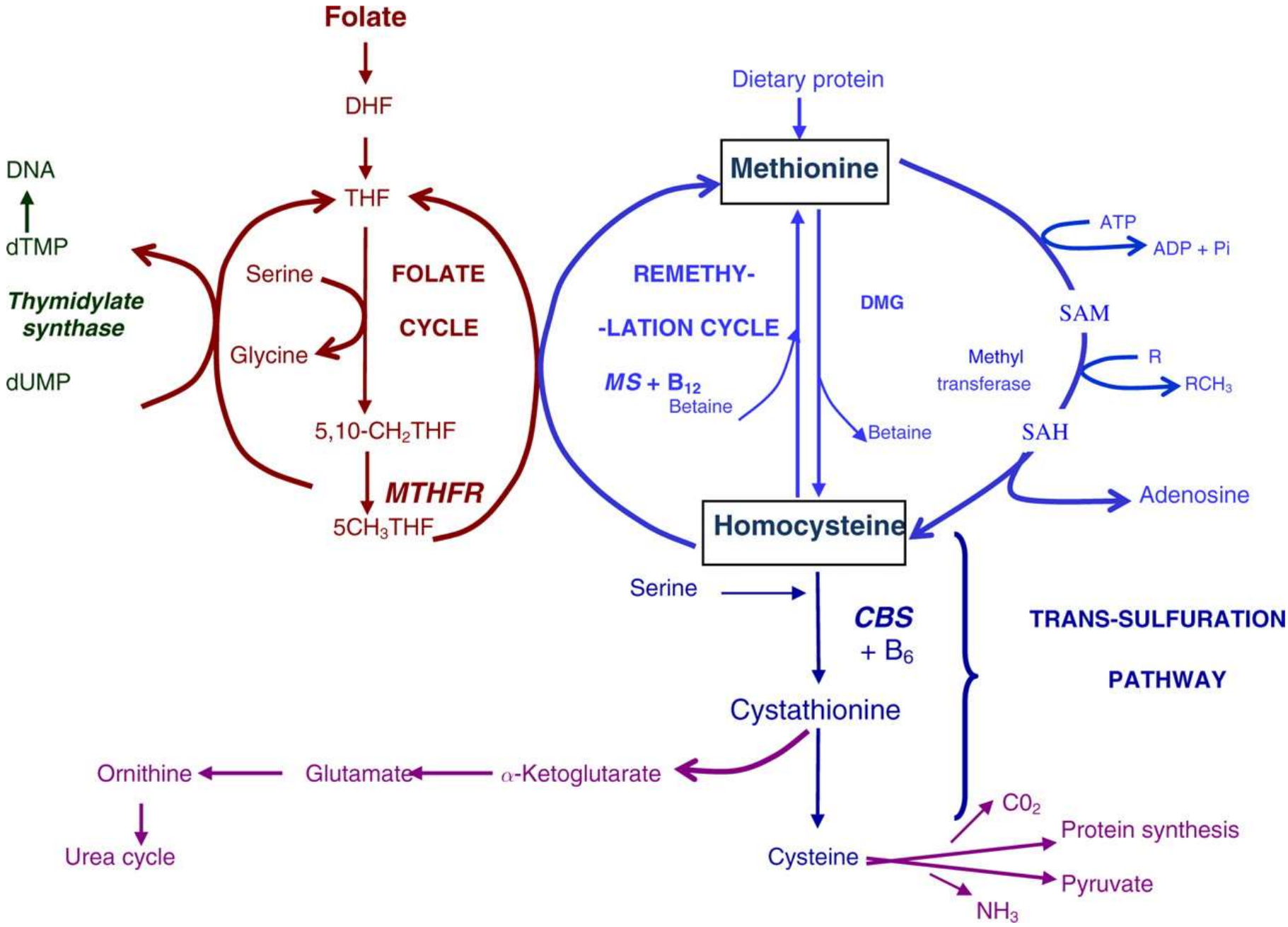
www.exhibithealth.com

# Dietary Folate and Depression

- Suboptimal serum and red blood cell (RBC) folate levels associated with
  - A poorer response to antidepressants
  - A greater severity of symptoms
  - Later onset of clinical improvement
  - Overall treatment resistance
- In America, all grain-based food is supplemented with folic acid after processing, rare to have low folate level
- Link to depression believed due to low L-methylfolate
- RBC folate levels will generally reflect CNS folate levels

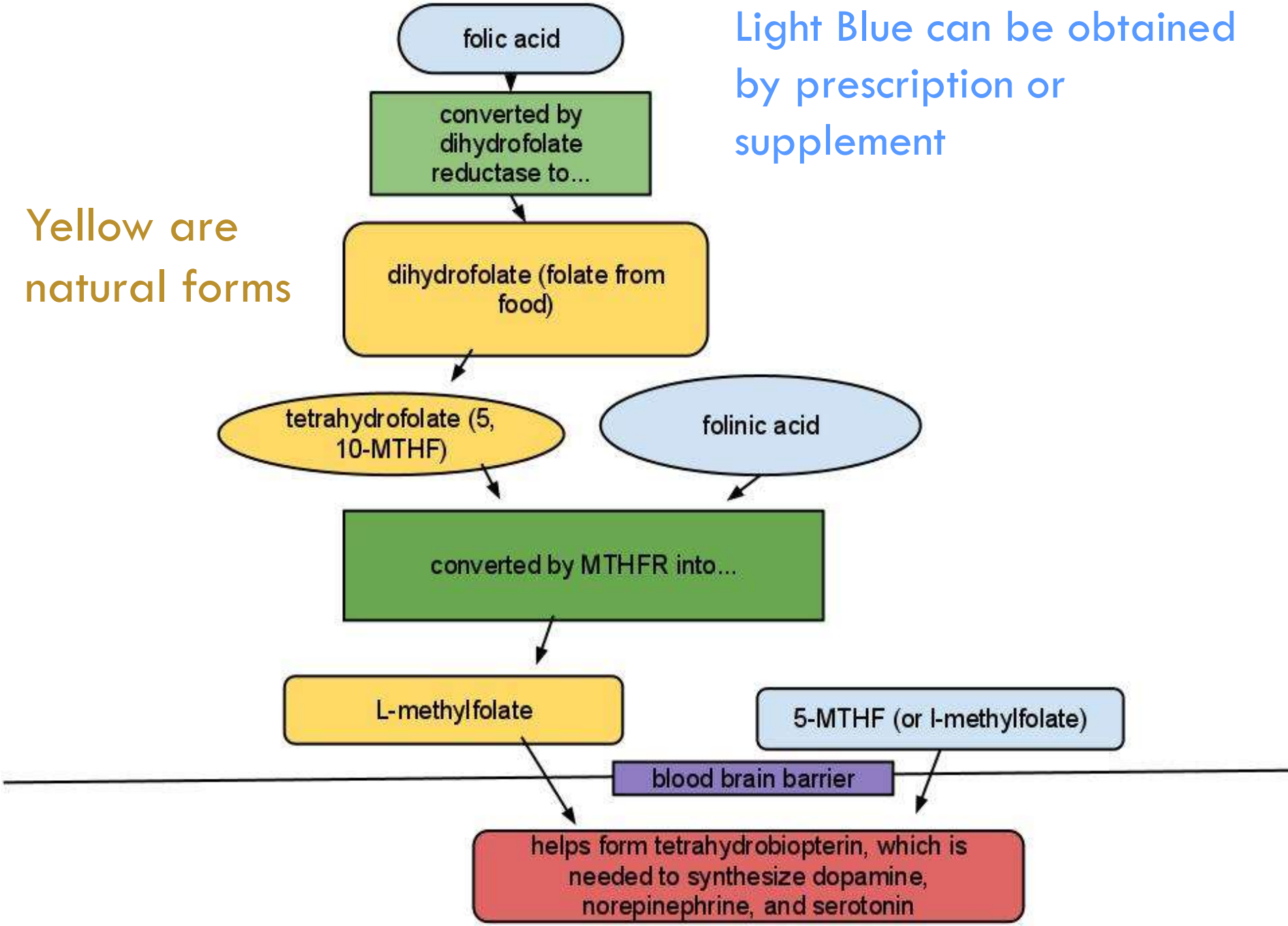
# Folate Deficiency

- Lower levels of folate can result from
  - Dietary intake
  - Diabetes
  - Gastrointestinal disorders
  - Hypothyroidism
  - Renal failure
  - Nicotine dependence
  - Alcoholism
- Folate can be depleted by medications
  - Oral contraceptives
  - AEDs: VPA: CBZ, phenytoin, lamotrigine (inhibits DHF Reductase)
  - Metformin
  - Methotrexate
  - Sulfasalazine
  - Warfarin
  - Triamterine
- Lamotrigine less effective when used with folic acid
  - May not be so with L-methylfolate


Folate
DHF
THF
DNA
dTMP
Thymidylate synthase
dUMP
Serine
Glycine
FOLATE CYCLE
5,10-CH2THF
MTHFR
5CH3THF
Dietary protein
Methionine
REMETHY-
-LATION CYCLE
MS + B12
Betaine
DMG
Betaine
ATP
ADP + Pi
SAM
Methyl transferase
R
RCH3
SAH
Adenosine
Homocysteine
Serine
CBS
+ B6
TRANS-SULFURATION PATHWAY
Cystathionine
Ornithine
Glutamate
α-Ketoglutarate
Urea cycle
Cysteine
C02
Protein synthesis
Pyruvate
NH3

Light Blue can be obtained by prescription or supplement

Yellow are natural forms



# MTHFR and Single Nucleotide Polymorphisms (SNPs)

- Most common SNP is gene that codes for (MTHFR)
  - C/C - C/T - T/T (known as C677T polymorphism)
- Roughly 30% of the US population has one abnormal copy and 12% has two
  - Two abnormal copies: your body synthesizes less than 1/3 of the typical amount of L-methylfolate
  - Up to 74% of treatment-resistant depressed patients have a polymorphism
  - L-methylfolate is the only folate that crosses blood brain barrier
  - L-methylfolate is a necessary cofactor in the synthesis of monoamine neurotransmitters

# How do I get more Folate?

- Plants: Leafy green vegetables, fruits, legumes, fortified cereals and grains
- Animal products: organ meat (**liver**, heart, kidney), egg yolks, seafood
- Supplements: RDA 400mcg, Depression 500mcg/day, pregnant women 600mcg/day, UL 800mcg/day
  - The results for folic acid supplementation itself have been mixed
- Deplin®
- L-Methylfolate approved as a prescription medical food for depressed patients with folate deficiency
  - Doses are usually 7.5 to 15mg daily
  - ~$160/month
- Generic L-Methylfolate: ~$25/montn
- EnLyte®
  - L-Methylfolate 7mg, folic acid, folinic acid, B1, B2, B3, B6, B12, Fe, Mg, Zn, CoQ10, Omega-3 FA
  - Trial of MDD patients with MTHFR abnormality: 0.9 Effect size
  - Cost: $90/month

# Problems with Folate and Supplementation

- Folic Acid supplementation shown to mask some of the first symptoms of B12 deficiency
  - Not true of L-Methylfolate
- Excess folic acid in the serum may actually reduce the amount of l-methylfolate that reaches the brain
- Folate is also a growth factor
  - The risk of colorectal cancer the most studied and the possible risk increased by widespread folic acid supplementation
    - Not true of L-Methylfolate
  - The results of the epidemiological studies are mixed however, with a large US Study showing no correlation

# People with depression are more likely to have

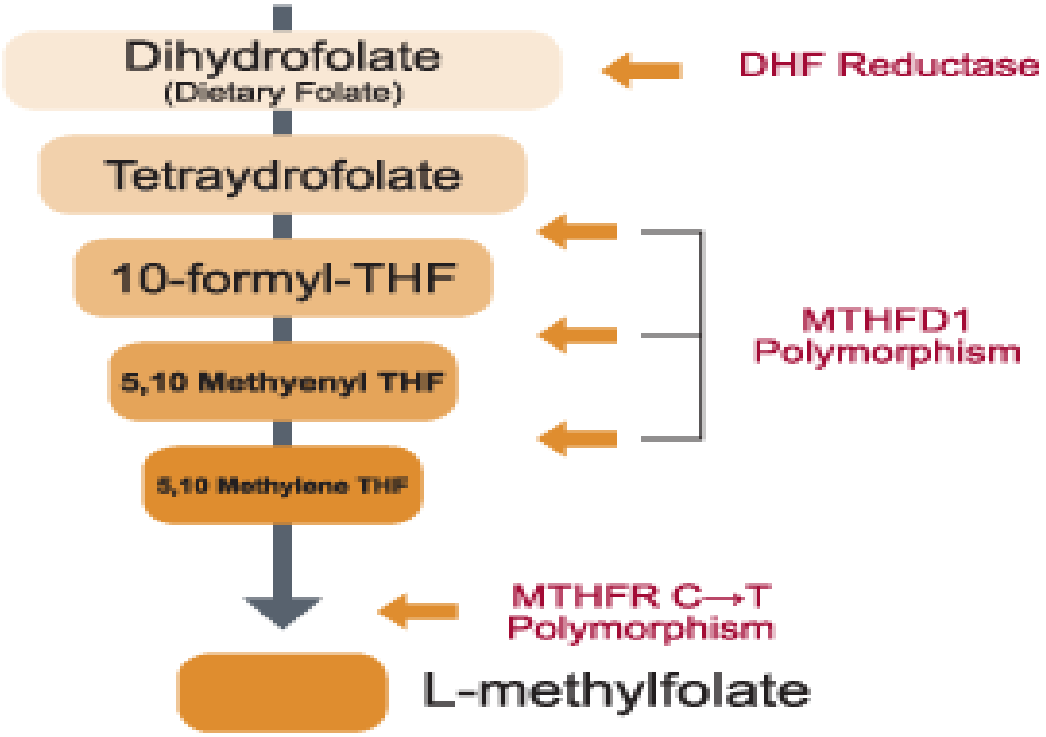
1. Poor DHF reductase activity

deplin
L-METHYLFOLATE

Folate =
Dihydrofolate=
Folic Acid

L-methylfolate

vs Synthetic Folic Acid




2. Problems with MTHFR enzyme

# L-Methylfolate (Deplin®)


- *Animal products: organ meat (**liver**, heart, kidney), egg yolks, seafoo
- Prescription medical food regulated by FDA
- Biologically active form of dietary folate
- Patients with folate deficiency less likely to respond to antidepressant
- L-methylfolate is a necessary cofactor in the synthesis of monoamines
  - Inefficient MTHFR allele methylates less folate (Measure Homocysteine)
  - Homozygous individuals process 1/3 less folate
    - Caucasian: 10-15%
    - Hispanic: >25%
    - Consider testing in anti-depressant resistant patients
    - If homozygous consider treatment
- Best chance of response
  - Patients non-responsive to SSRIs
  - Patients with obesity and inflammation (CRP>3)

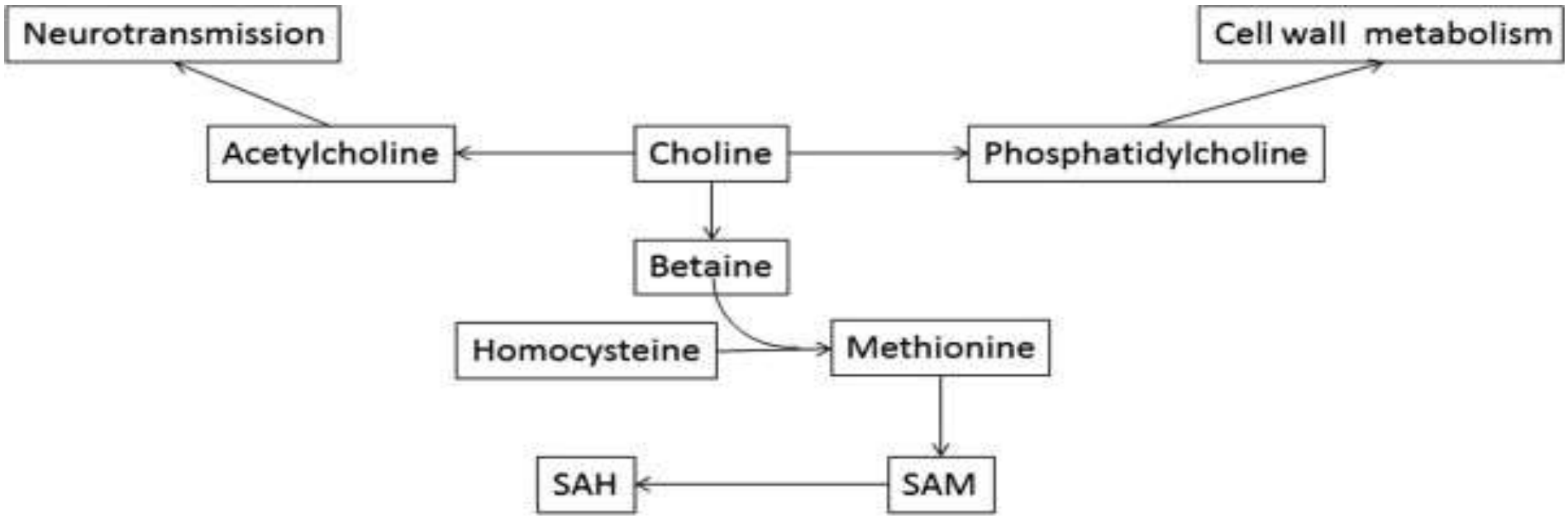
# L-Methylfolate (Deplin®)

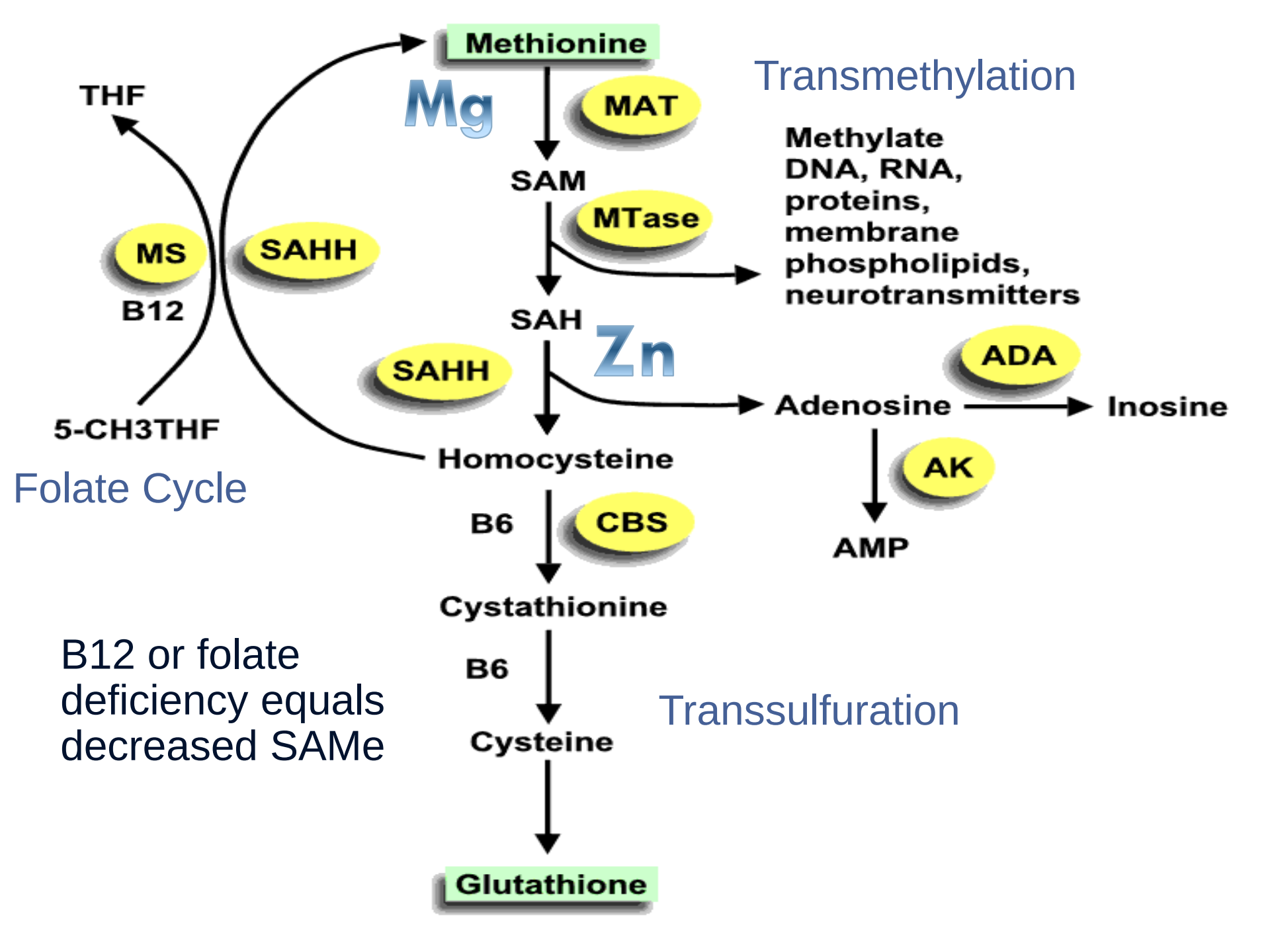
- 2012 double-blind placebo controlled trial
  - Statistically significant difference between 15mg/day as augmentation from placebo
    - 32.3% vs 14.6% response, NNT 6
  - Remission rates were not statistically significant
  - Treatment length: 30 days
  - Side effects were comparable to placebo
- Overall effect size is 0.3-0.5 (up to 0.9 with MTHFR deficiency)
  - Better than many augmenting agents
  - Not necessary to check MTHFR to treat, however patients may be more likely to believe in the treatment if they see a folate level or MTHFR

Papakostas GI et al. L-Methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry*. 2012;169:1267–74.
Macaluso M. L-Methylfolate in Antidepressant Non-responders: The Impact of Body Weight and Inflammation. Front Psychiatry. 2022 Mar 17:13:840116.

# S-Adenosyl Methionine (SAMe)

- The major donor of methyl groups needed for the synthesis of monoamine neurotransmitters and choline for cell membranes
- Donates sulfate groups for major antioxidant glutathione






B12 or folate deficiency equals decreased SAMe

# SAM for the Treatment of Depression

- 1st line, mainstream, treatment for depression in Europe for over 40 years
- Over 40 studies, 24,000 patients, 8 double blind studies vs. placebo, 10 double blind studies vs. antidepressants
  - Superior to placebo
  - Comparable or more effective than antidepressants
  - Faster (1-2 weeks)
  - Better tolerated and fewer adverse effects (ie lacks ASEs)
  - 2024 meta-analysis confirms these results
    - ES 0.58-0.92 compared to placebo
    - No statistical difference when added to AD or compared to AD

Limveeraprajak N et al. Efficacy and acceptability of S-adenyl=L-methionine (SAMe) for depressed patients: a systematic review and meta-analysis of randomized controlled trials. Eur Psychiatry. 2024 Aug 27;67(Suppl 1):S328-S329.

# SAM Clinical Use

- Monotherapy or augmenting agent
  - May be synergistic with antidepressants (not MAOI)
- Electroencephalogram profile of SAM is similar to TCA
  - Increased serotonin turnover, dopamine, and NE levels
  - Neuroimaging shows SAM affects brain similarly to conventional antidepressants
- Augmentation with B vitamins
  - 1000mcg/day B12, 800mcg folate, and 50-100mg/day B6 may enhance the antidepressant effects of SAM

# SAMe/SAM-e

- Dosing
  - Start 200mg BID with titration up 200mg per day to 800mg BID
  - 1600mg: max used in clinical trials
- Side effects
  - Mild nausea, gastric irritation (dose limiting factor)
  - Activating: consider with low energy, hypersomnia
  - Risk of precipitating mania in bipolar patients
  - Take on empty stomach for maximal absorptions
- No sexual side effects, weight gain, or cognitive interference

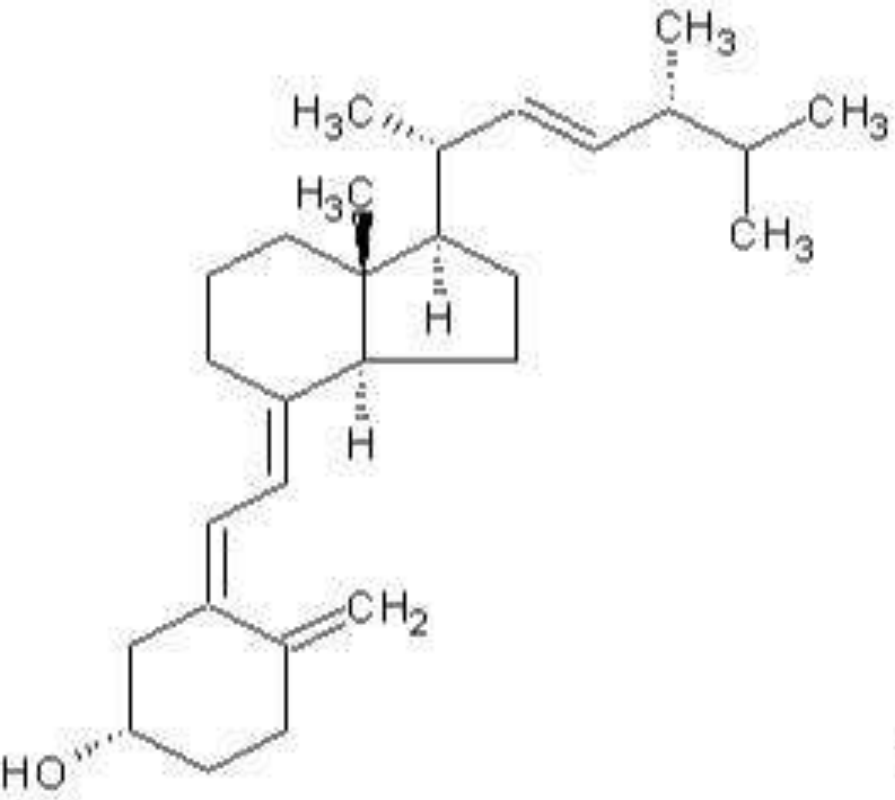
# Limiting Issues


- Cost
  - $30-40/month
  - Not covered by insurance
- Studies show heterogeneity in dosage and trial length and many don't have adequate controls or blinding (Sarris 2009)
- Quality and Potency
  - SAMe rapidly oxidizes when exposed to air
  - It is given an enteric coating, individually wrapped

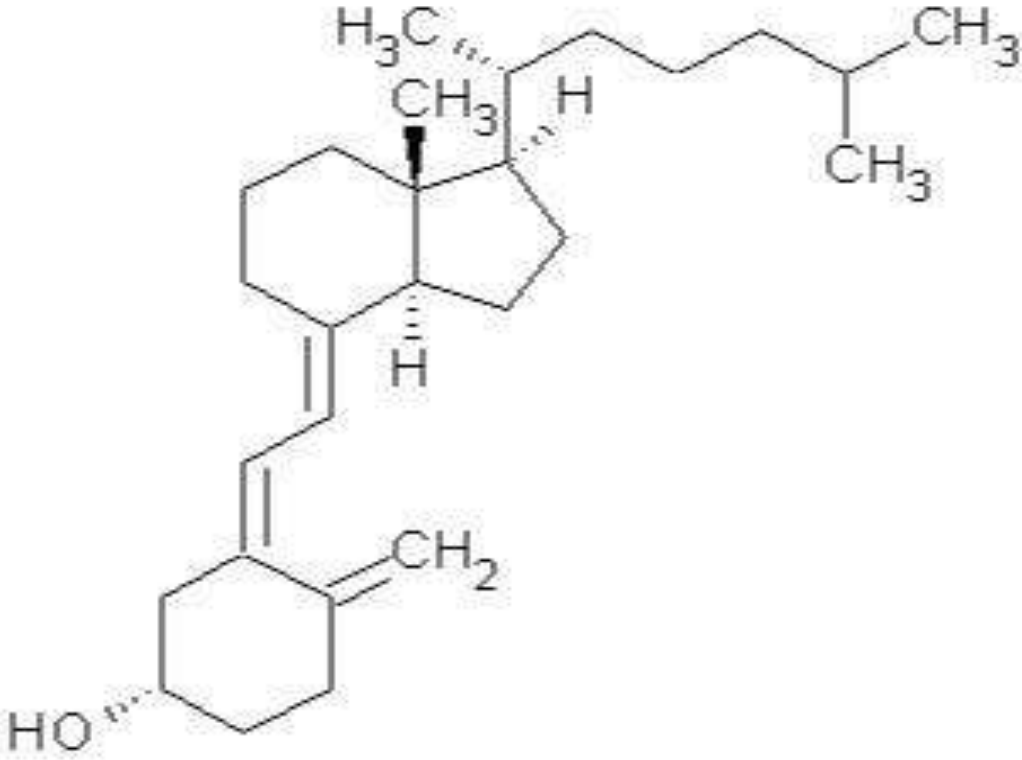
# Medical Uses for SAM

- Osteoarthritis
  - SAM has analgesic and anti-inflammatory effects on OA
  - Six studies positive for improved both depression and pain in patients with fibromyalgia
    - 800mg / day with no adverse effects
  - Efficacy inconclusive; no large RPCTs
- Liver disease
  - May protect against liver damage, reverses elevations in LFTs
    - Consider in patients receiving statins
  - Alcohol abuse depletes liver of SAM and causes oxidative stress that contributes to tissue damage
  - No large RPCTs

# Vitamin D: A fat soluble, ‘steroid’ hormone




Vitamin D2 - ergocalciferol

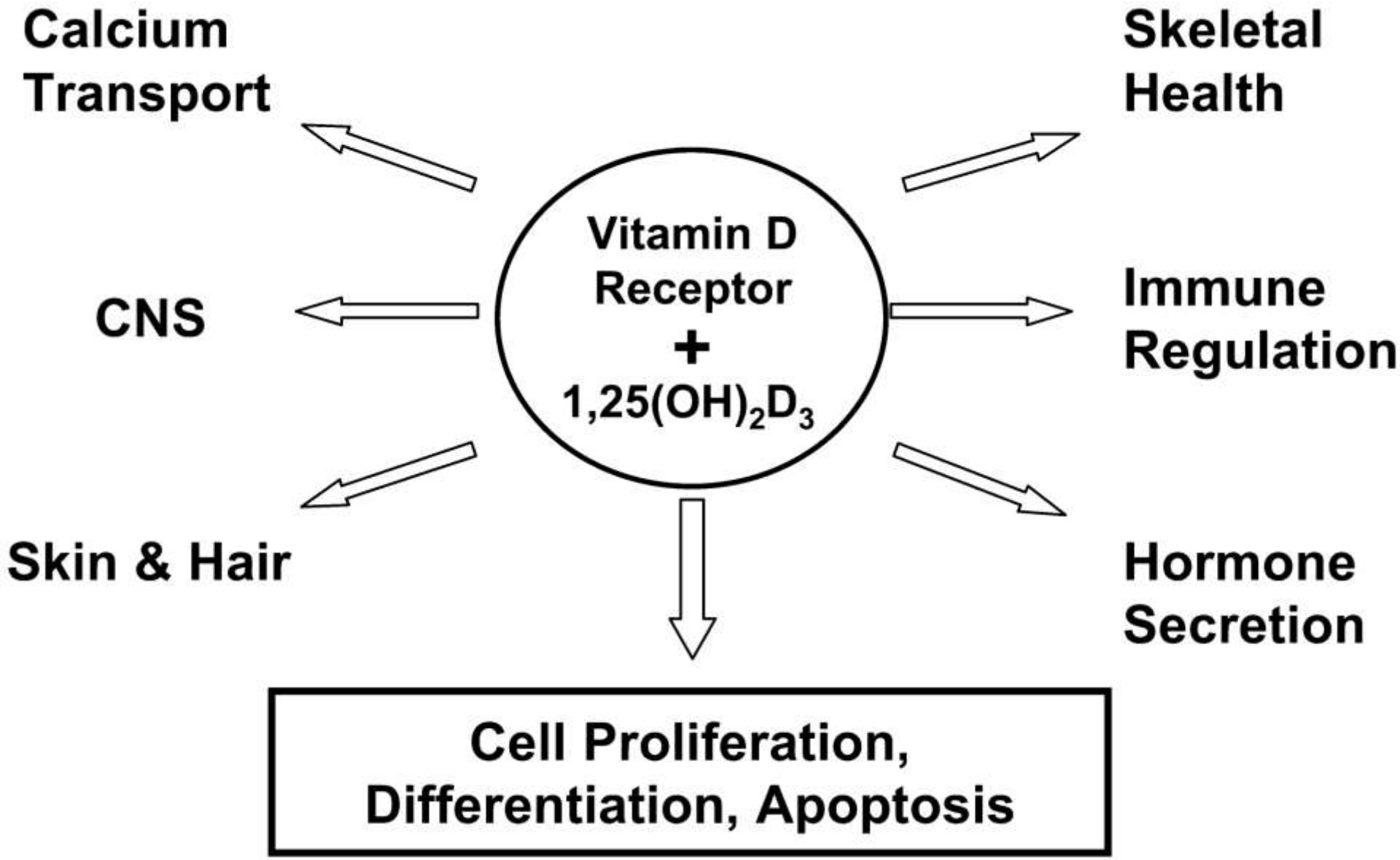



Vitamin D3 - cholecalciferol

**Cell membranes of yeast/fungi**
**Fortification and supplements**

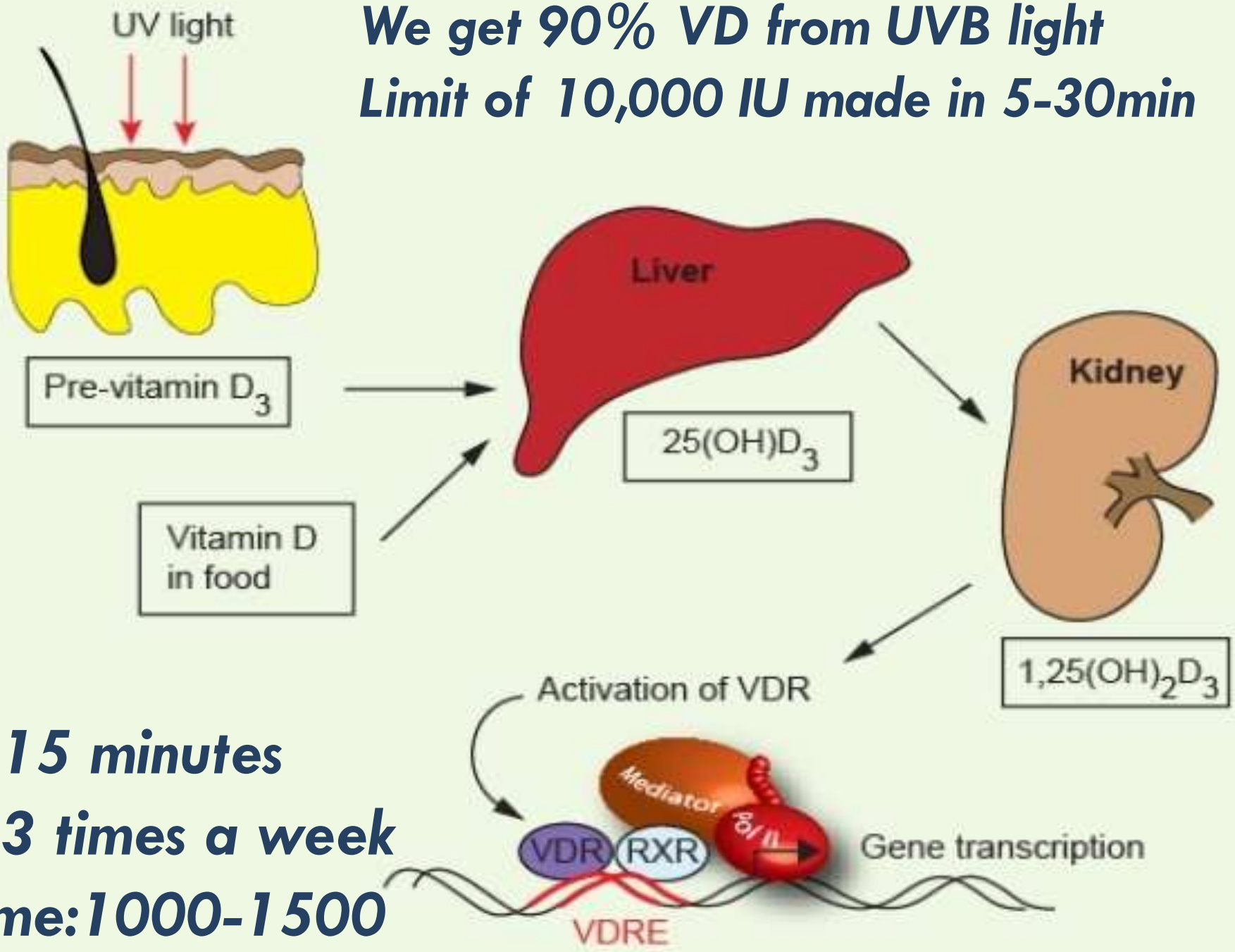
**From skin changed by sunlight**

# Transcription of more than 1000 genes known to be under control of vitamin D



*We get 90% VD from UVB light*

*Limit of 10,000 IU made in 5-30min*




*5-15 minutes*

*2-3 times a week*

*Time:1000-1500*

# Vitamin D Deficiency

- At risk
  - Pregnant and breastfeeding women
  - Children and older adults
  - People with limited sun exposure and darker skin
  - Chronic inflammatory disease and stress
  - Kidney and liver failure
  - Hyper- and hypo-parathyroidism
  - Obesity and bariatric surgery
  - Medications: AEDs, antifungals, glucocorticoids, cholestyramine
- Symptoms
  - Most are asymptomatic
  - Prolonged severe deficiency: reduced absorption of calcium and phosphorus, leading to hypocalcemia and hyperparathyroidism; ultimately osteomalacia

# Low Vitamin D and the Brain

- Impacts brain development and function through numerous effects on regulatory processes
  - Neurotrophin expression (NGF, BDNF, GDNF)
  - Anti-inflammatory defenses
  - Synaptogenesis, synaptic plasticity (memory formation)
  - Catecholamines, especially dopamine
- Brain has both VDR and activating enzyme

# Psychiatry and Low Vitamin D

- Possible association with
  - Depression, suicide
  - Seasonal Affective Disorder
  - Schizophrenia
  - Alzheimers Disease
  - Parkinsons disease
  - Cognitive Decline
  - Autism

# The Evidence: Vitamin D and Depression

- Population based studies
  - Several have investigated relationship between vitamin D status and depression
    - Conflicting results with similar designed studies
    - Many have design flaws
- Clinical trials: few with similar problems
- Strongest association
  - Those with more severe depression and lower vitamin D
  - Chronic illness

# Clinically…..Vitamin D and Depression

- Result of disease or causal?
  - Reduced activity, diet, increased stress
  - **Data as a cause for depression is scanty**
- Hard to establish clear recommendation when evidence lacking
- Need more RCTs with clinically depressed patients

# Levels for Optimal Skeletal Health

- IOM (Institute of Medicine)
  - 25(OH)D above 20ng/ml (50 nmol/mL) (in healthy people)
- National Osteoporosis Foundation, International Osteoporosis Foundation, American Geriatric Society
  - Above 30ng/ml (75nmol/mL)
- Endocrine Society
  - Since 2024 no longer sets levels due to lack of evidence

# New Endocrine Society Guidelines (2024)

- Empiric treatment
  - Ages 1-18 due to prevention of rickets
  - Age >75
  - Pregnant patients (empiric supplementation, don't need to check levels)
    - Reduce risk of preeclampsia, preterm birth, intrauterine mortality
  - High risk prediabetes
    - May lower risk of progression to diabetes
- Who to screen
  - Those with a bone disorder (ie osteoporosis)
  - Malabsorption (ie celiac disease, roux-en-y, IBD)
  - Medications that interfere with absorption
  - Hypocalcemia
- Don't screen: dark complexion, obesity; **no mention of mental health sxs**
- Abandoning of blood level ranges for deficiency and insufficiency
- RDI: 19-69 (600 IU/day), 70-74 (800 IU/day)

# Levels of Serum 25(OH)D

- Although there is no formal definition of vitamin D deficiency, some groups use the following values in adults
  - Deficiency is <12 ng/ml (30 nmol/mL)
  - Insufficiency is between 12 and 20 ng/ml (30-50 nmol/mL)
- Lab: Order 25(OH)D, not 1,25(OH)D
- For those with levels < 12 ng/mL
  - Check calcium, phosphorus, AP, PTH, electrolytes, BUN, creatinine, and tissue transglutaminase antibodies
- Follow-up Vitamin D level: 3-4 months

# Vitamin D Supplementation

- No evidence long term use of high doses are good and may be harmful
- Ergocalciferol (Vit D2)
  - <12ng/mL: 50,000 IU/wk
- Cholecalciferol (Vit D3)
  - 12-20ng/mL: 800-1000IU/day
  - 20-30ng/mL: 600-800IU/day
- General Rule
  - 1000 IU/ day increase blood levels by 10ng/ml
  - Upper safety recommendation IOM 4000IU/day

# Minerals

# Minerals

- Naturally occurring, inorganic, solid substance with specific chemical composition and crystalline structure
- Mineral comes from latin and translates and mine or ore
- Essential minerals
  - Inorganic substances
  - Body needs for various functions
- Major minerals
  - Calcium (1.5%), phosphorus (1%)
  - Potassium, sodium, magnesium, chorine, sulfur (0.85%)
- Trace elements (0.15%)
  - Iron, cobalt, copper, zinc, manganese, molybdenum, iodine, selenium, bromine, chromium?
- Come from the soil, absorbed by plants, eaten by animals

# Magnesium

- Found in every cell of the body
- Biological function
  - ATP must bind to magnesium to be active
  - Over 300 enzymes require magnesium ions for catalytic action
    - ie Methylation cycle
  - DNA/RNA synthesis
  - Production of testosterone
  - Nerve conduction
- Name derived from Magnesia, a region of Greece where it was first found

# Magnesium

- Research supports the influence of Mg (Ueshima 2005)
  - Glucose tolerance and diabetes
  - Migraine headaches
  - Hypertension (ie magnesium sulphate)
  - Allergies
  - Healthy muscles and bones
  - Asthma
  - Neurocognitive function
- Lack of magnesium may promote
  - Depression
  - Affect serotonin receptor function
  - Influence synthesis and release of a variety of neurotransmitters
- Lack of well-designed, decent-sized randomized controlled trials of various psychiatric disorders and magnesium supplementation

# Low Magnesium Signs & Symptoms

- Classic
  - Tics
  - Muscle spasms and cramps
  - Seizures
  - Irregular heart rhythms
  - Constipation
- 'Sub-clinical'
  - Migraine headaches
  - Insomnia
  - Depression
  - Chronic fatigue
  - Irritability

# Factors for Mg Deficiency Risk

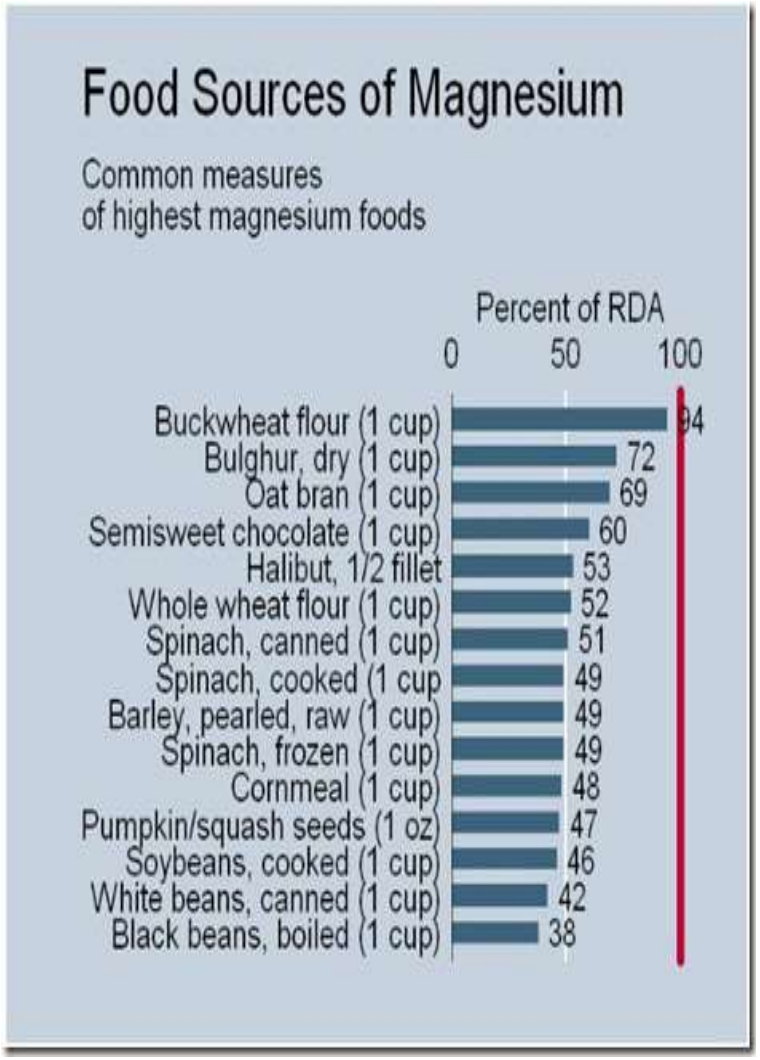
- Malabsorption / malnutrition
  - Chronic diarrhea, pancreatitis, bypass surgery
- Alcoholism
- Balance is maintained through intestinal absorption and renal excretion
- Chronic disease and stress
  - DMII
- Medications
  - PPIs
  - Diuretics
  - Nephrotoxic drugs

# Assessing Magnesium Status

- Level may not be accurate
  - 99% intracellular or in bone
- Normal serum magnesium level can occur in the presence of a total body magnesium deficiency
- There is some observational evidence that the Ca/Mg ratio may be a better clue
- Look for signs and symptoms of low magnesium and predisposing risk factors

# Mg in Food


Top food sources of magnesium
By PositiveMed.com
Source: National Institutes of Health
Wheat Bran
Almonds
Spinach
Cashews
Soybeans (organic)
Oatmeal
Peanuts
Baked potato with skin
Black-eyed peas
Brown rice


Food Sources of Magnesium
Common measures of highest magnesium foods
Percent of RDA
0
50
100
Buckwheat flour (1 cup) 94
Bulghur, dry (1 cup) 72
Oat bran (1 cup) 69
Semisweet chocolate (1 cup) 60
Halibut, 1/2 fillet 53
Whole wheat flour (1 cup) 52
Spinach, canned (1 cup) 51
Spinach, cooked (1 cup 49
Barley, pearled, raw (1 cup) 49
Spinach, frozen (1 cup) 49
Cornmeal (1 cup) 48
Pumpkin/squash seeds (1 oz) 47
Soybeans, cooked (1 cup) 46
White beans, canned (1 cup) 42
Black beans, boiled (1 cup) 38

# Mg Supplementation – How much?

- Not readily available in a normal multivitamin
  - Too bulky to fit into the small pills
- Goal
  - Total daily levels between 400-800mg
  - Most people can safely supplement with 200-350mg daily
- Caution (avoid supplementation)
  - Kidney disease
  - Myasthenia gravis
  - Bowel obstruction
  - Bradycardia

# Mg for Depression: The Evidence

- Rasmussen HH, Mortensen PB, Jensen IW. Int J Psychiatry Med. 1989;19(1):57-63. **Depression and magnesium deficiency**.
- Murck H. **Magnesium and affective disorders.** Nutr Neurosci. 2002 Dec;5(6):375-89.
- Barragan-Rodriguez L. Rodriguez-Moran M. Guerrero-Romero F. **Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial.** Magnesium Research. 21(4):218-23, 2008 Dec.
  - Same results as imipramine
- Eby GA. **Magnesium for treatment-resistant depression: a review and hypothesis.** [Review] ]132 refs]. 3rd. Eby KL. Medical Hypotheses. 74(4):649-60, 2010 Apr.
- Moabedi et al. **Magnesium supplementation beneficially affects depression in adults with depressive disorder: a systematic review and meta-analysis of randomized cliniclal trials.** Front. Psychiatry. 22 December 2023.
  - 7 trials, 325 individuals, Effect size 0.919

# Mg Supplementation: Forms

- Magnesium oxide/sulfate
  - Cheap, has very low absorption, may help constipation and GERD
- Magnesium citrate powder good option
  - 1tsp QD/BID (too much has laxative effect)
- Magnesium taurinate/orotate (may help CV health)
- Magnesium lactate/malate (well absorbed, little laxative effect)
- Magnesium L-threonate (may help cognition, brain health)
- Magnesium glycinate (may help anxiety, insomnia)
- Magnesium glutamate and aspartate may worsen depression
- Pico-ionic magnesium
  - Non-laxative
  - Small size allows absorption 100% at the cellular level
  - 100mg may have same effect as 5-10 times other forms
- Space out magnesium/zinc/calcium intake as all these minerals fight for absorption if taken at the same time

# Zinc

- Essential mineral
  - May be lacking in processed and strict vegetarian diets
  - No ability to store
  - Name origin likely from Persian for “stone”
- Co-factor to over 200 enzymes
  - Neurotransmitter production: dopamine and melatonin
  - Protein synthesis
  - Regulation of gene expression
  - Important in normal cell growth
  - Found in high levels in hippocampus and cerebral cortex
  - Modulates BDNF gene expression
  - Has as a role in blocking lead absorption

# Signs and Sx Zinc Deficiency

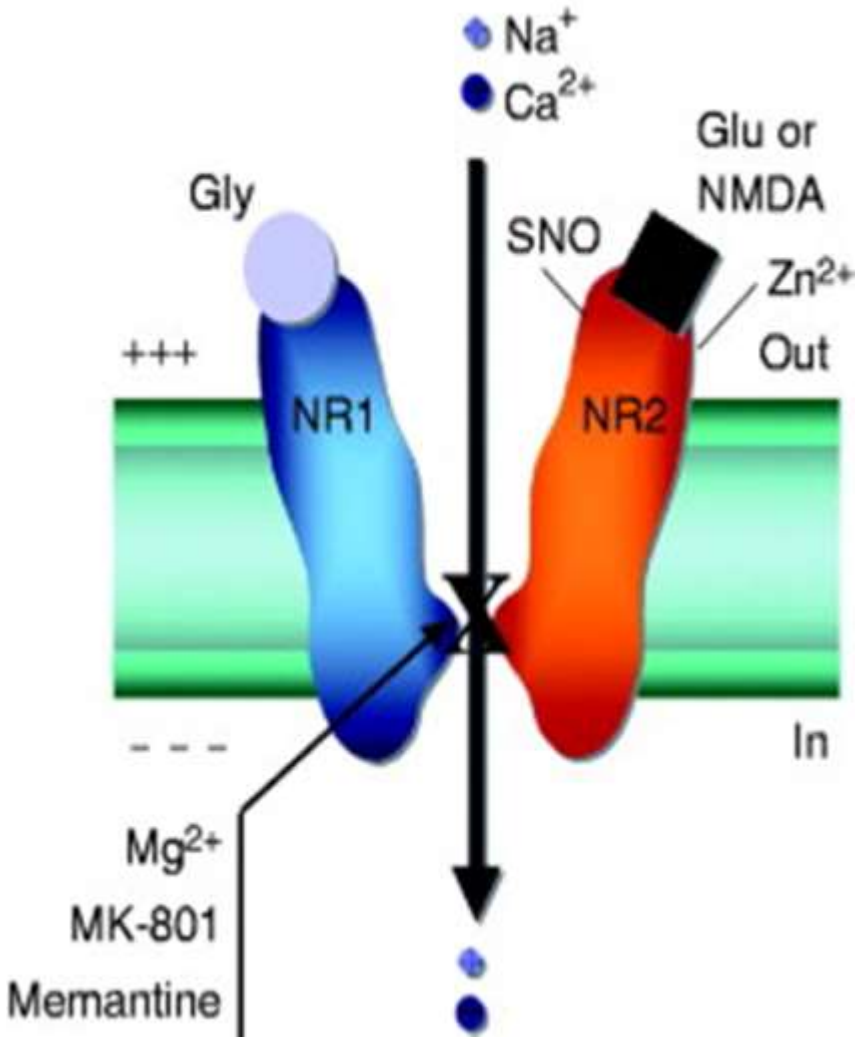
- Compromised immune system (Inflammation and immunity)
- Hair loss and skin lesions (Poor cell growth)
- Loss of appetite and/or anorexia
- Impairment of cognitive and motor functions
  - Especially important in developing fetus
- Reduced fertility
- Rashes on the skin
- Spots on fingernails
- Sleep disturbance
- Loss of libido
- Loss of taste or smell
- Mild anemia

# Zn Deficiency Risks

- People with intestinal problems (celiac disease, inflammatory bowel)
- Vegetarians and vegans
- Chronic kidney and liver diseases
- Alcoholics
- The elderly
- Medications
  - Diuretics (thiazide, loop, K-sparing) increase renal excretion
  - Antibiotics (quinolones, tetracyclines) can bind zinc in the GI tract
  - BP meds (ACEis and CCBs)
  - PPIs can reduce zinc absorption
  - Iron supplementation can interfere with zinc absorption
  - Valproic acid, penicillamine, corticosteroids

# Zinc and the Brain

- Zinc is a non-competitive allosteric inhibitor of NMDA receptors in brain
- Impact on learning, memory, and affective functions



# Zinc: Rat Research

- Antidepressants increase the ability of zinc to work as an anti-inflammatory agent in rat brains
- Appears to be an antidepressant for rats
  - Combination of zinc + small amounts of ADs (TCAs and SSRIs) enhanced the ability of ADs
    - Rats swam longer in hopeless situations
    - Endured being held by their tails

# Zinc and Depression

- Observational Studies
  - Zinc supplementation plus antidepressant therapy can work better for depression than antidepressants alone
  - Higher levels of depression have correlated to lower zinc levels
  - Low zinc levels in pregnant women associated with peri-partum depression
- Ranjbar et al. **Effects of zinc supplementation in patients with major depression.** Iran J Psychiatry. Jun 2013.
  - 5 point difference in drop AD + zinc 25mg vs placebo on BDI
  - 2014 study: 12 point difference in drop AD + zinc 25mg vs placebo on HDRS
- Yasaee et al. **Zinc in depression: From development to treatment: A comparative/dose response meta-analysis of observational studies and randomized controlled trials.** General Hospital Psychiatry. 2022.
  - Decreased depression scale by 4.15 points
  - Only useful as monotherapy
  - Highest level of zinc intake associated with 28% reduced risk of depression (RR:0.66)

# Zinc and ADHD

- Granero R et al. **The Role of Iron and Zinc in the Treatment of ADHD among Children and Adolescents: A Systematic Review of Randomized Clinical Trials.** *Nutrients* 2021;13(11):4059.
  - Included 9 studies
  - 10mg zinc vs placebo + 0.5-1mg/kg MPH improved inattention
  - 10mg zinc + 0.3mg/kg MPH improved teacher ratings but not a parents
  - 15-30mg zinc + d-AMP improved teacher ratings but not parents
  - 15mg zinc vs placebo + MPH improved teacher and parent ratings
  - 5mg/kg iron + MPH improved hyperactivity and impulsiveness
  - Zinc + iron improved ADHD severity of inattentiveness, hyperactivity, and impulsivity
  - The studies included had high risk of biases, however no other studies exist and this is a fairly cheap and low risk strategy to try

# Zn in the Diet

- Best sources are protein-rich meats
- Pumpkin seeds good non-meat source
- Vitamins C, E, and B6 help absorption

## Foods with zinc

| FOOD | SERVING | mg |
|---|---|---|
| Oysters *(raw)* | 6 *(medium)* | 76.3 |
| Beef *(cooked)* | 3 oz | 5.2 |
| Lobster *(cooked)* | 3 oz | 2.5 |
| Pork *(cooked)* | 3 oz | 2.4 |
| Brand Flakes* | 1 cup | 2.0 |
| Yogurt | 1 cup | 1.5 |
| Salmon *(cooked)* | 1/2 fillet | 1.3 |
| Milk *(2% milkfat)* | 1 cup | 1.0 |
| Egg *(hard-boiled)* | 1 *(large)* | 0.5 |

* *different cereals will have different levels of zinc.*

# Zinc Diet and Supplementation

- RDA is 11mg/day for men and 8mg/day for women
  - Americans average 14mg (men) and 9mg (women)
  - Max RDA is 40mg/day
- Nasal formulations can cause permanent loss of smell
- May help with hair loss, particularly alopecia areata
- Intake of >50mg a day may lead to improper copper absorption
  - Likely not a serious problem until 150mg daily
  - Studies of ADHD showed correlation of this effect with improvement of ADHD symptoms

# Zinc: The Verdict

- Zinc deficiency doesn't necessarily cause depression (though it might play a role)
- Depression (inflammation) may cause low serum zinc
- Low serum levels of zinc may be a biomarker for depression like high CRP is a biomarker for inflammation
- Consider patients have adequate zinc as part of overall dietary and nutritional recommendations
- Studies suggest zinc supplementation may improve depression and ADHD

# Omega-3 Fatty Acid

# Fatty Acids (*VPA and zinc)

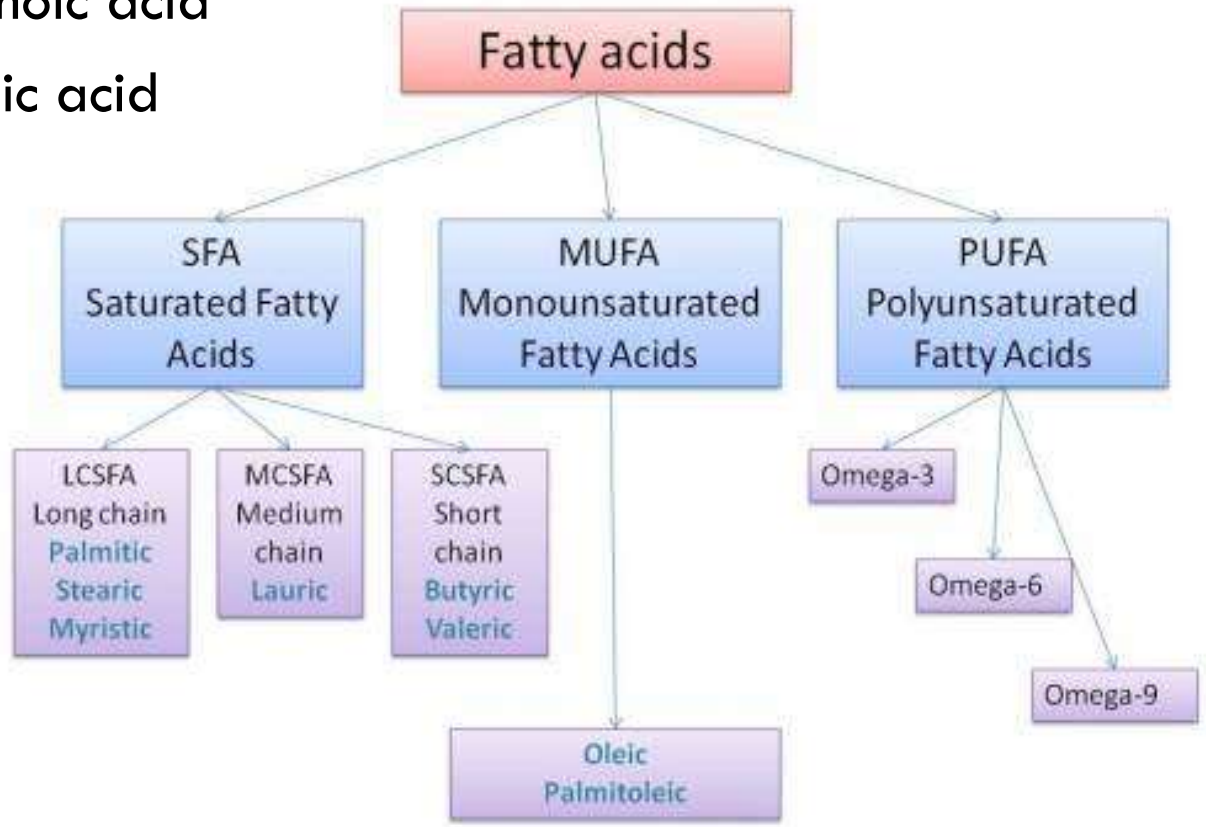
- Saturated: no double bonds
  - Short-chain
    - Butyric Acid - 4C
  - Medium-chain
    - Lauric Acid – 12 C
      - Coconut oil, palm kernel oil, breast milk
  - Long-chain
    - Myristic Acid – 14 C's
      - Cow's milk and dairy products
    - Palmitic Acid
      - Palm oil and meats
    - Stearic Acid – 18 C
      - Meat and cocoa butter
  - Solid at room temperature
  - Not oxidized
- Unsaturated
  - Mono
    - Oleic Acid
    - Palmitoleic Acid
  - Poly
    - One or more double bonds
    - Named by bond location
    - Omega-3 (ALA, DHA, EPA)
      - Nuts, Seeds, Fish, Algae, Krill
      - Grass-fed livestock
    - Omega-6 (AA, LA)
      - Nuts, seeds, and their oils (corn, peanut, cottonseed, sunflower)
      - Processed foods
  - Trans
    - High heat can create trans bond

# Vitamin F

- Essential fatty acids used to be known as vitamin F until they were reclassified as fats
- There are only two essential fatty acids
  - ALA: can be converted in limited quantities to EPA and DHA
  - LA: can be converted into AA
- Saturated fatty acids
  - Can be made in the liver from excess carbohydrates
- Monounsaturated FAs
  - Oleic acid can be made from stearic acid
  - Palmitoleic acid can be made from palmitic acid

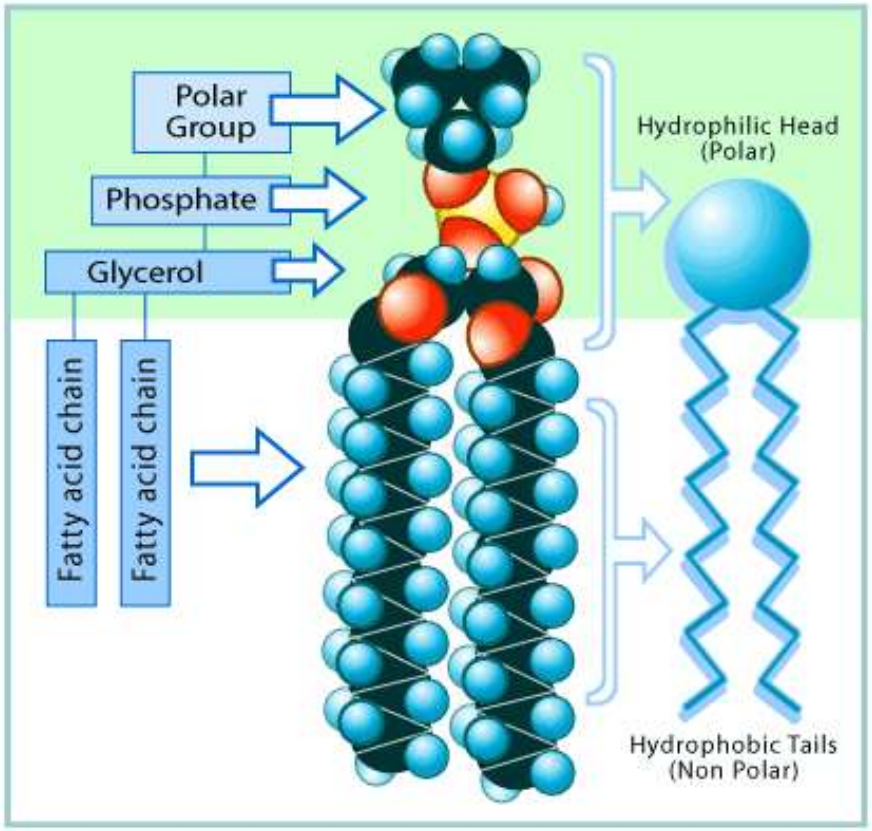
# The Free Fatty acids

- DHA: Docosahexaenoic acid
- EPA: Eicosapentaenoic acid
- ALA: Alpha-linolenic acid



# PUFAs and the Brain

- Critical for membrane structure and neuronal function and signal transduction
- Usually either DHA (Omega-3) or Arachidonic Acid (Omega-6)
- DHA and AA act as second messengers
- Effect alters ion channels, cyclic nucleotides and gene function



# Omega-3 Fatty Acid (FA)

- The amount and ratios of Omega-3/6's in our brain are dependent upon what we consume in our diet
- DHA and EPA Omega-3 is made by photosynthetic algae eaten by krill or fish or oysters, etc which we eventually consume
  - Farmed fish not likely to contain much Omega-3
- ALA is found in nuts, seeds, grass, insects, and livestock that have a diet of these foods
  - Livestock are able to convert some ALA into DHA and EPA
- Dampens inflammatory cascades that are required for necessary cellular function
  - May helps dampen excessive cascade that occur in depression and cognitive disorders
  - May contribute to neuronal membrane stability and longevity

| TARGET OF HEALTH IMPROVEMENT | DOSAGE USED IN HUMAN CLINICAL STUDIES |
| --- | --- |
| Cardiovascular Health | 600- 4000mg per day of combined EPA and DHA. Low doses (600- 900mg per day) deliver highly significant benefit. Larger dosages (2000- 4000mg per day) provide some further benefit. See discussion below. |
| Improved Mood | No less than 1000mg of **EPA** per day. The oil should contain significantly more EPA than DHA. |
| Childhood Attention Mood Concentration | In children ages 5 and up, 500- 1000mg of EPA per day. The oil should contain significantly more EPA than DHA. |
| Joint Health | 2000- 4000mg of combined EPA and DHA. |
| Pregnancy and Breastfeeding | No less than 300mg of DHA per day. The oil should contain more DHA than EPA, unless otherwise recommended by a healthcare practitioner. |
| Bowel Health | 2000- 4000mg of combined EPA and DHA per day. |
| Respiratory Health | 2000- 4000mg of combined EPA and DHA per day. |

# Omega-3 FA and Mental Illness

- Mounting evidence 'links' Omega-3 deficiency to
  - Depression
  - Aggression and violence
  - Bipolar disorder
  - Borderline PD
  - ADHD
  - Cognitive decline

# Borderline PD and Omega-3 FAs

- Karaszewska D et al. **Marine Omega-3 Fatty Acid Supplementation for Borderline Personality Disorder: A Meta-Analysis.** *Journal of Clinical Psychiatry*. 2021:81(3):20r13613.
  - Meta-analysis of 5 RCTs comparing omega-3 fatty acids to placebo or active comparator
  - Effect size
    - Overall BPD symptom severity: 0.54
    - Affect dysregulation: 0.74
    - Impulsive behavior: 0.45
    - Cognitive-perceptual symptoms (no significant effect)
  - These effect sizes are higher than for antidepressants and antipsychotics

# ADHD and Omega-3 FAs

- Bloch MH et al. **Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis.** *J Am Acad Child Adolesc Psychiatry* 2011; 50(10):991–1000.
  - 10 studies involving 699 children
  - Small but significant effect in improving ADHD symptoms
    - Effect size of 0.31 overall
  - EPA dose within supplements significantly correlated with efficacy
    - Effect size >0.5 for dose ~600+mg
- Severity of illness often proportionate to deficiency

# Omega-3 FA Recommendations

- Meta-Analysis of effects of EPA 2011
  - "EPA identified as effective treatment component in depression"
  - Recommendation: Supplement of at least 60% EPA
  - Best results 1000mg-2000mg of EPA in excess of DHA
    - Not pure EPA
    - Much better to get from diet but supplements are aplenty
  - Many discrepancies between studies
    - Use of fish oil vs fish
    - EPA/DHA ratio
    - Dose
    - What was placebo?: Olive Oil?
    - Method of detection: food questionnaire
    - Studying depression in non-depressed people
    - Huge individual variation and response to supplementation

# Omega-3 FA and Medical Illness

- Chronic disease risk reduction
  - Cardioprotective
    - Lowers BP, decreases TG and LDL, increases HDL, decreased risk of arrhythmias and thrombosis, improve endothelial function
  - Colorectal Cancer
- Neuroprotective in Alzheimer's and Parkinson's neurodegenerative diseases
- Decreased risk for preterm birth / low birth weight

# NAC, Creatine, Aromatherapy

# N-Acetylcysteine (NAC)

- Increases the synthesis of glutathione
  - Helps to reduce oxidative stress in the mitochondrial electron transport chain
  - May help to protect brain cells similar to mood stabilizers
- **The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial.** J Clin Psychiatry. 2014.
  - 2000mg for 12 weeks, followed to 16 weeks
  - No improvement in MADRS
  - LIFE-RIFT scale of functional impairment improved 2.11 on 20 pt scale
- **Effects of adjunctive N-acetylcysteine on depressive symptoms: Modulation by baseline high-sensativity C-reactive protein.** Psychiatry Research. 2018.
  - 1800mg, 12 wks, improvement on several scales for individuals only with CRP >=3
  - HDRS17: 11 -> 5.2; HAM-A: 20.93 -> 7.47; CGI: 4 -> 2.8; Placebo: no change
- **Efficacy of N-acetylcysteine for patients with depression: An updated systematic review and meta-analysis.** General Hospital Psychiatry. 2024
  - 12 studies, 904 patients, 1000-3000mg, 8-24 wks, ES: 0.24, more effect for BD
- 7 RCTs in bipolar disorder showed more benefit with higher CRP

# Creatine

- Used to regenerate ATP in cells
- Produced in the body from non-essential amino acids glycine and arginine and catalyzed by SAMe
- 95% in skeletal muscles; much of the rest is in the brain
- One of the few supplements **proven** to enhance exercise performance
  - Typical dose: 4-5g PRN or daily
- Reports that it causes baldness were refuted in a 2021 systematic review
- A number of studies suggest creatine may also enhance cognitive functioning during sleep deprivation and hypoxia
  - Typical dose in studies: 20mg/day
- Several studies on MH disorders with best evidence in **depression**
  - Typical dose in studies: 3-10mg/day
  - 10mg/day appears much more effective; dosing up to 20mg could be studied
  - Safe and cost effective
  - Effect size in one study of 1.13 (Lyoo et al. 2012)

# Aromatherapy

- Essential oils: extracts from bark, flowers, leaves, stems, roots, etc
- May work through absorption through the skin as well as inhalation
- The Effectiveness of Aromatherapy for Depressive Symptoms: A Systematic Review
  - 2017: 2/5 inhalation trials showed benefit; 5/8 massage trials showed benefit
- Effects of aromatherapy on depression: A meta-analysis of RCTs
  - 2023: 32 trials, ES: 0.56, inhalation and blended oils most effective
- Risk is very low, however:
  - DO NOT consume essential oils
  - Some may have allergic response
- Oils with some evidence of effect
  - Lavender: anxiety, mood, insomnia, blood pressure
    - Lavender + Damascus rose: anxiety, mood
    - Lavender + Ylang-ylang: anxiety
  - Sweet orange: anxiety, mood
  - Yuzu: anxiety, mood
  - Bergamot: anxiety
  - Chamomile: anxiety, mood
  - Rosemary: anxiety
  - Sage/Spanish sage: mood

# Complementary Wrap-Up

# Ineffective Therapies

- The following is a short list of therapies with no evidence of benefit over placebo
- Keep in mind that placebo and belief can be extremely powerful
  - Up to 80% of antidepressant effect is placebo
  - If something is low risk and a patient benefits, then may suit some patients
    - If patient avoids evidence-based treatment that may provide substantial benefit in favor of these treatments, then this could harm the patient
- My list:
  - Homeopathy: drinking water
  - Reiki: waving hands over the patient
  - Reflexology: basically a foot massage
  - Crystal healing: putting crystals near patient
  - Colon cleanses (can be harmful): flushing out colon and often putting other things in
    - Coffee enema: can be harmful
  - Magnetic therapy: magnets near patient
  - Detox (can be harmful):
    - Fasting, ingesting teas/herbs, stopping evidence-based treatments, dietary changes
  - Naturopathy: "using body's natural healing" and avoiding proven treatments
    - Lifestyle, herbs, vitamins, homeopathy, acupuncture, colon cleanse, ozone, reflexology, massage, rolfing, hydrotherapy, Chinese medicine, iridology; reject evidence-based med

# Framework for Recommending Supplements in Psychiatry

- Healthy diet as a foundation
  - Supplements may have limited benefit if diet is poor
  - Dietary improvements should be the basis for a good nutritional program
- Evidence base that includes sound rationale and mechanism
- Positive risk-to-benefit
- Defined dose and time frame to assess
- Targeted population to treat
  - Patients with adverse or inadequate responses to medication
  - Patients who would like to try nutritional and/or natural therapies as part of health care approach
  - Vulnerable populations who may have inadequate dietary nutrient intake

# Practical considerations

- Validated common testing
  - B12
  - RBC folate
    - Better evaluating long-term folate status
  - Homocysteine
    - Can help differentiate B12 from folate deficiency
  - RBC magnesium
    - Tests magnesium level in cells
  - Zinc

# Practical considerations: Supplementation

- Recommend a foundational program with good supportive data
- Supplements with reasonably good evidence
  - Comprehensive Multivitamin and mineral complex
    - B vitamins, Iron
  - L-Methylfolate
  - SAMe
  - Omega-3
  - Magnesium, zinc mineral complex
  - Creatine
- Alternatives to conventional antidepressants
  - SJW
  - Rhodiola
  - Kanna

# Somatic Therapies

# Somatic Therapies

- ECT
- Bright light therapy
- Vagal nerve stimulator
- TMS (rTMS, SAINT, NeuroStar)
- Cranial electrotherapy stimulator

# Electroconvulsive Therapy (ECT)

- Mechanism of action not well understood
  - Discovered surreptitiously after evaluating epilepsy patients with improved mood after seizures
  - Preceded the discovery of psychiatric medications
  - Likely increases levels of BDNF and ultimately increases activity of mTOR
    - mTOR increases protein synthesis at synapses
    - This in turn increases synaptogenesis, especially in the prefrontal cortex
  - Turns on rapid response genes that activate structural genes in the limbic system neurons and starts replacing receptors and transport systems
- One of the most common medical procedures
  - More than cardiac bypass
  - 50-100K patients/year
- High response rate, well tolerated, rapid onset
  - Effect size: 2.1
  - Psychotic depression
    - 95% remission (83% for non-psychotic depression); can be a first line option

# ECT: Indications

- Treatment-resistant depression
- Severe vegetative symptoms
- Catatonia
- Psychotic depression
- Intense SI
- Pregnancy
- Intractable mania
- Schizophrenia (less effective than mood disorders)

# ECT: Procedure

- Takes around 3 hours
- Caution with seizure inducing/inhibiting meds
- Seizure induced after administering premedications
  - Anticholinergic drugs
    - Minimize oral and respiratory secretions
    - Block bradycardia and asystoles
    - Atropine, glycopyrrolate
  - General anesthetics (lasts around 10 minutes)
    - Methohexital: often preferred due to short duration and decreased sympathetic tone
    - Etomidate: often preferred due to prolonged seizures but does not blunt sympathetic tone
    - Propofol: less preferred due to raising seizure threshold the most
    - Ketamine: May have best remission rate; has more AEs: fear, hallucinations, and delirium
  - Muscle relaxant
    - Succinylcholine
- Electrical stimulus applied to the head for a few seconds
- Seizure lasts 30 seconds to 2 minutes
- Procedure changed very little since 1980s

# ECT: Medical Evaluation

- Ensure patient has stable vital signs
  - Beta blocker may be needed, but not typically prophylactically
  - Avoid ECT within 3 months of MI
  - Delay ECT with unstable angina, decompensated heart failure, and severe symptomatic valvular disease
  - Anticoagulants are generally safe
    - Those on warfarin should have an INR < 3.5
  - Other cardiac conditions are mostly well tolerated including pacemakers
  - Obtain a cardiology consult if concerned
- Patients with brain tumors, intracranial metallic objects, cerebral aneurysms, and structural abnormalities are generally safe for ECT in the absence of increased intracranial pressure
  - Obtain neurology consult if concerned
- Patients with certain neuromuscular diseases should avoid succinylcholine

# ECT: Medical Evaluation

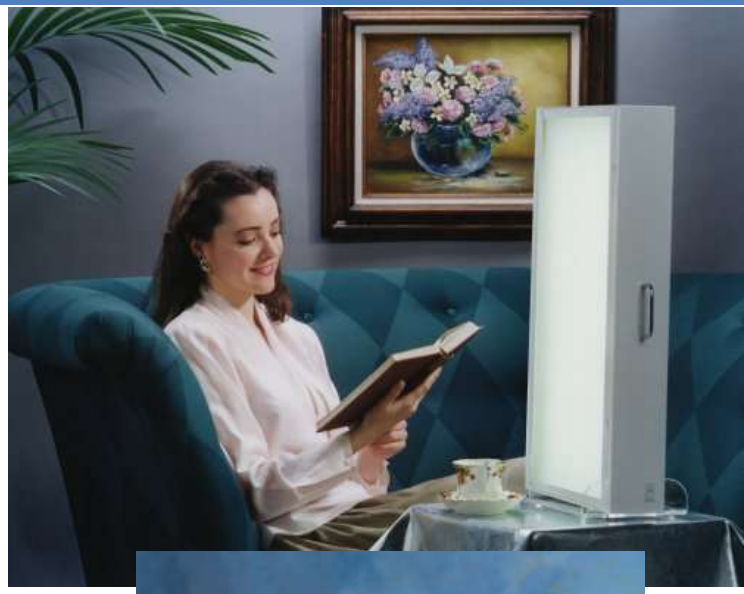
- Patients taking benzodiazepines
  - If possible hold the dose the night before and morning of
  - Switch to a short-acting medication if unable to hold dose
  - If unable to alter, attempt to induce seizure
    - If unsuccessful, consider fumazanil prior to procedure
    - Follow procedure with midazolam if needed
- Patients taking anticonvulsant medications
  - Hold if possible
  - If taking for epilepsy, attempt to induce seizure without altering dose
- Insulin and hypoglycemics should be held the morning of procedure
- Consider holding lithium the night before if at higher level due to concern for increased cognitive adverse effects
- Theophylline should be avoided due to association with prolonged seizure
- Hold diuretics

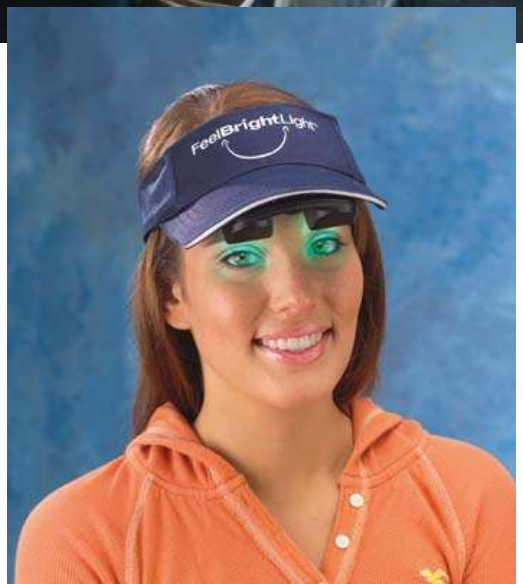
# Electroconvulsive Therapy

- Adverse Effects
  - Very low risk
  - Headaches, muscle aches, nausea
  - Confusion, usually retrograde amnesia, long term memory loss very rare
    - Actually increases hippocampal volume
- Treatment cycle
  - 3x/week bilaterally has rapid response
  - Right unilateral ECT has less adverse cognitive effects
  - Sustained response and remission (more than ketamine and TMS)
  - Usually 9-15 tx for depression
- Preventing depression after ECT
  - Nortriptyline + $Li^+$ is recommended
  - Maintenance ECT

# Bright Light Therapy

- May be helpful for
  - Seasonal affective disorder
  - Insomnia
  - Circadian shifting
- 10,000 lux for 30min in the morning (light box)
  - Sunglasses filter light
    - Glasses do not
  - Go outside and look at the sky (NOT sun!)
    - Bright day: 100,000 lux
    - Cloudy day: 25,000 lux
    - Very overcast: 10,000 lux
    - Industrial lighting: 5,000 lux
    - Office lighting: 500 lux
    - Home lighting: 50 lux
    - Windows reduce sunlight by 50 fold
- Blue wavelength of light
  - May be effective for suppressing melatonin





# Bright Light Therapy

- Menegaz de Almeida A. Bright Light Therapy for Non-seasonal Depressive Disorders: A Systematic Review and Meta-Analysis. JAMA Psychiatry. 2025.
  - 11 trials, 858 patients, compared BLT to dim red light or antidepressant
  - 40.7% vs 23.5% remission, OR 2.42, P<0.001
  - 60.4% vs 38.6% response, OR 2.34, P<0.001
  - Better for <4 wks and >4 wks
  - Fewer adverse effects
  - Faster initial response
- Proper use
  - In the morning
  - 16-24 inches (40-60cm) from your face
  - Eyes open, not looking directly at the light
  - Can read or other activity during therapy time

# Vagal Nerve Stimulation

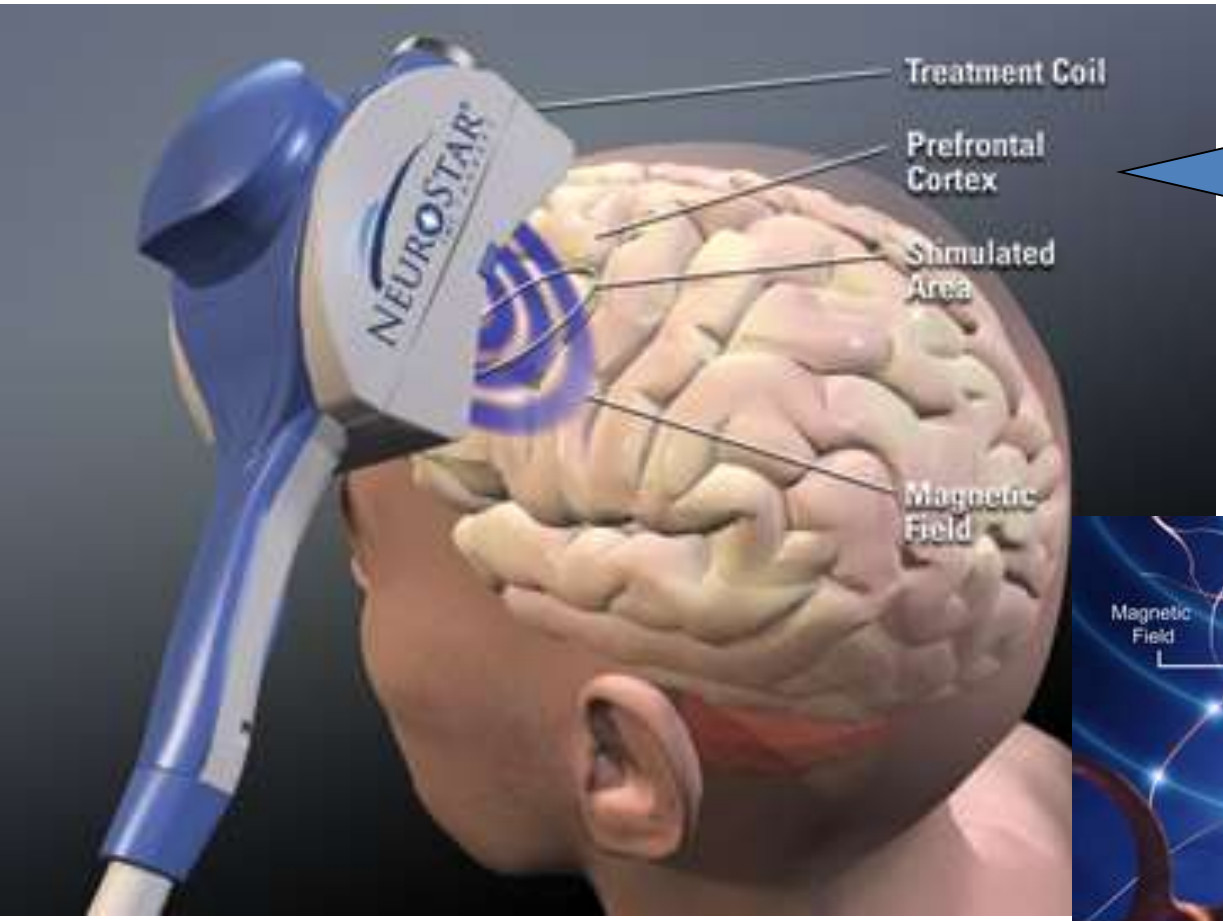

- Implantable Vagal Nerve Stimulation (VNS) Therapy System approved to treat TRD
- Indicated for adjunctive long-term treatment of chronic or recurrent depression in adults with MDD and inadequate response to four or more adequate antidepressant treatments
- Not proven to be useful in acute phase of depression
  - May take up to 9-12 months
- **VNS in treatment-resistant depression: A one-year randomized, sham-controlled trial.** 2024.
  - No difference in remission or MADRS
  - Significant improvement in partial remission and CGI-I, QIDS-SR, and QIDS-C
- 2024 Phase 1 trial demonstrated 100% remission of PTSD for 9 patients up to 6 months
- Increasing interest for several disorders, particularly those tied to inflammation

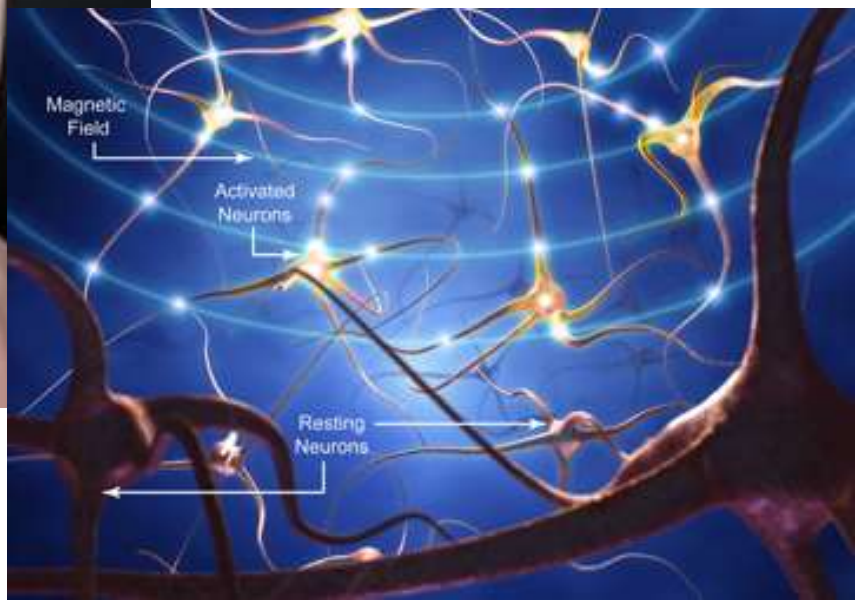
# Vagal Nerve Stimulation

- Therapy is delivered by pulse generator (like a pacemaker) and thin, flexible wires that send mild pulses to the vagus nerve in the left side of the neck
- Delivers pulses to areas of the brain involved in regulation of mood
- Targets specific areas of the brain that affect the production or activity of NT
- Procedure: 1 hr under general anesthesia on outpatient basis
- **BBW:** Device is permanent
- Side effects
  - Temporary hoarseness
  - Cough
  - Feeling of SOB on exertion
- Cost of $25K
  - **Estimating the potential savings with vagus nerve stimulation for treatment-resistant depression: a payer perspective.** 2008
    - 2.3-5.7 years of device life break even


3 months post procedure

# Repetitive Transcranial Magnetic Stimulation (rTMS)



# rTMS

- Administers repetitive subconvulsive magnetic stimulation to the dorsolateral prefrontal cortex
  - Induces small electrical currents affecting activity of nerve cells
- 36 sessions over 6-9 weeks; cost $6-15K
- Better cognitive side effect profile than ECT but may work less well in certain types of depression
- Effect size of 1.3 is one of the highest for depression treatment
- Negative predictors of response
  - Elderly
  - Medication resistance
  - Longer duration of illness
  - MDD with psychotic/melancholic features

# rTMS

- Adverse effects
  - Tinnitis
  - Headache (58% but similar to sham results)
  - Activation site pain
    - Most adjust within 1-2 weeks
    - Can use OTC analgesics
    - Lower the motor threshold
    - Use of theta burst may be better tolerated
  - Muscle twitches
- Rare adverse effects
  - Mania and seizures
    - Incidence of seizures 1 in 30,000
      - 25 cases between 1980-2015
      - Most involved sleep deprivation, polypharmacy, incorrect coil placement, or excessive EtOH use
      - Avoid with hx of seizures
    - Lower with lower motor threshold rTMS

# TMS SAINT™

- SAINT
  - Stanford Accelerated Intelligent Neuromodulation Therapy
- FDA cleared in 2022
- Accelerated TMS Protocol
  - 10 sessions per day
  - 10 minute treatments with 50 minute breaks
- Uses “Theta Burst”
  - Requires specialized equipment
- Relief of depression in 1-5 days (average 3 days)
- 90% achieved remission within 5 days in study
- Around $20K for a week of treatment
- Unclear whether it is significantly better than rTMS

# NeuroStar® TMS

- FDA cleared
  - MDD
  - OCD
  - Anxious depression
- Cleared for use from age 15
  - Only TMS approved for adolescents

# Cranial Electrotherapy Stimulator

- May help with depression, anxiety, insomnia
- Cervella®
  - Delivers micro pulses of electrical current across the brain via conductive electrodes
  - Controlled via an app installed on patient's smart device
  - Treatment is 30 minutes
  - Can listen to music while using
- Alpha-Stim®
  - Works similarly to Cervella®
  - Works through electrodes attached to the ears


# Cranial Electrotherapy Stimulator

- Lee M et al. **Effects of cranial electrotherapy stimulation on improving depressive symptoms in people with stress: A randomized, double-blind controlled study.** Journal of Affective Disorders. 2023.
  - 62 participants (58 female)
  - BDI 31.3 to 10.8
  - Greater improvement than sham; P=0.020