Antidepressants

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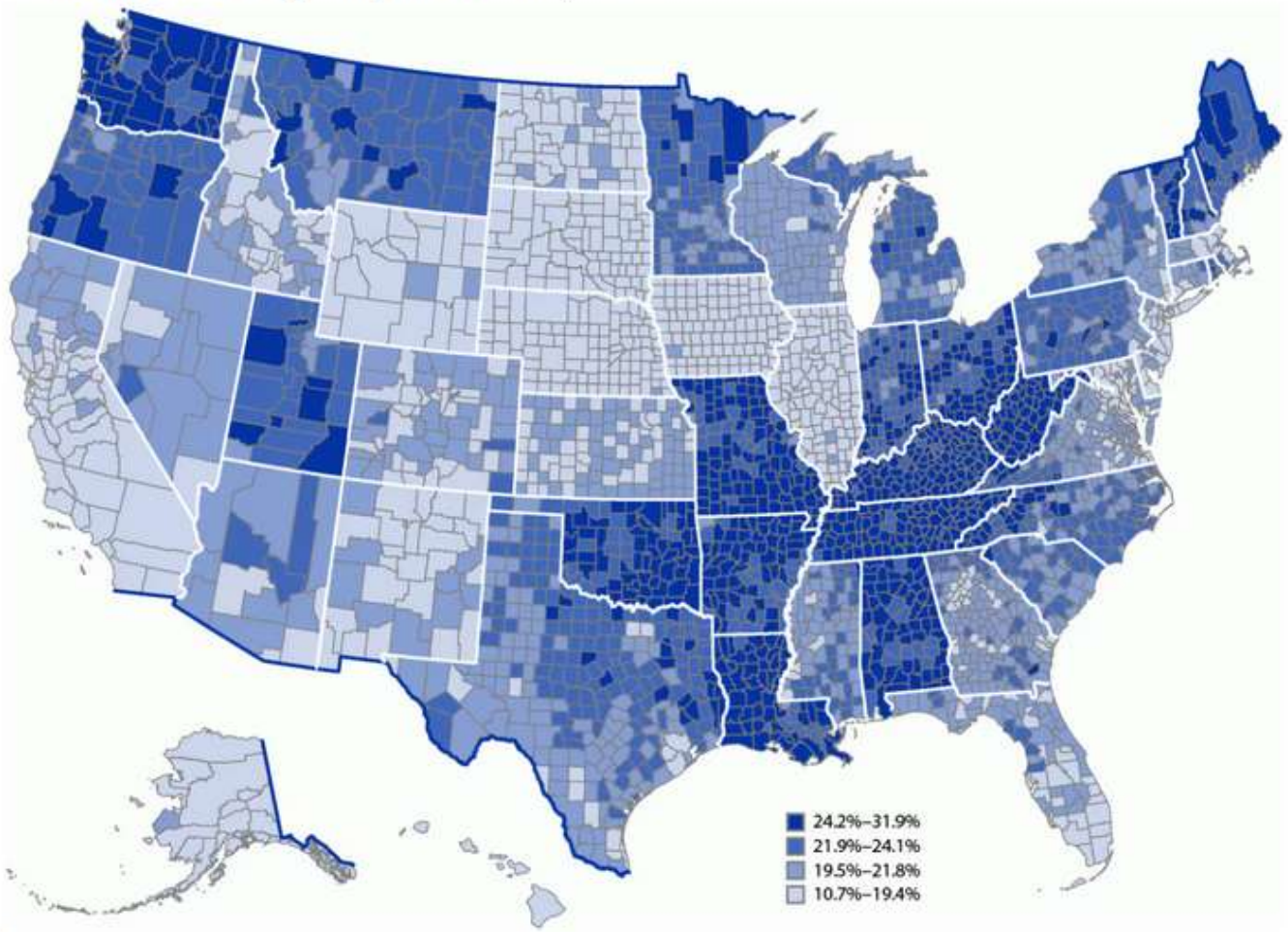
Overview

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

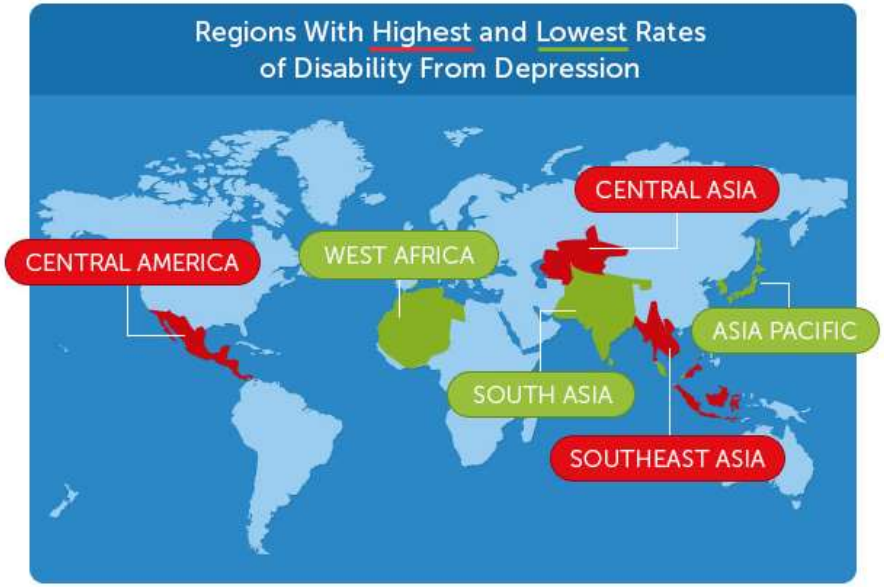
Epidemiology

- 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.



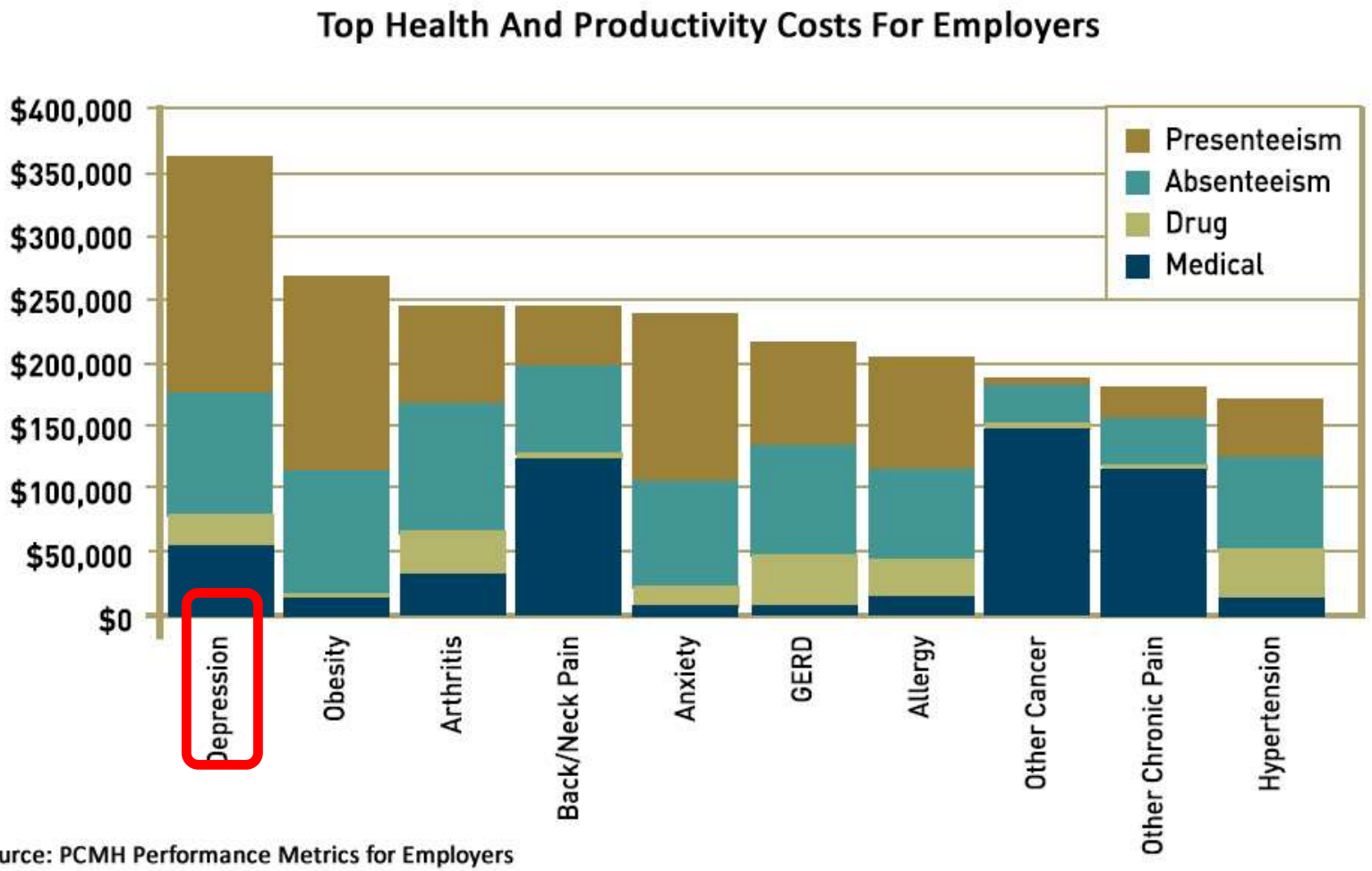
More Facts About Depression and Disability

- 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

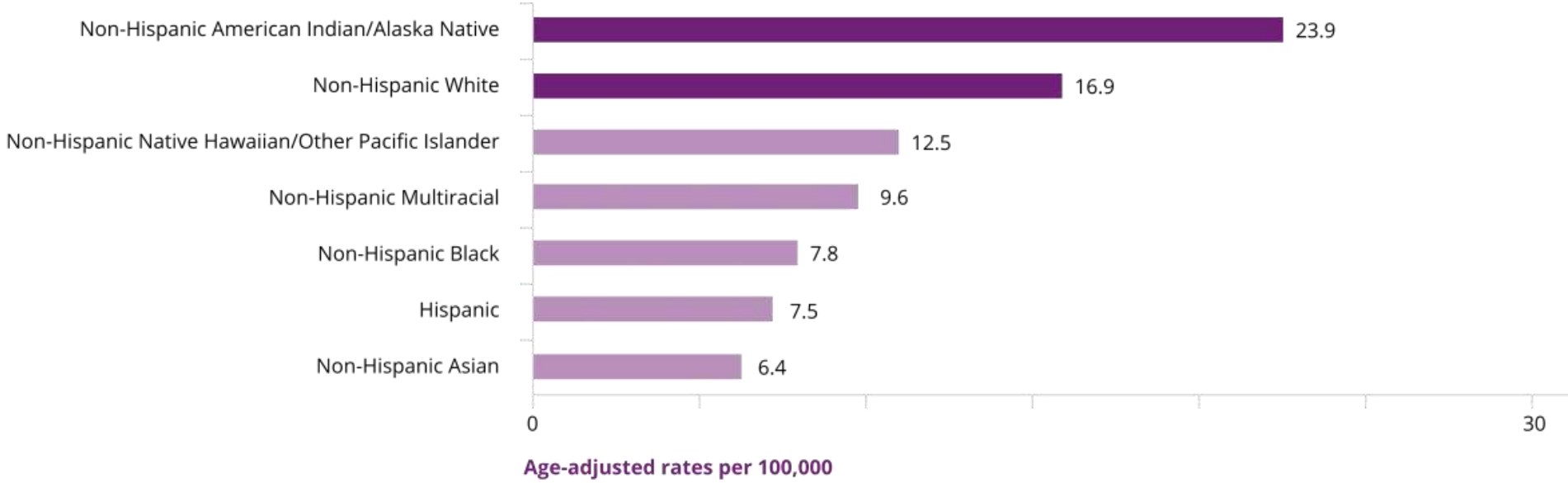
Suicide

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

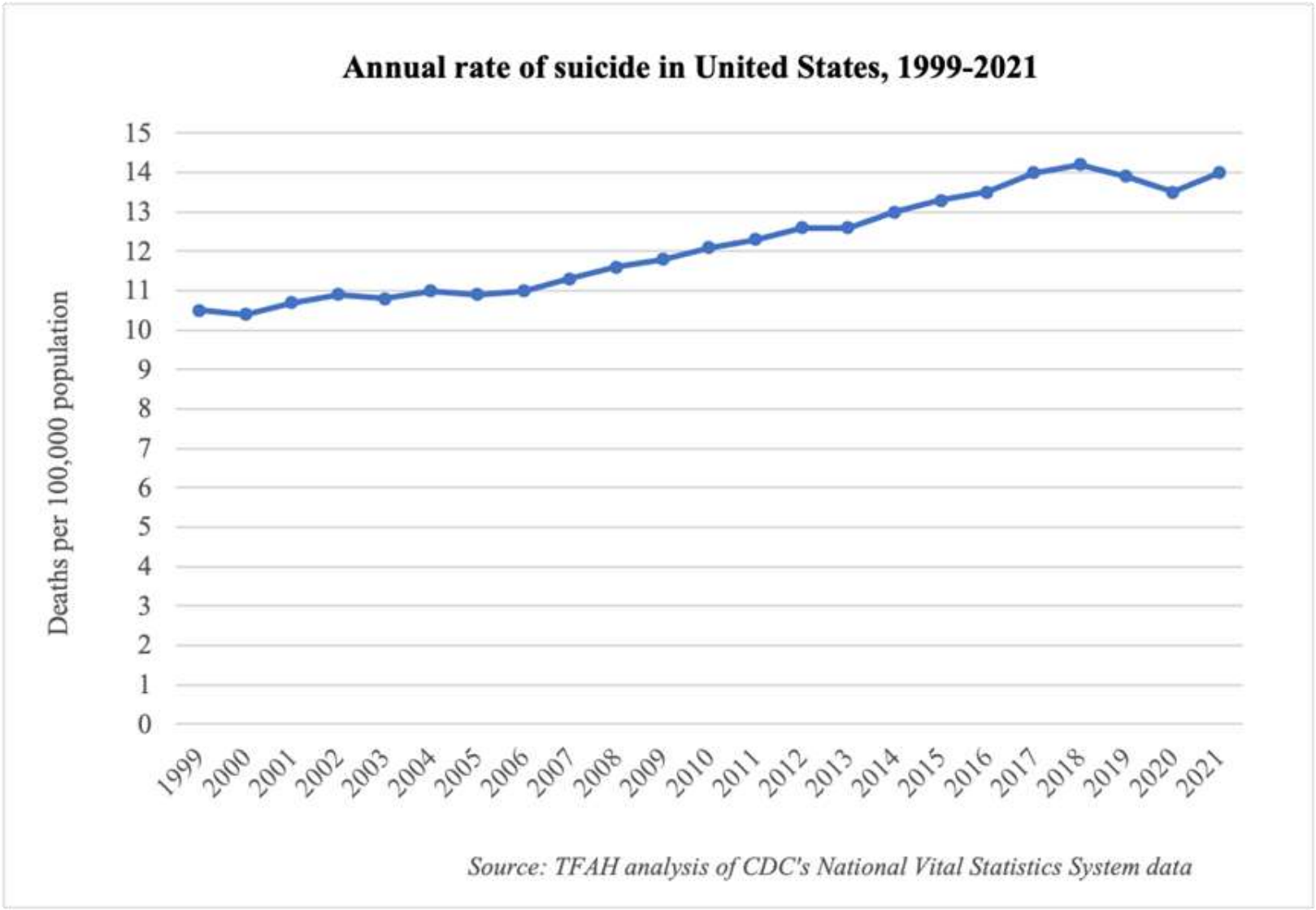
Suicide Method	Males (%)	Females (%)
Firearms	57	32
Suffocation	23	20
Poisoning	13	38

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

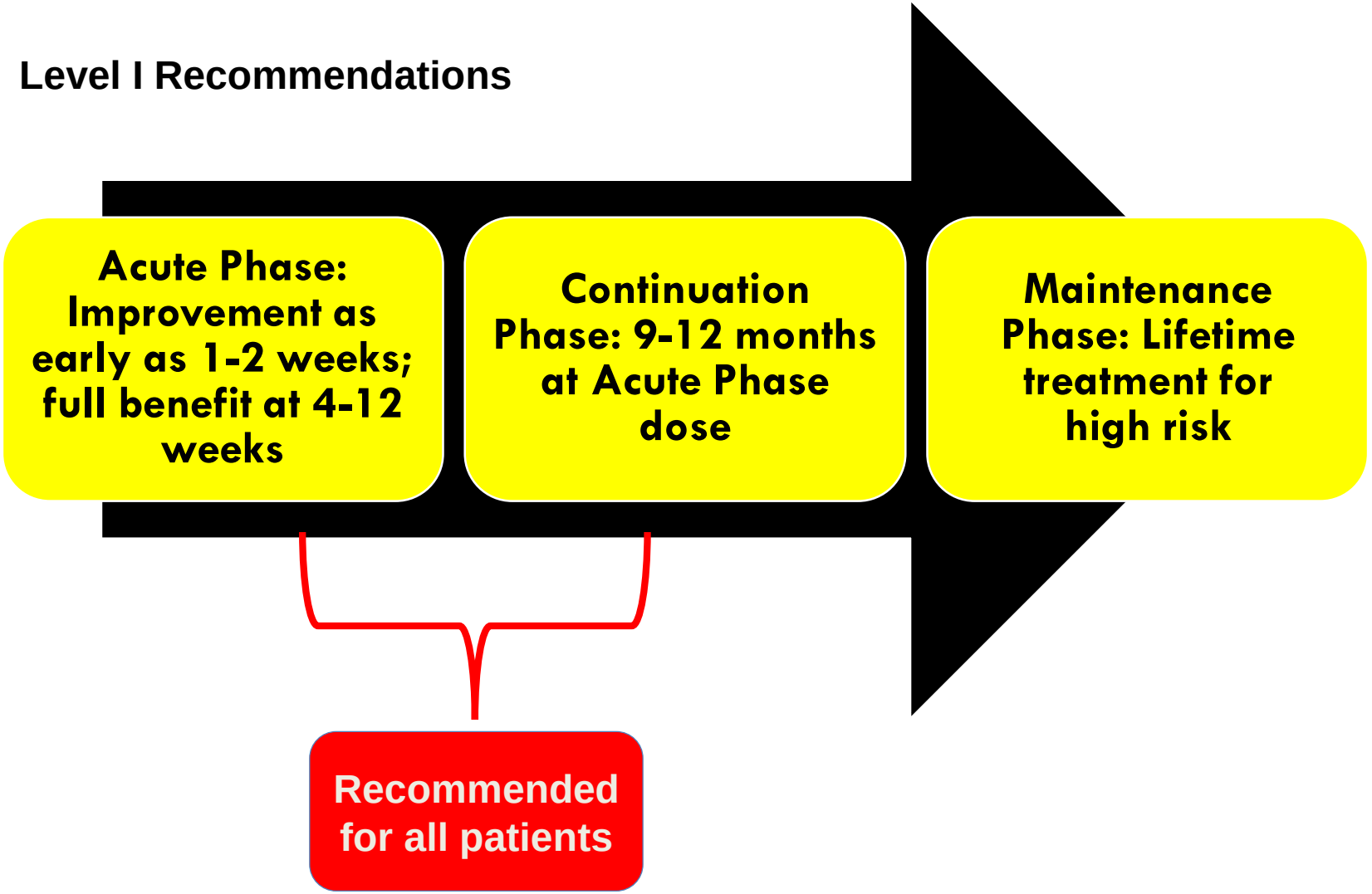
- Rating Scales
  - Patient rated (PHQ-2, PHQ-9), Clinician rated (QIDS)
- Comorbidities and PMH
- Family and personal psychiatric history
- Medication history
- Laboratory findings
  - TSH
  - CBC (Hb, MCV)
    - B12/Folate (more for the elderly, alcoholism, atypical or vegan diets)
    - Iron
  - Chemistry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

Assessment of Suicide Risk

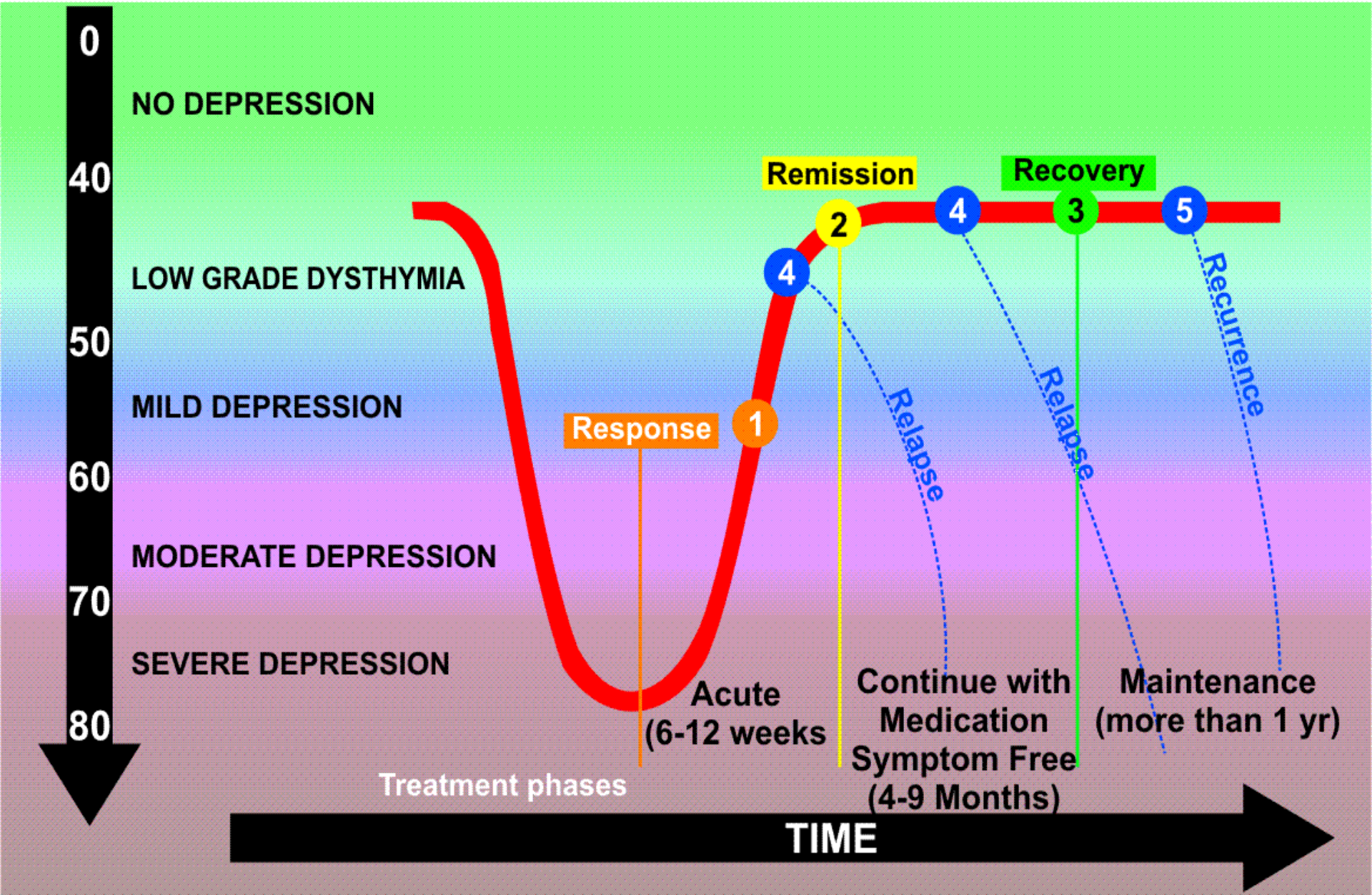
- Presence of suicidal or homicidal ideation, intent, or plans
- History and seriousness of previous attempts
- Access to means for suicide and the lethality of those means
- Presence of severe anxiety, panic attacks, agitation, and/or impulsivity
- Presence of psychotic symptoms, such as command hallucinations 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

Treatment Course

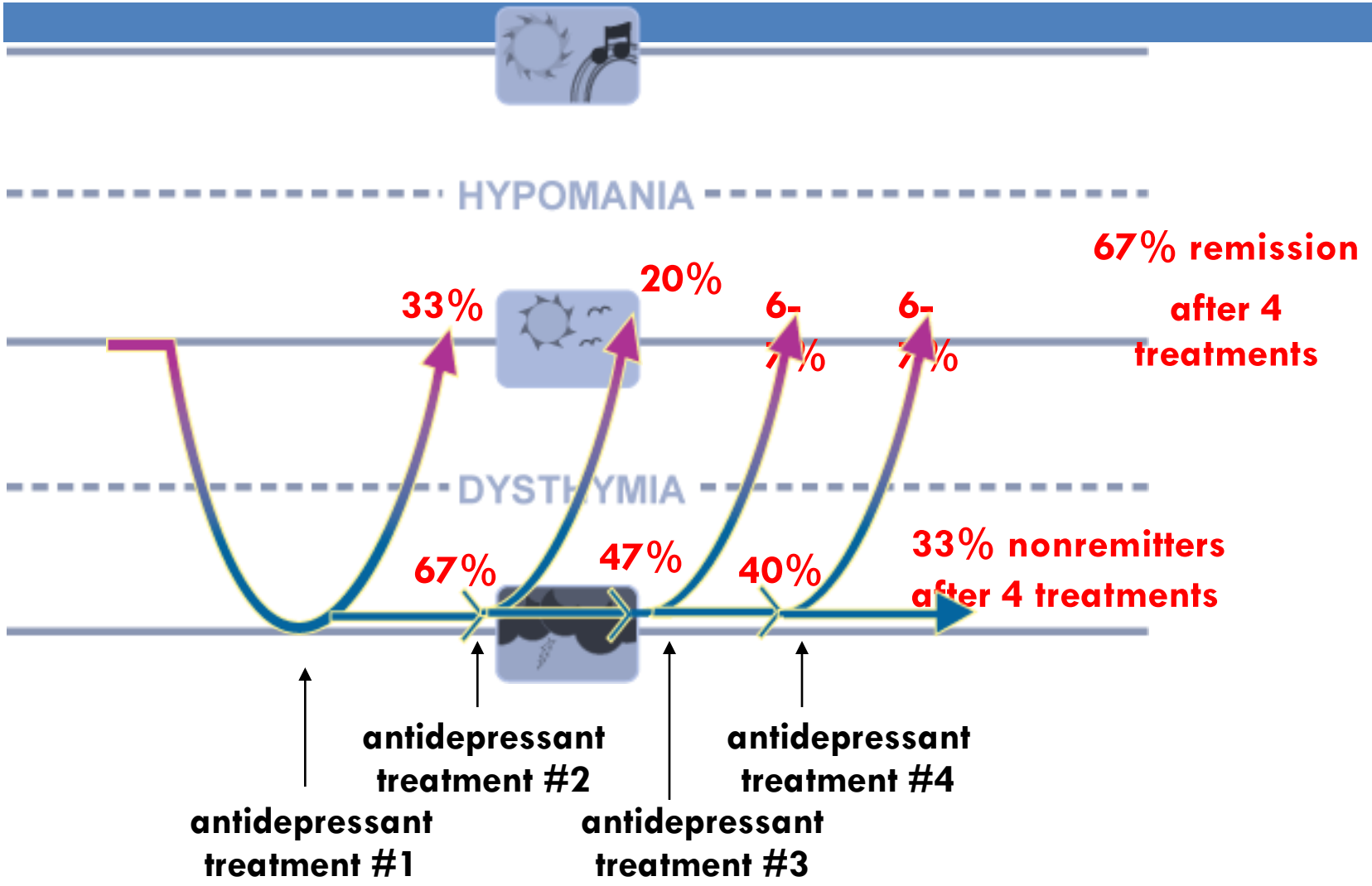
American Psychiatric Association Practice Guidelines: Duration of Treatment of Antidepressant



INDICATION HOW LONG MEDICATION SHOULD BE TAKEN



What Proportion of MDD Remits?



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

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

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
- For MDD
- >=22 years old

Complementary and Somatic Therapies

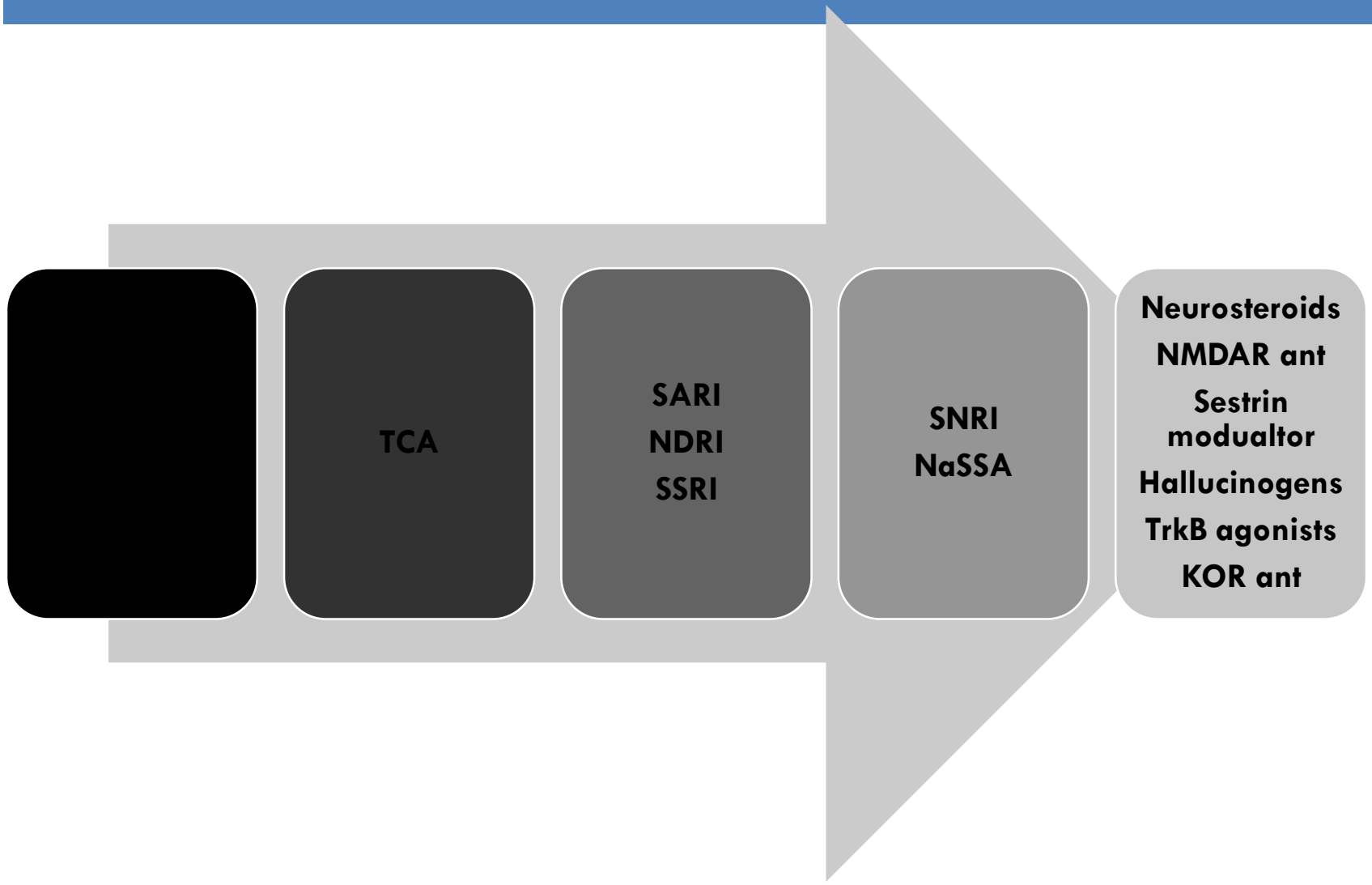
- Complementary Therapies
  - Vitamins and minerals
  - St. Johns Wort
  - L-methylfolate
  - SAMe
- Somatic Therapies
  - Electroconvulsive therapy (ECT)
  - Phototherapy
  - Vagal nerve stimulation
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Cranial Electrotherapy Stimulator

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

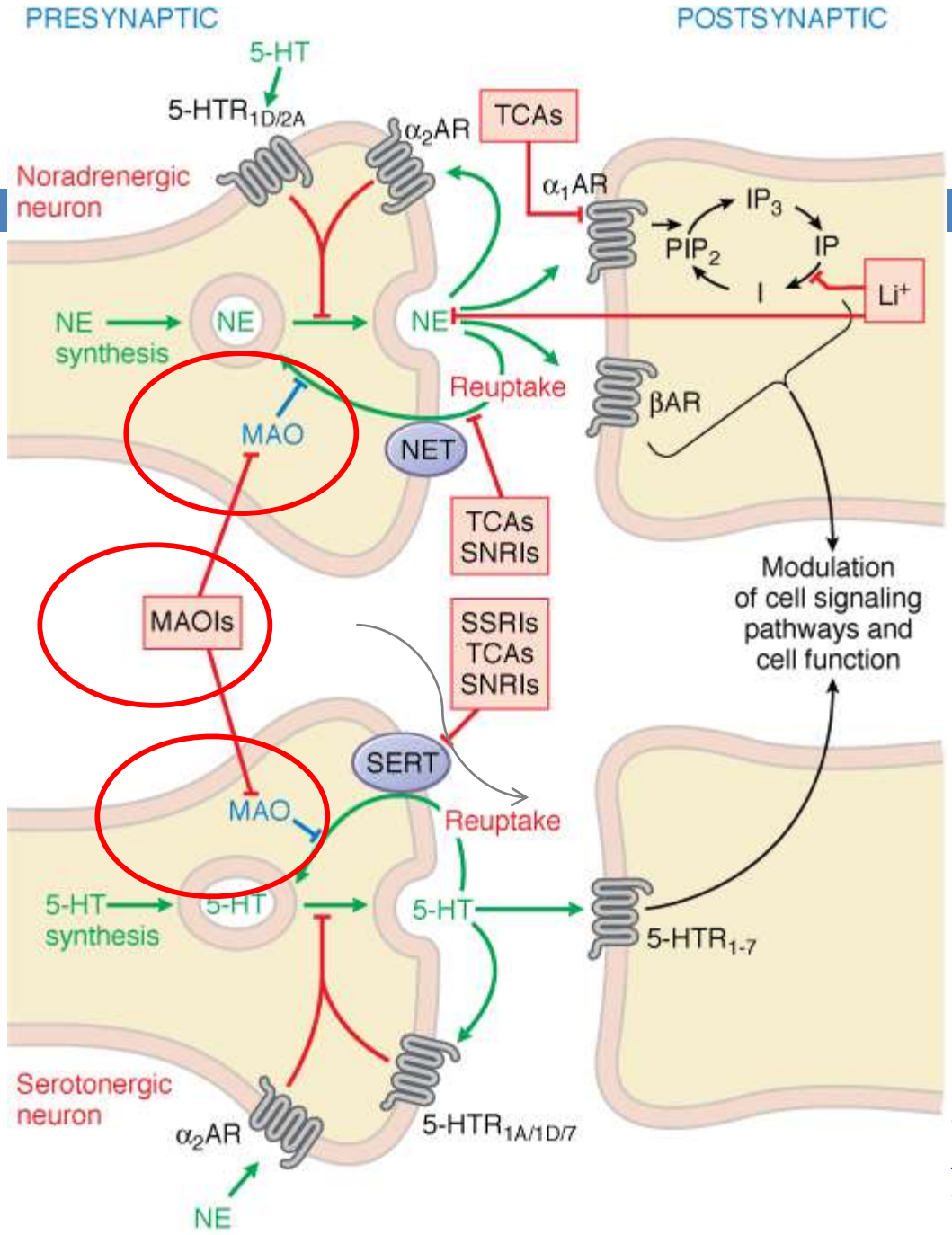


Antidepressant Mechanism of Action

- 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 improvement and ↓ in 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

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

MAOi FDA Indications

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

Mechanism of Action

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

Isocarboxazid (Marplan®) (1959)

- **Less activating** than other MAOIs
- Less studied than other MAOi's so less information on comparable efficacy
- Monitor **LFTs**
- Start with 10 mg test dose on the first day and 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)

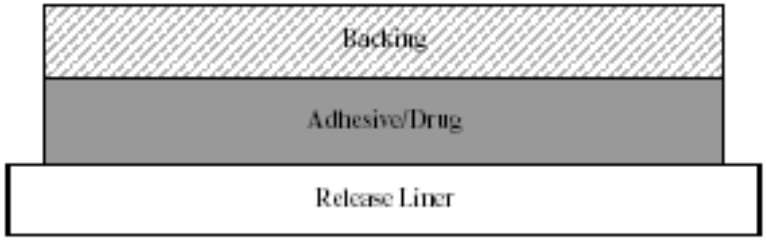
- Most often used MAOi
- Also a GABA transaminase inhibitor
  - Good for panic, anxious distress
  - Twice as effective for social anxiety as SSRIs
  - Sedating
- Can use with amoxapine if started simultaneously
- Most **anticholinergic** and **sedating** of the MAOIs
- Most weight gain, hypotension, and sexual dysfunction
- Can cause B6 deficiency
- Monitor **LFTs**
- 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)

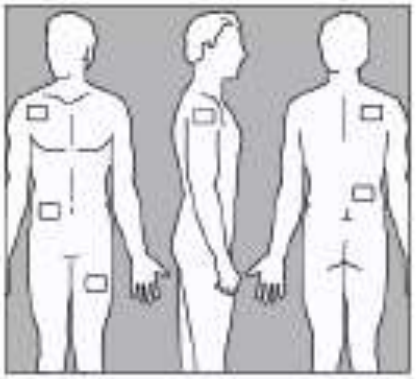
- May have faster onset of action
- **Most activating** MAOI with more insomnia—can tx with Trazodone
  - Has amphetamine properties (dopaminergic) at higher doses
    - UDS will be positive for amphetamines
  - Activating
  - Melancholic/apathetic depression
- Better tolerated than phenelzine and equally effective
- Positive reports re its use in **bipolar depression**
- Start with 10 mg test dose on the first day and 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/20cm^2, 30mg/30cm^2, 40mg/40cm^2
  - Deliver on average of 6, 9, 12mg over 24 hours, respectively



Selegiline (EMSAM®)



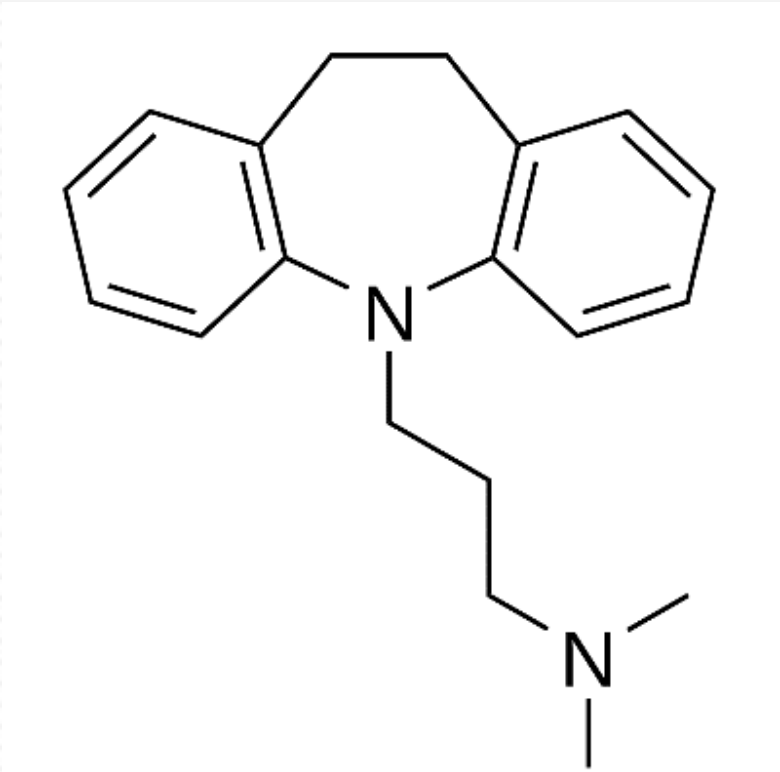
- Application of EMSAM
  - Apply to dry intact skin on upper torso (below neck, above waist), upper thigh or outer surface of upper arm
  - Alternate application site
  - Do not touch sticky side, med can come off
  - External heat sources may result in ↑ drug absorption
    - Saunas, heating pads, prolonged 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 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: 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, 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
  - 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	✓						

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

Receptor Binding Affinity (Ki): TCAs

TCA	SERT	NET	5-HT_{2A}	5-HT_{2C}	α_{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

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-HT2C: weight gain
  - Amitriptyline, nortriptyline, amoxapine
- α-1: orthostasis
  - Tertiary amines are stronger
- H1: weight, sedation
  - Most except desipramine
- mACh
  - 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)

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)

- Xerostomia
  - Dental problems (tooth decay, gum inflammation)
- Constipation
  - Bowel obstruction
  - Paralytic ileus
- Urinary Retention
  - UTI
  - Renal/bladder damage
- Confusion, restlessness
- Ocular
  - Xerophthalmia
  - Relaxation of the ciliary muscles
    - Blurry vision, loss of accomodation
  - Relaxation of the iridocorneal angle
    - Acute angle closure glaucoma

Dangers of TCA Overdose

- Delayed repolarization of sodium fast channels cause for 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
- 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
    - Sedative agents

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)
  - 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

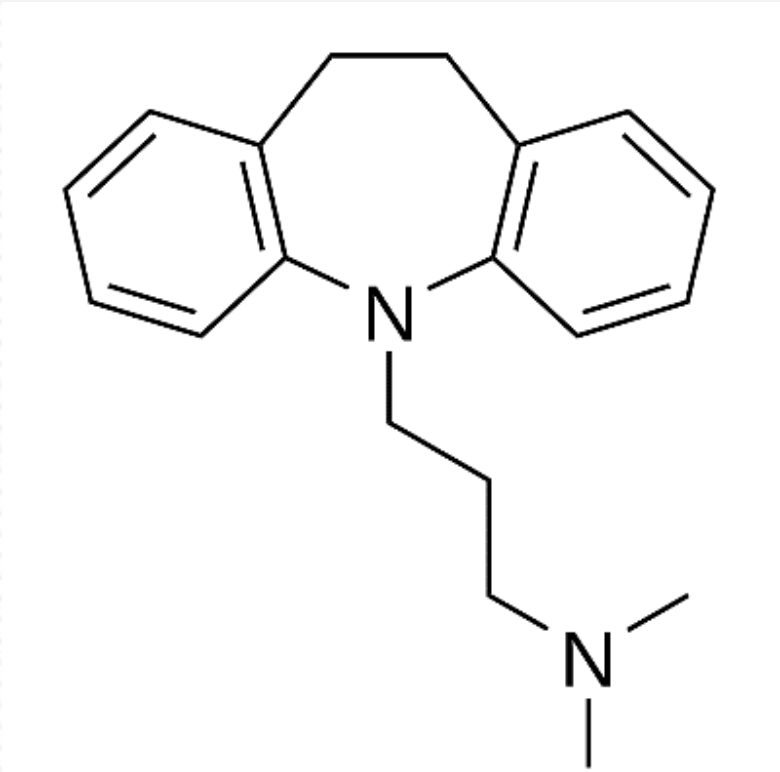
Advantages

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

Disadvantages

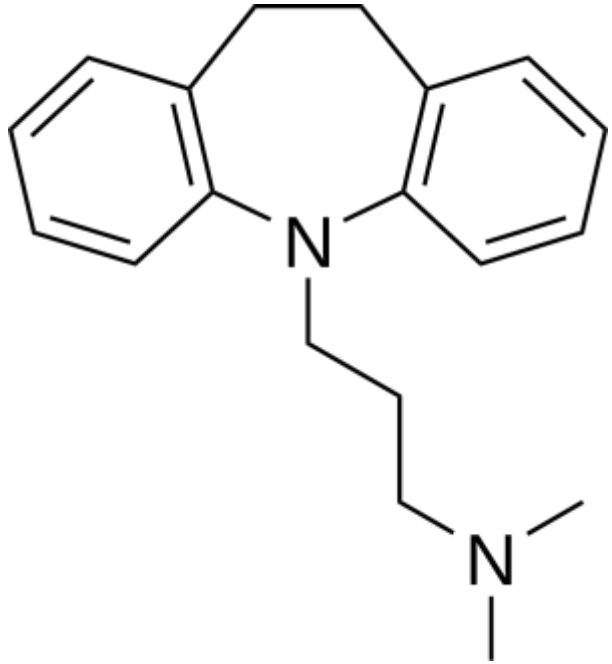
- Very lethal in overdose
- Cardiac toxicity
- Lower seizure threshold
- Many adverse effects
- Caution in BPH, glaucoma, elderly, concomitant medications
- Children and Elderly
- Weight gain
- 7% of population has reduced activity of 2D6 making TCA a poor choice
- Do not mix with 2D6 inhibitor
- Anticholinergic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

Tertiary Amines



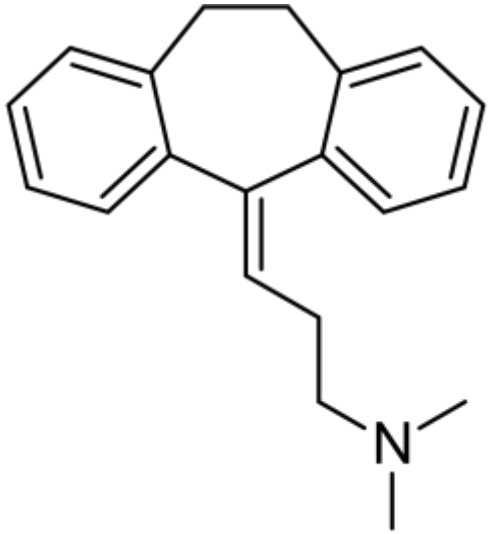
Imipramine (Tofranil) (1959®)

- A serach 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
    - ADHD
- Used off label for
  - Functional dyspepsia
  - IBS-associated pain
  - Chronic neuropathic pain



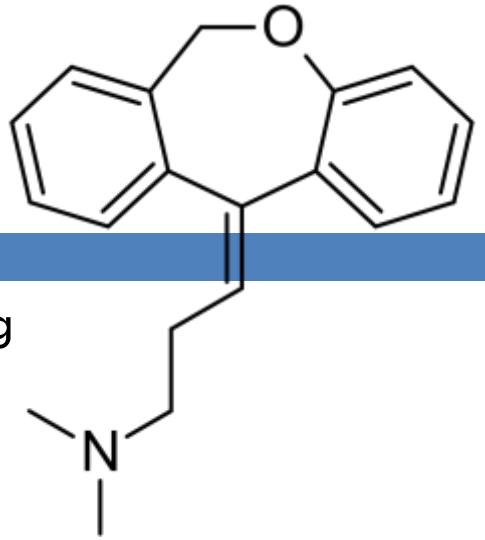
Amitriptyline (Elavil®) (1961)

- Most anticholinergic of the TCAs
- Differs chemically from imitriptyline 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
  - GI discomfort syndromes
  - Headaches
  - Neuropathic pain.
  - 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

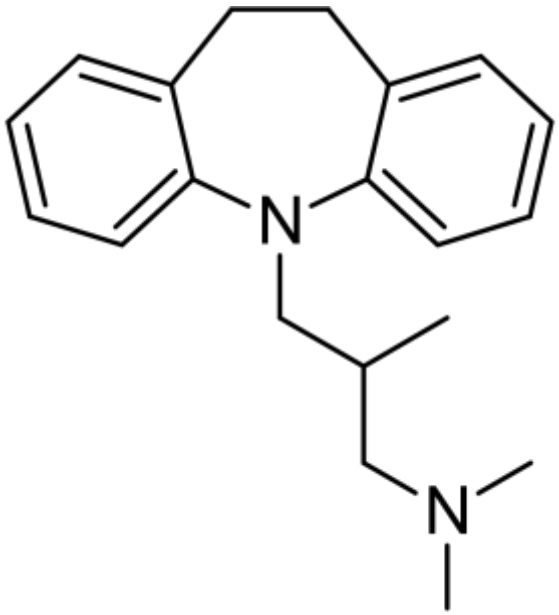
Doxepin (Sinequan®) (1969)



- 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 is may be possible to empty half out if 3-6mg dose is desired
    - Generic doxepin is around $0.30-0.70/pill
    - Generic Silenor® is around $4-17/pill
    - Branded Silenor® is around $22/pill
  - Pruritis (Prudoxin®, Zonalon®)
    - Up to 8 days of atopic dermatitisor lichen simplex chronicus
- Increases Ramelteon by 66%

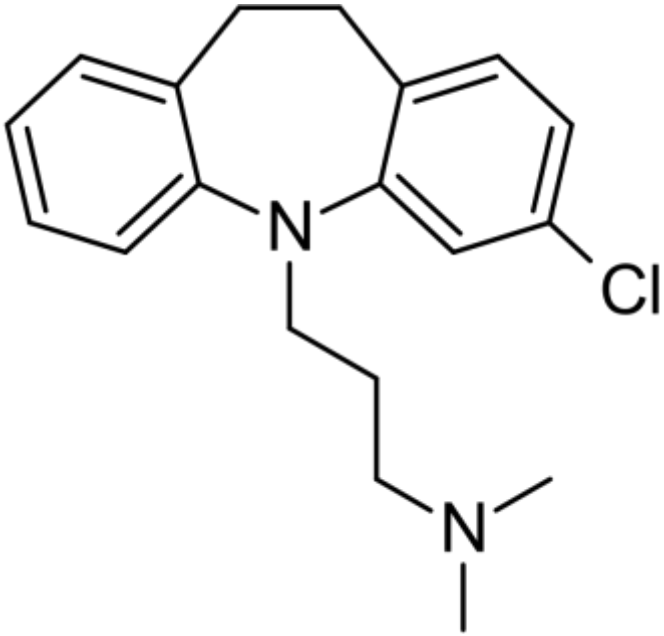
Trimipramine (Surmontil®) (1979)

- Etymology: tri+(i)mipramine
  - Similar to imipramine with a 3rd methyl group (tri-)
- Approved for
  - MDD
- Relatively weak at SERT and NET
- Relatively stronger at receptors that cause adverse effects
- Rarely used

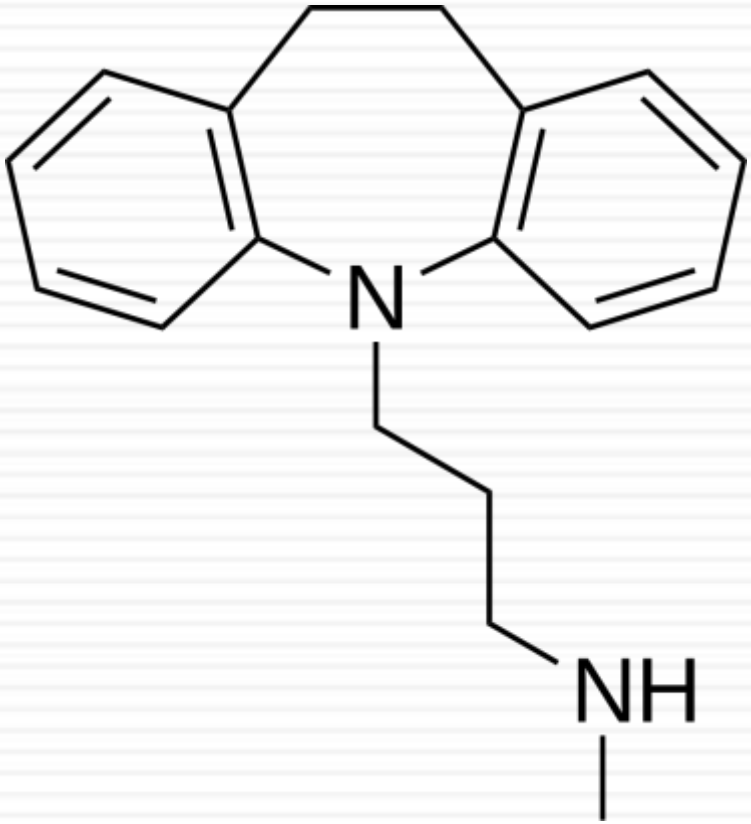


Clomipramine (Anafranil®) (1990)

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

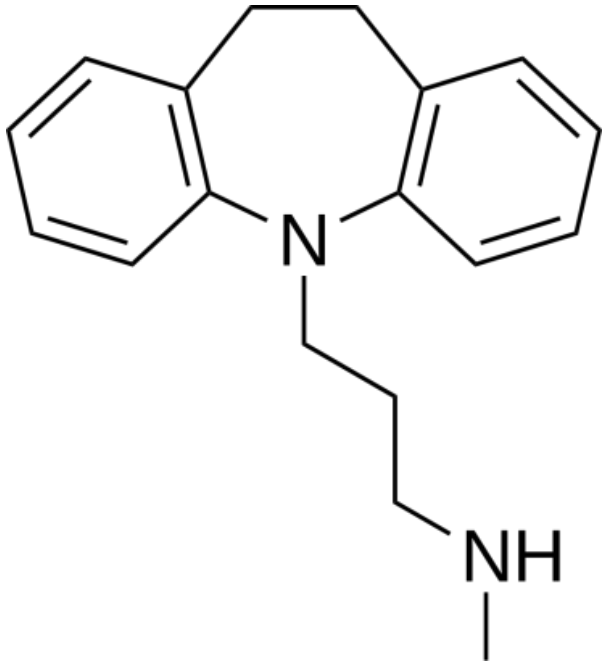


Secondary Amines



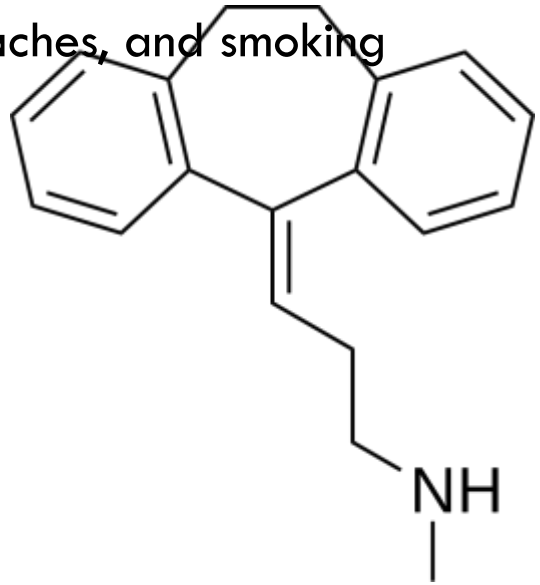
Desipramine (Norpramin®) (1963)

- 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



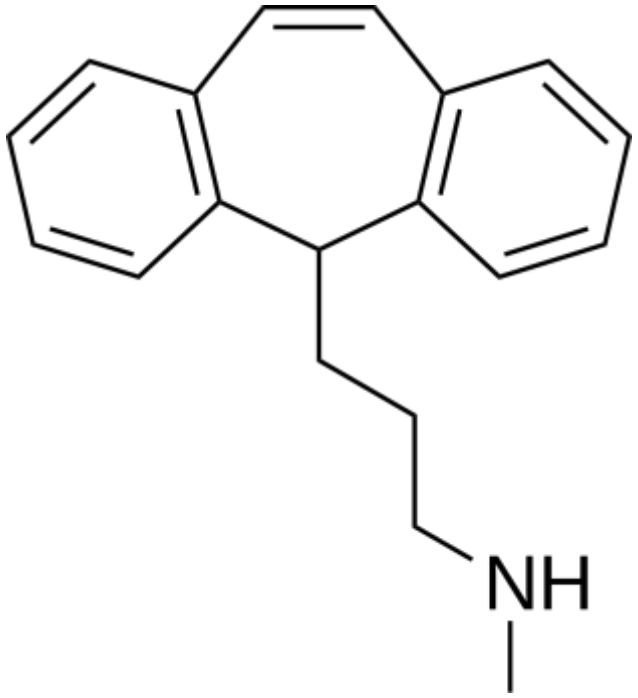
Nortriptyline (Pamelor®) (1964)

- 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

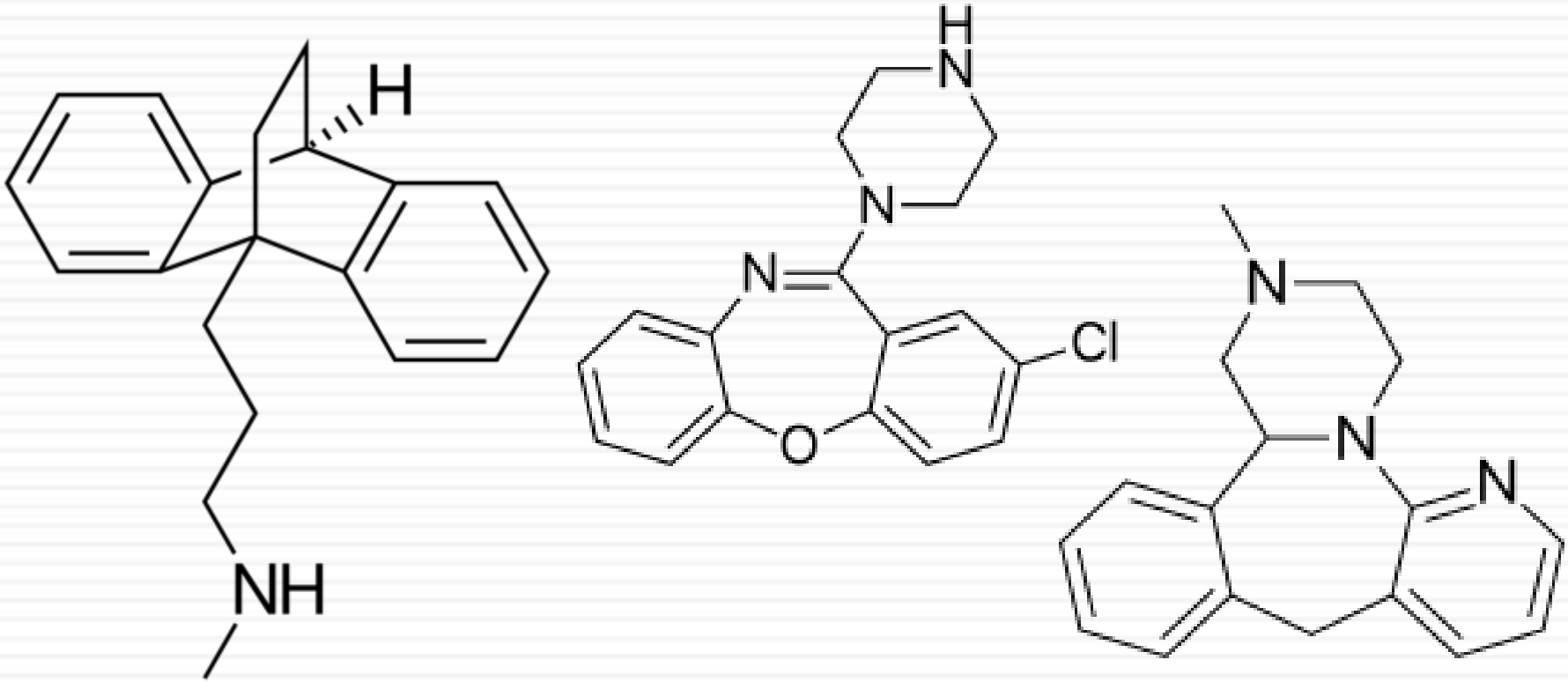


Protriptyline (Vivactil®) (1966)

- 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
  - 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
  - May be considered to be tetracyclic
  - Will review later where it is classed as an atypical antidepressant
    - Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

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)
- Inflammation associated with COVID (Fluvoxemine through σ1 agonism)

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®)
- Vilazodone (Viibryd®)

SSRIs

- Mechanism of action
  - Blocks serotonin reuptake pump: All
  - Anticholinergic activity: paroxetine
  - Blocks dopamine reuptake pump: sertraline

Dosing Considerations

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

Adverse Effects (SSRIs)

- 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

Adverse Effects (SSRIs)

- 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 (SSRIs)

- Bleeding/anemia
  - All serotonergic drugs have potential
  - Due to platelet serotonin depletion
  - Caution in patients with defect in platelet number or function and with chronic NSAID treatment
- Emotional dulling
- 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

Adverse Effects (SSRIs)

- Sweating
  - Antidote 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
- Hyponatremia
- ↓ bone mineral density
  - 4% less BMD in elderly

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 medication
- 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 postmenopause
- Serotonin modulation
  - 5-HT1A partial agonism can mediate serotonergic intensity
    - Buspirone 15-60mg daily: Limited evidence (also a-2 adrenergic antagonism)
    - Vilazodone and vortioxetine
  - 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
    - Yohimbine 5.4mg BID to TID: Limited evidence (also 5-HT1A agonism)
  - 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
- Ginkgo Biloba 60mg daily to 120mg BID: Limited evidence
- Topicals
  - Estrogen creams (females only)
  - Lubricants
  - Zetra or Galaxis (OTC topicals for women)

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
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)

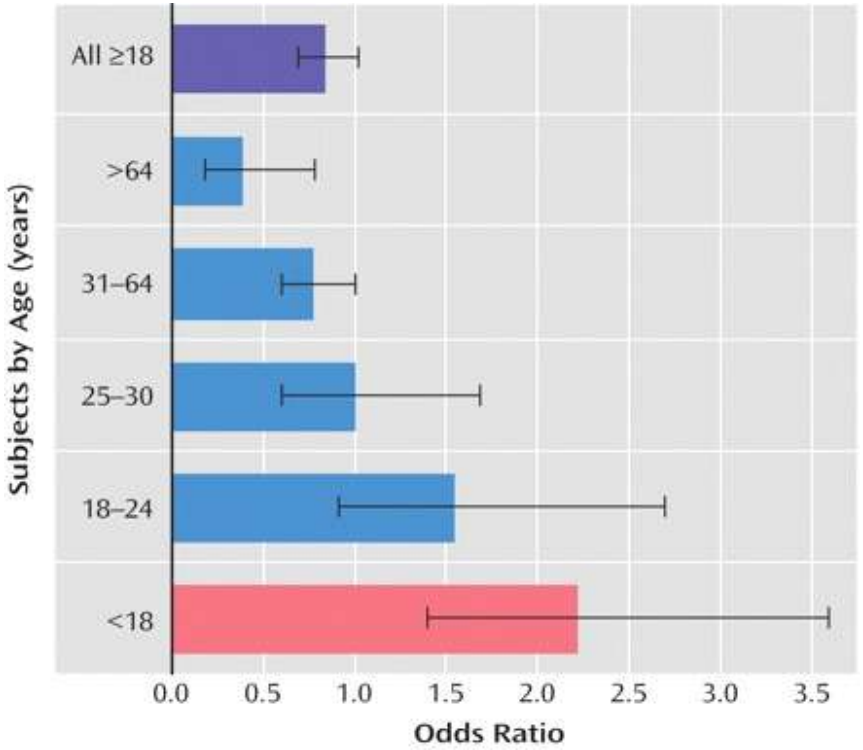
- PDE1 is found in the brain, heart, and vascular smooth muscle
  - Causes vasodilation, flushing, and tachycardia
- PDE6 is in the eye
  - Can alter color perception (rare)
- Adverse Effects
  - Headaches, Nasal Congestion, Facial flushing, Stomach/back pain, NOT PRIAPISM!
- Combination with alpha blocker
  - 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

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

Suicide Risk History 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
- 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.

Suicide Risk with SSRI

- 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
- All newly approved antidepressants or agents for treatment of depression must also carry warning
- Since then more prospective data has emerged that does not support an association
- There is a very small increased risk of SI and attempts but not completed suicides in children and adolescents
- Since warning was issued there has been an increase in the rate of suicides in severely depressed patients associated with decrease in antidepressant prescriptions
- Patients should be informed of and monitored for suicidality
- Warning should not prevent prescribing to depressed patients

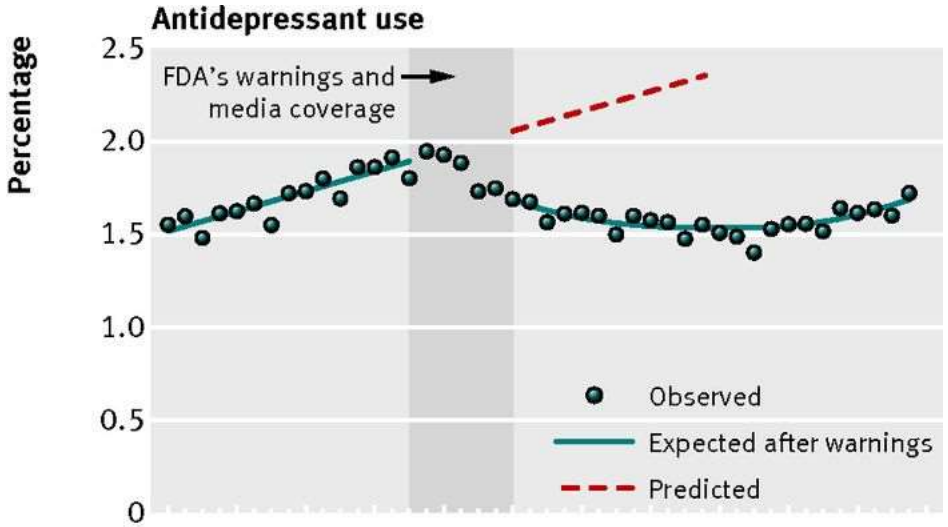
Culpepper L et al. Suicidality as a possible side effect of antidepressant treatment. Prim Care Companion J Clin Psych 2004;6(2):79-88 www.fda.gov/cder/drug/antidepressants/default.htm

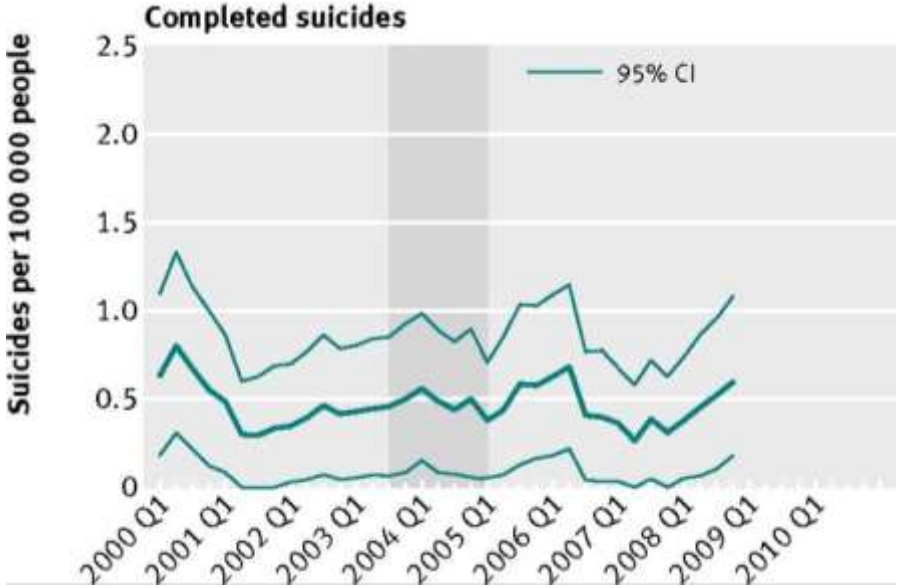
BMJ

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*





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
- 3A4 inhibition
  - **Moderate: fluvoxamine**
  - Mild: fluoxetine
- No inhibition: vilazodone
- 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
  - Iin 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
- Contraindications
  - Use of MAOI within past 2 weeks
  - Allow 5 weeks to elapse when starting an MAOI after fluoxetine
  - Thioridazine, pimozide → QT prolongation, arrhythmias

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

Serotonin syndrome

- Symptoms
  - Anxiety, agitated delirium, disorientation, diaphoresis, tachycardia, HTN, vomiting, diarrhea, tremor, muscle rigidity, **clonus**, **hyperreflexia**
- Hunter Criteria (meets one of the below):
  - 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, TCAs (Amitriptyline, Imipramine, Clomiprapine), fenfluramine, sibutramine, cocaine, St. John's Wort, metoclopramide, ziprasidone, lumateperone
- 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)

Serotonin Withdrawal Syndrome

- Due to abrupt discontinuation of meds, especially meds with short half-lives
  - Meds 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 in overdose
- Less titration
- Easy dosing schedule
- Useful for anxiety disorders, eating disorder, menstrual disorders
- Lower SE incidence vs TCAs, MAOIs
- Patient familiarity

Disadvantages

- Short term SE
- Delayed full response
- Sexual dysfunction
- Drug interactions
- Increased risk of suicide in children/adolescents
- N/V/D
- Emotional dulling

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 as well
- 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, decreased efficacy of tamoxifen)
  - 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
  - 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
  - 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

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

- Disadvantages
  - Anticholinergic effects (ie constipation)
  - 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
  - May cause more weight gain and sexual dysfunction than other SSRIs
  - Shorter half-life requires consistently taking at same time daily
  - Withdrawal worse than other SSRIs (akathisia, GI, dizziness, tingling)
  - Most sedating SSRI; Fatigue, low energy
  - Only SSRI with D rating for pregnancy

Fluvoxamine / Luvox® (1994)

- Advantages
  - CR formulation available and may be better tolerated
  - 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 and 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

Escitalopram / Lexapro® (2002)

- Advantages
  - 10mg may be equivalent to 40mg of citalopram due to R-citalopram interference with S-citalopram binding
  - 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
  - 2nd highest risk for QTc prolongation

Vilazodone / Viibryd® (2012)

- 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
- 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

SNRIs

Serotonin Norepinephrine Reuptake Inhibito (SNRI)

- 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
  - Suicide risk
- 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

SNRI Summary

Advantages

- Useful for multiple pain disorders and indications (esp. duloxetine)
- Added benefits of NRI
  - Energy
  - Concentration
  - 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 / 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 2D6 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 / Cymbalta® (2004) / Drizalma® (2019)

- Advantages
  - No titration required
  - Treats urinary incontinence (approved in many countries)
  - 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)
  - 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
  - Less withdrawal than venlafaxine
  - Longer ½-life than venlafaxine
- Disadvantages
  - Duloxetine has similar advantages over venlafaxine and is 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

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

Levomilnacipran / Fetzima® (2013)

- Advantages
  - Stronger NRI than SRI may lead to improvements in pain, concentration, and motivation
  - Least sexual adverse effects due to least serotonergicity
- 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

Atypical Antidepressants

Atypical Antidepressants

- Serotonin Receptor Antagonists
  - Nefazodone (Serzone®), Trazodone (Desyrel®), Trazodone XR (Oleptro®, discontinued)
  - Mirtazapine (Remeron®)
- Norepinephrine-Dopamine Reuptake Inhibitor
  - Bupropion (Wellbutrin®, Wellbutrin XL®, Aplenzin®, Forfivo®)
- Vortioxetine (Trintellix®, formerly Brintellix®)
- Gepirone (Exxua®)

Serotonin Antagonist and Reuptake Inhibitors (SARI)

- Mechanism of action of phenylpiperazines is complex
  - Block presynaptic reuptake of serotonin (both weakly)
  - Block reuptake of NE and DA (nefazodone weakly)
  - Block postsynaptic 5-HT2A/C receptors (both, trazodone weakly on 2C)
    - Trazodone metabolite mCPP is strong agonist at 2C which has antidepressant effects
  - Block postsynaptic alpha 1 receptor (both)
  - Block postsynaptic H1 receptor (mostly nefazodone)
- Trazodone typically used as sedative-hypnotic, not for depression
  - 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
  - Last line for depression due to risk of hepatotoxicity **(BBW)**
  - Serzone® removed from market by manufacturer

Adverse Effects

- CNS: Sedation (traz > nefaz), dizziness, confusion
- CV: Orthostasis (traz > nefaz)
- Hepatotoxicity: nefaz > traz
  - **BBW** with nefazodone
  - In US, about one case of liver failure reported for every 250,000 to 300,000 patients using the drug for one year
  - 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

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

SARI Summary

Advantages

- Safe in overdose
- Sedation
- Minimal sexual dysfunction
- Inexpensive
- Good in SSRI non-responders

Disadvantages

- Daytime sedation
- Dose titration required
- Priapism

Trazodone (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 or weight gain
  - Insomnia, non-addictive
  - May have added antidepressant effect when used for insomnia as adjunct to other antidepressant
- Disadvantages
  - 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 (1994)

- Advantages
  - May help in SSRI non-responders with less sedation than trazodone
- Disadvantages
  - Hepatotoxicity, though risk is low
  - Potent 3A4 inhibitor
  - Not widely available
  - BID dosing

Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

- Mirtazapine (Remeron®)
- 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 throuh a2)
  - Blocks postsynaptic 5-HT2C receptor → weight gain
  - Blocks postsynaptic 5-HT3 receptor → no GI SEs
  - Blocks H1 receptor → sedation, weight gain
- Adverse Effects
  - Sedation: commonly seen at lower doses
  - Weight gain
- Minimal drug-drug interactions except when with other sedative agents and ETOH

Mirtazapine / Remeron® (1996)

- Drug Interaction
  - Possible decreased antihypertensive effects when combined with clonidine
  - Concomitant sedative agents may decrease motor skills, cognition
  - Avoid combination with MAOI, ETOH
- Dosing
  - Start at 7.5-15mg
  - Max dose is 45mg
    - Doses higher than 30mg rarely helpful

Mirtazapine

- 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

Mirtazapine

- Disadvantages
  - Weight gain
    - Can use SSRI, SNRI, 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

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

- Generic renamed from amfebutamone in 2000
- Mechanism of action
  - Blocks reuptake of NE and DA
  - Noncompetitive antagonist of nicotinic receptors
  - Activates proopiomelanocortin (POMC) neurons in the hypothalamus
    - Appetite suppression
  - No blockade of alpha-1, M1, H1 receptors or SERT
- Clinical Uses
  - Depression*, smoking cessation*, seasonal affective disorder*, ADHD, neuropathic pain, weight loss (FDA approved as combination with naltrexone: Contrave®), treatment of sexual dysfunction

*FDA approved indications

Bupropion Formulations

- Bupropion hydrochloride
  - Immediate release
    - Peaks at 2hrs
    - 100mg BID, 100mg TID, 450mg (divided TID/QID)
  - Sustained release (Wellbutrin SR®, Zyban®)
    - Peaks at 3 hrs
    - 150mg daily, 150mg BID
    - Can be split but swallow whole
  - Extended release (Wellbutrin XL®)
    - Peaks at 5hrs
    - 150-450mg qAM
  - Extended release (Forfivo XL®)
    - 450mg qAM
- Bupropion hydrobromide
  - Aplenzin®: 174mg, 348mg, and 522mg dosage

Bupropion

- 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

- Caution when combined with other risk factors for seizures
  - AV malformation, head injury, severe stroke, CNS tumor, CNS infection, hypoglycemia, hyponatremia, severe hepatic impairment, hypoxia
- Caution with history of anorexia/bulimia
- Caution 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
  - 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
- 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
- Bromide has anticonvulsant properties so HBr formulation may (not proven) reduce seizure risk
- 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

- Patients with history of or higher risk for seizures
- Patients with eating disorder
- May worsen tics
- Concern over low weight
- Over activation (dose in morning)
- May worsen anxiety in some
- May increase blood pressure
- When used with dopaminergic agents, may precipitate psychosis, delirium, and dyskinesias
- Irritability, agitation "jittery"

Vortioxetine (2013)

- Originally called Brintellix®
  - Changed to Trintellix®
- Mechanism of Action
  - 5-HT reuptake inhibitor via SERT (antidepressant effect)
  - 5-HT1A receptor agonist (anxiolytic effect)
  - 5-HT1B receptor partial agonist (?antidepressant effect)
  - 5-HT1D receptor antagonist (?antidepressant effect)
  - 5-HT3 receptor antagonist (Lower GI AEs)
  - 5-HT7 receptor antagonist (antidepressant, sleep/wake modulation)
- Indications: Major depression

Vortioxetine

- 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
  - 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
  - Reports of improved cognitive ability (?)
  - May be better for weight (?)
  - Reportedly lower sexual dysfunction (?)
    - Fluoxetine originally reported as 1.8% 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
  - Above listed advantages are from trials only
  - Effect size is on the low end at 0.28

Gepirone ER / Exxua® (2023)

- Mechanism of Action
  - Selective 5-HT1A receptor partial agonist
    - Similar to buspirone
  - Metabolite (1-PP) is same as buspirone
    - a-2A antagonist
      - Dizziness, nausea, headache
- Indications: Major depression

Gepirone ER

- 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
  - Bioavailability: 14-17%
  - Moderate (72%) protein binding
  - Extensively metabolized via CYP3A4
  - Terminal half-life: **~5 hours**

Gepirone ER

- Adverse Effects
  - Nausea (35%), dizziness (49%), fatigue (15%), headache (31%), insomnia (14%)
- Pregnancy Category: not yet determined
- Drug Interactions
  - Strong inhibitors/inducers of CYP3A4 have X rating
  - Moderate inhibitors/inducers of CYP3A4 have D rating
  - Contraindicated with concurrent use of MAOI as well as for 14 days after stopping
  - Caution with use with other QT prolongating agents

Gepirone ER

- Advantages
  - Potentially similar efficacy as other antidepressants without serotonergic adverse effects like sexual dysfunction
  - Does not affect CYP enzymes
- Disadvantages
  - 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
  - Dizziness, nausea, headaches are relatively frequent
  - Vulnerability to 3A4 inhibition
    - Interactions are D/X ratings
  - Very short ½-life (is daily dosing adequate?)
  - QT prolongation

Optimal Daily Dose Ranges for 2nd-Gen ADs

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

- 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

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, doxepin, selegeline, phenelzine
  - No recommendations made but caution advised
    - All others
- Renal dosing
  - All SNRIs
  - Gepirone
  - Paroxetine

Next Generation ADs

Next Generation of Antidepressants

- Neurosteroids
- NMDAR antagonists
- 5-HT2A agonists
- Sestrin modulators
  - mTOR
- 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

Brexanolone (Zulresso®) (2019)

- FDA approved for post-partum depression
  - 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
- 60 hour IV infusion due to risk of loss of consciousness
- Cost: $34K for the drug alone
- Boxed warning: Excessive sedation and sudden loss of consciousness
- Breastfeeding is contraindicated
- 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
  - Phase III: 45% remission vs 23% placebo; held 45 days later
- Currently under investigation for depression, insomnia, Parkinsons, GAD, and bipolar disorder
- Requires a fatty meal for absorption

Zuranolone (Zurzuvae®) (2023)

- **BBW**
  - Avoid driving or other potentially hazardous activities for 12 hours after taking
- Pending scheduling
- Breastfeeding is contraindicated, however transmission into breast milk may be minimal
- Adverse effects: drowsiness, diarrhea, dizziness
- Drug dose adjustments may be needed with 3A4 inducers/inhibitors
- Cost is ~$15K for a 2 week course of treatment

Glutamate Activity

- Ketamine IV (off-label for suicidality since late 1990s)
  - FDA approved as dissociative anesthetic (1970)
  - NMDA receptor antagonist
  - 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
  - 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 weeks
  - Hold sedatives and stimulants during treatment
  - 100% bioavailability

Glutamate Activity

- Esketamine (Spravato®) (2019)
  - FDA indications
    - Treatment-resistant depression
    - MDD with suicidality
  - Intranasal given in clinic twice weekly changing to weekly at week 5
  - 2 hour monitoring after dose given in clinic
  - 30-50% bioavailability
  - 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

Glutamate Activity

- Esketamine (Spravator®) (2019)
  - Almost as effective as IV ketamine, but requires more treatments for effect
    - 27-50% response rate for treatment-resistant depression
    - 2023 study shows 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

Glutamate Activity

- REL-1017 (esmethadone, dextromethadone, S-(+)-methadone)
  - 20 times lower affinity for opioid receptors than levomethadone
  - Antagonizes NMDA receptors
  - Low risk for respiratory depression and abuse
  - Phase III trials
- Hydroxynorketamine
  - Activates AMPA glutamate ion channel with downstream effects increasing BDNF and mTOR
  - Demonstrated rapid antidepressant activity in animal models
  - Does not bind the NMDA glutamate receptor
  - No abuse potential and no dissociative effects

Glutamate Activity

- DXM+Bupropion (Auvelity®) (2022)
  - FDA approved for MDD
  - More rapid onset of symptom relief (1 week)
  - 46.5% vs 16.2% bupropion alone achieved remission in 6 week trial
  - Dextromethorphan (DXM)
    - NMDAR antagonism
    - σ1 agonism
      - Altered trafficking of AMPA
      - Increased synthesis of BDNF
      - Interferes with pro-inflammatory compounds
    - SSRI

Glutamate Activity

- DXM+Bupropion (Auvelity®) (2022)
  - Bupropion
    - 2D6 inhibitor: extends ½-life of DXM, DXM peak levels increased 40x, AUC by 60x
      - Other antidepressant 2D6 inhibitors can contribute to serotonin syndrome with DXM
    - NDRI
  - Adverse Effects: somnolence, nausea, dizziness, headache, dry mouth
    - No cases of psychosis, serotonin syndrome, dissociation, addictive behaviors
  - 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 26D
    - Also allows flexibility in dosage of each used
    - Doses of DXM as high as 60mg BID have been tested

5-HT2A agonists

- Currently Schedule I substances
  - Psilocybin
    - Being researched in psychotherapy
  - LSD
  - MDMA

Sestrin Modulators (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 II trials

BDNF Modulators (ALTO-100)

- ALTO-100 has been studied since 2010 for MDD, bipolar disorder, and PTSD
- Studies have been mixed, but there has been some recently positive data.
- ALTO-100 has been shown to enhace hippocampal neuroplasticity and neurogenesis.
- Mechanism is currently unknown but it indirectly modulates BDNF, which is enhanced by a number of things to include healthy diet, exercise, psychotherapy, etc.
- Alto Neuroscience is currently developing several other medications to treat depression
  - ALTO-203: H3 receptor inverse agonist
  - ALTO-300: MT1 and MT2 receptor agonist and 5-HT2C antagonist
  - ALTO-202: NR2B subunit-containing NMDA receptor antagonist

Treatment Issues

Selecting an Antidepressant

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

Tips for Selecting an Antidepressant

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

Tips for Selecting an Antidepressant

- Select based on side 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

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

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

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.

Switching Antidepressants: MDD Disease Medication Management Guideline

Switch drug with washout period

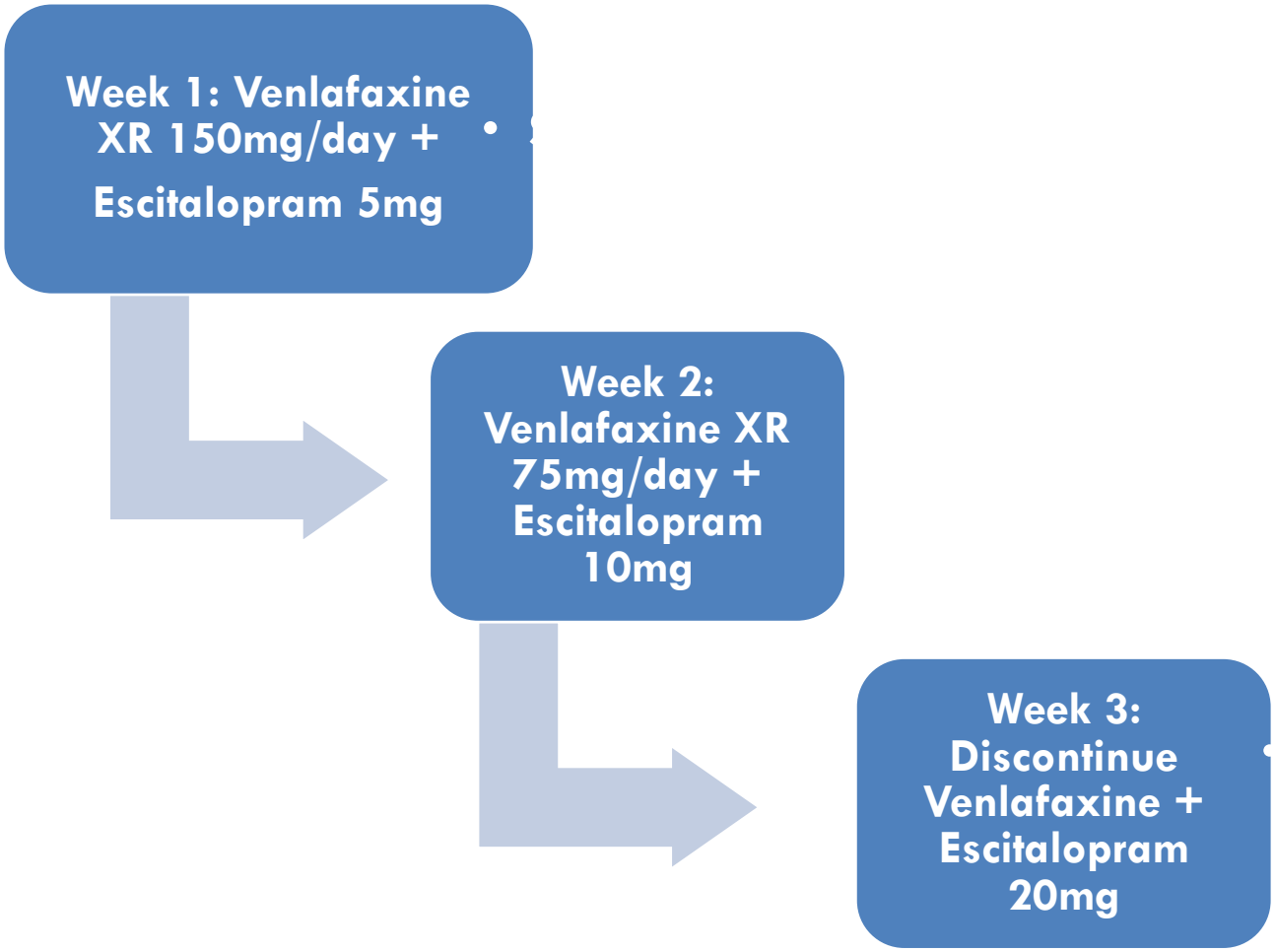
Direct switch with no washout period

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 (MAOIs), a wash-out period between antidepressants is necessary
  - Direct switch
    - SSRI to SSRI can be done by direct switch.
    - Consider waiting 4-7 days when switching from fluoxetine, then starting a low dose of another SSRI
  - Cross-taper
    - Often used when switching to an antidepressant with a different mechanism of action
    - SNRI to SSRI

Example: Cross-Tapering Strategy



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

Discontinuation of Therapy

- Patients should be treated for at least 9-12 months before considering taper
  - Risk of relapse is higher if discontinuing sooner
- All SSRI 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

Psychogenomic/Pharmacogenetic Testing

- Recommended tests
  - CYP2D6, CYP2C19: How fast or slow they metabolize
  - HLAB: Carbamazepine sensitivity
  - MTHFR: L-methylfolate
- Insufficient evidence for testing benefit
  - COMT gene
  - 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

Augmentation Strategies

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

Augmentation Strategies

- Lithium
  - Best evidence for augmentation
- Bupropion, mirtazapine
  - May be combined with SSRI at lower doses
- Pindolol
  - $5HT_{1A}$ antagonist ($\uparrow$5HT)
  - May accelerate response (but inconclusive studies)
  - Dose = 2.5mg TID
- CNS stimulants
  - Methylphenidate and dextroamphetamine
- Modafinil
  - Useful for patients with low energy in addition to depressive symptoms
  - Should not be used alone for depression
- Pramipexole
  - D3 agonist
  - Dose = 1-5mg daily
- Buspirone
  - No advantage over placebo

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/day x 2 days, then 150mg/day, range 150-300mg/day)
      - Brexpiprazole (0.5 or 1 mg/day, range 0.5-3mg/day)
      - Cariprazine (1.5mg/day, range 1.5-3 (4.5)mg/day)
    - Non-FDA-approved which have some evidence
      - Risperidone, lurasidone
    - Ineffective: Pimavanserin

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 SZP
    - 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.

Depression Sub-Types

Treatment-resistant depression

- 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: Dynamics

- Some patients are resistant **to** medications
  - Typically are ambivalent about some element of the treatment
    - Worry about adverse effects
    - Worry about becoming dependent
    - Not wanting to take medications
  - Leads to non-adherence or strong nocebo effects
- Some patients are resistant **from** medications
  - They like and want medications
  - Medications undercut their agency and development to heal
  - May misuse the medications
  - They report that they feel better but they don't appear to be better
- Usually there is overlap of the two
- How you talk about the medications can affect how they help or harm
- Addressing these psychological and interpersonal dynamics can help to resolve symptoms

Treatment-resistant depression

- FDA-approved treatments
  - Aripiprazole
  - Brexpiprazole
  - Olanzapine
  - Quetiapine
  - Esketamine
  - ECT
  - rTMS
- Off-label treatments
  - Lithium
  - MAOis
  - TCAs
  - Pramipexole
  - Vagus nerve stimulation
  - Deep brain stimulation

Psychotic Depression

- 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 subclinical hypomanic symptoms
  - 1st line: Lurasidone
  - 2nd line: Quetiapine
  - Other medications may be effective but have not been studied

Depression with Anxious Features (Anxious Depression)

- Responds less well to
  - Medications studied in STAR*D
    - 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
  - Disturbed affect that is unresponsive to improved circumstances
  - Anhedonia
  - Psychomotor agitation or retardation
  - Neurocognitive impairment
  - Interrupted sleep
  - 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

Special Populations

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 fluvoxmine as liquids
  - Duloxetine as sprinkles

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
- Nortriptyline: Depression, >=13 yo
  - TCAs associated with **increased** diastolic BP; baseline EKG recommended

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

Pregnancy

- High prevalence during & after pregnancy
- 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
- Consider medication
  - Severe past episode of depression
  - Hx of suicidality, psychosis, hospitalization
  - Multiple depressive episodes
  - Hx of post-partum depression

Pregnancy

- 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

Pregnancy

- Mild to moderate depression
  - Psychotherapy, brisk walking, Mediterranean diet, light box
- Patients with severe depression, acute suicidality, psychosis, bipolar disorder should receive psych referral
- www.MotherToBaby.org (866) 626-6947
- Severe depression
  - Antidepressant
  - ECT
  - Post-partum psychosis
    - Lithium (most effective) +/- antipsychotic
    - Antipsychotic
    - ECT

Pregnancy

- 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
    - Increased risk of pre-eclampsia: SNRI, TCA
  - Older SSRIs preferred
    - Fluoxetine (however not preferred for breastfeeding (neonates only))
    - Sertraline
- CYP enzyme activity can increase during pregnancy
  - May need to increase dose towards the end of pregnancy

Pregnancy

- Some risk of withdrawal in newborn known as neonatal adaptation syndrome
  - Irritability, crying, jitteriness, increased muscle tone, dyspnea, altered sleep patterns, tremors, trouble eating
  - Most cases are mild and go away within weeks with no treatment
  - Most babies are not affected
- Persistent pulmonary hypertension in newborns of mothers who took SSRIs in second half of pregnancy*
  - Risk was 6x more likely in babies whose mothers took SSRI after 20th week of pregnancy
  - FDA requested labeling changes for all SSRIs but FDA does not recommend altering "current clinical practice"

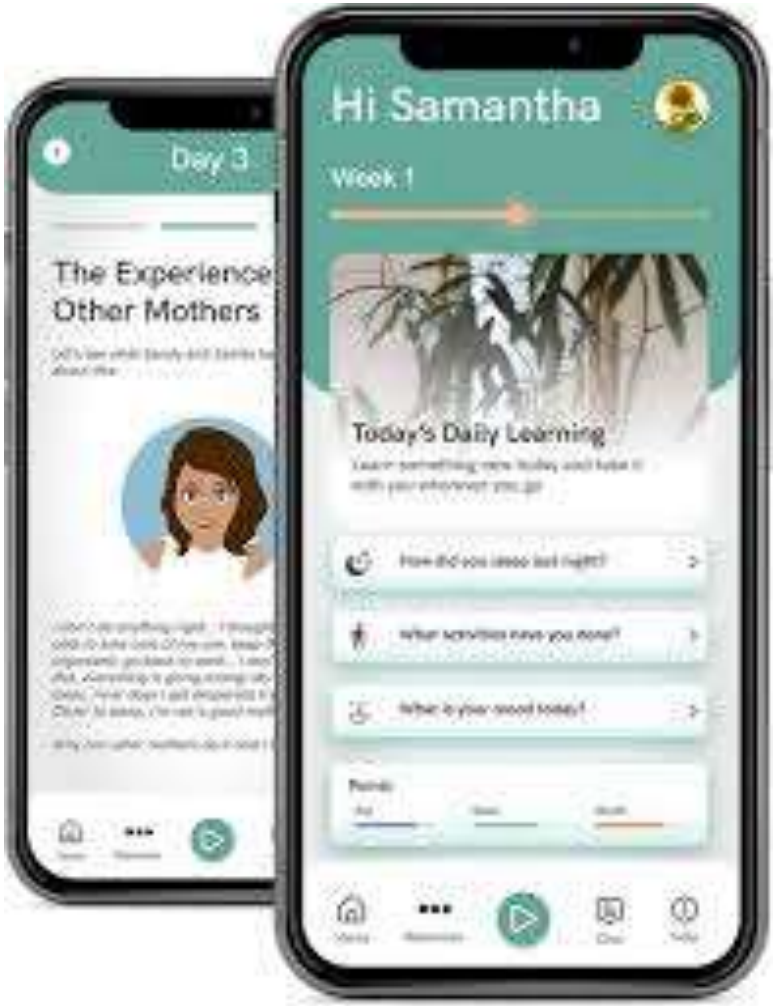
*Chambers CD et al. NEJM 2006;354:579-87; FDA warning, 12/14/11.

Post-partum

- Prevalence of postpartum depression: 10-22%
  - Postpartum blues: ~50%
- 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

MamaLift Plus® (2024)

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



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

Breastfeeding

- 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
- Caution with
  - Doxepin
    - Excessive accumulation in the newborn, poor suckling, vomiting, hypotonia
  - Bupropion
    - Small seizure risk
    - OK if no other seizure risks

Breastfeeding

- L1 (Safest, risk of harm is remote or not bioavailable)
  - Sertraline
- L2 (Safer, risk of harm is remote, limited studies)
  - TCAs
    - Imipramine, Amitriptyline, Clomipramine, Desipramine, Nortriptyline, Amoxapine
  - SSRIs
    - Fluoxetine (L3 neonatal, L2 older infants), Paroxetine, Fluvoxamine, Trazodone
  - Benzo
    - Quazepam
  - Mood Stabilizers
    - Valproic Acid, Carbamazepine
  - APs
    - Haloperidol, Olanzapine

Breastfeeding

- L3 (Moderately safe, no studies or minimal risk)
  - Citalopram, Escitalopram, Venlafaxine, Bupropion, Vortioxetine, Mirtazapine, Maprotiline
  - Most benzodiazepines
  - Buspirone
  - Lamotrigine
  - Aripiprazole, Chlorpromazine, Clozapine, Fluphenazine, Risperidone
- L4 (Possibly hazardous, evidence of risk, may use if safer drug not available)
  - Nefazodone
  - Lithium
  - Loxapine, Pimozide, Quetiapine, Thioridazine, Thiothixene, Ziprasidone
- L5 (Contraindicated, risk of use outweighs benefit)
  - Doxepin
  - Kava Kava

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)
  - 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 neurotransmitters are being metabolized, so patients respond to medications/changes quickly
  - Can take just during symptoms
  - If already taking an AD, take increased dose just during symptoms
  - Effectiveness: 70-80%
- 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)
- SSRI
- Estradiol (oral, patch, cream, insert, ring, vaginal tablet)
  - <60 and within 10 years of menopause are lowest risk
  - 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 UID for this
  - Consider tapering after 5 years
    - 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
  - Low dose vaginal preparations are not systemically absorbed
  - Highest caution with oral
  - 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 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

Misc

- Hypertension, cerebrovascular disease
  - Avoid venlafaxine, duloxetine
- Diabetes
  - Avoid paroxetine, MAOIs, TCA, mirtazapine (weight gain)
  - CYP3A4 inhibitors (DDI sulfonylurea)
- CV disease
  - SSRI > TCA, MAOIs
- Parkinson's
  - Bupropion preferred (↑ DA)
  - Avoid amoxapine and antipsychotics
- HIV/AIDS
  - Avoid nefazodone, fluvoxamine (or other CYP3A4 inhibitors)
- Seizures
  - Avoid bupropion and TCAs

Non-pharmacologic

Non-pharmacologic

- Psychotherapy
- Lifestyle interventions
- Complementary
  - St. John's Wort
  - L-methylfolate 15mg daily
  - SAMe 800-1600mg daily
- Somatic
  - ECT
  - Light therapy
  - Vagal nerve stimulator
  - TMS
  - Cranial electrotherapy stimulator

Complementary Therapies

St. John's Wort (Hypericum perforatum)

St John's Wort

- Mechanism of Action
  - GABA, 5HT, central BZD receptor affinity
- Synergistic and/or additive effects of several different constituents of St. John's Wort
  - The German Commission E monograph initially classified St. John's Wort as a monoamine oxidase inhibitor, may be stronger SSRI
  - 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

St John's Wort

- Safe, effective treatment for mild-moderate depression
  - Possible option in major depression, but may require higher doses (1,500mg daily or more)
- Active Ingredient for depression thought to be hypericin and hyperforin
  - These compounds are used for standardization at 0.3%
- Patient selection
  - Good history of positive response to low dose SSRI, but intolerant AEs

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

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

Yong-hua C. 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.

L-Methylfolate (Deplin®)

- 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 (OTC is cheaper and equally effective)

L-Methylfolate (Deplin®)

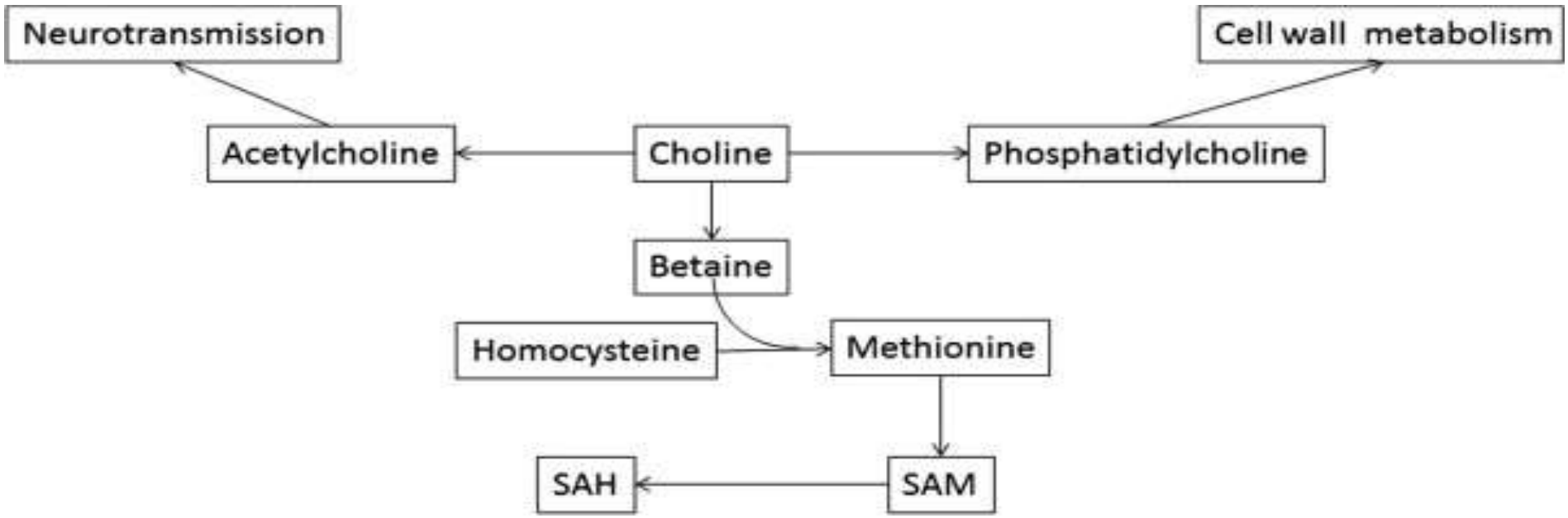
- 2012 double-blind placebo controlled trial
  - Statistically significant difference between 15mg/day as augmentation from placebo:
    - 32.3% vs 14.6% response, NNT 6
  - Remission rates were not statistically significant
  - Treatment length: 30 days
  - Side effects were comparable to placebo
- Patients non-responsive to SSRIs or with obesity/inflammation may respond
- Lamotrigine less effective when used with folic acid
  - May not be so with L-methylfolate

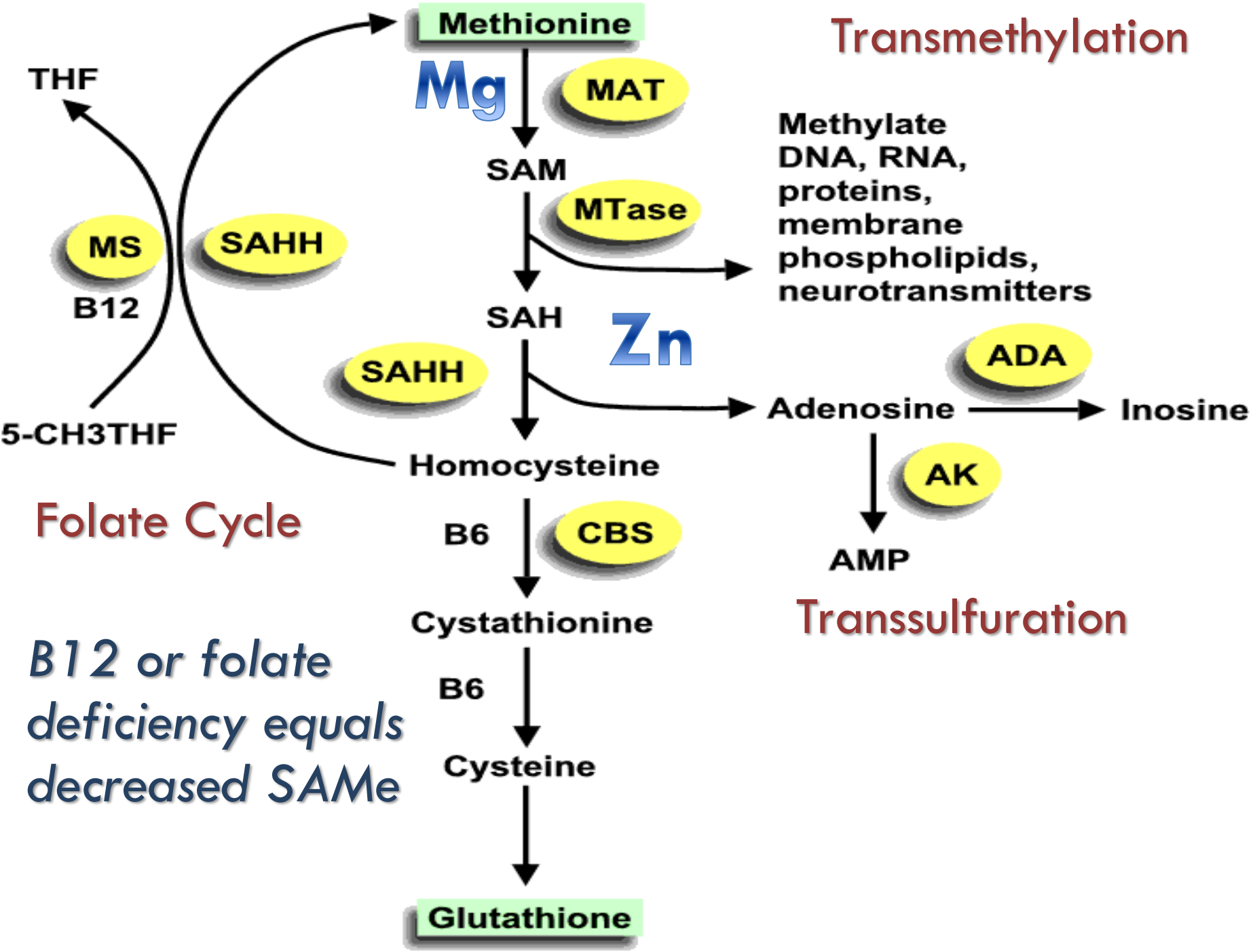
Papakostas GI et al. L-Methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry.* 2012;169:1267–74.

Macaluso M. L-Methylfolate in Antidepressant Non-responders: The Impact of Body Weight and Inflammation. Front Psychiatry. 2022 Mar 17:13:840116.

SAMe (S-Adenosyl Methionine)

- 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.**




Methionine
Transmethylation
THF
Mg
MAT
SAM
Methylate
DNA, RNA,
proteins,
membrane
phospholipids,
neurotransmitters
MTase
MS
SAHH
B12
SAH
Zn
SAHH
ADA
Adenosine
Inosine
5-CH3THF
Homocysteine
AK
AMP
Folate Cycle
B6
CBS
Cystathionine
Transsulfuration
B12 or folate
deficiency equals
decreased SAMe
B6
Cysteine
Glutathione

SAMe for the Treatment of Depression

- 1st line, mainstream, treatment for depression in Europe for over 30 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 side effects (ie lacks sexual side effects)

SAMe Clinical Use

- Monotherapy or augmenting agent
  - May be synergistic with antidepressants (not MAOI)
- Electroencephalogram profile of SAMe is similar to TCA
  - Increased serotonin turnover, dopamine, and NE levels
  - Neuroimaging shows SAMe 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 SAMe.

SAMe

- Dosing
  - Start 200mg BID with titration up 200mg per day to 800mg BID
  - 1,600 max that has been 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
  - SAMS CLUB AND COSTCO: good cost and quality
  - Can combine with other medications to reduce cost.

Medical Uses for SAMe

- Osteoarthritis
  - SAMe 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 side effects
- Liver disease
  - Can protect against liver damage, reverses elevations in LFT's, consider in patients receiving statins
  - Alcohol abuse depletes liver of SAMe and causes oxidative stress that contributes to tissue damage

Somatic Therapies

Electroconvulsive Therapy

- Mechanism unknown
- High response rate, well tolerated, rapid onset
  - Psychotic depression
    - 95% remission (83% for non-psychotic depression); can be a first line option
- Delivered in controlled environment
- Patients asleep during treatment
- Seizure induced after administering premedications
- Indications
  - Severe vegetative symptoms, psychotic depression, intense SI, pregnancy, catatonia, intractable mania
- Caution with seizure inducing/inhibiting meds

Electroconvulsive Therapy

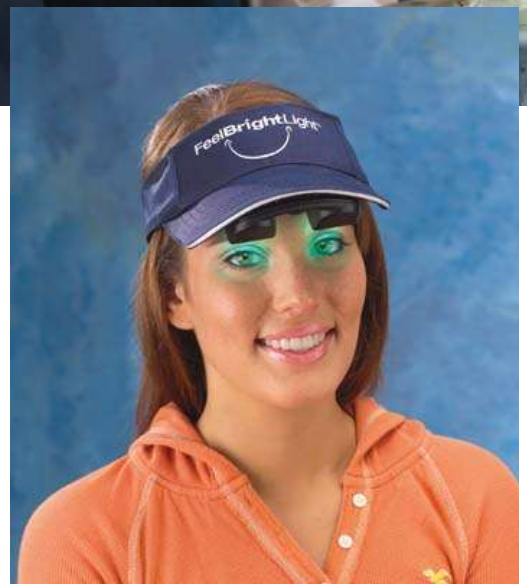
- Premedications
  - Anticholinergic drugs
    - Atropine, glycopyrrolate
    - Minimize oral and respiratory secretions
    - Block bradycardia and asystoles
  - General anesthetics
    - Methohexital, etomidate, ketamine, propofol
  - Muscle relaxants
  - Succinylcholine

Electroconvulsive Therapy

- Adverse Effects
  - Sedation, confusion, usually retrograde amnesia, long term memory loss very rare
- Treatment cycle
  - 3x/week bilaterally has rapid response
  - Sustained response and remission
  - Rght unilateral ECT has less cognitive effects
  - Usually 6-12 tx for depression
  - Seizure should last about 25 seconds
- Preventing depression after ECT
  - Nortriptyline + Li^+ is recommended

Bright Light Therapy

- May be helpful for
  - Seasonal affective disorder, insomnia, circadian shifting
  - Not enough evidence for routine recommendation
- Blue wavelength of light
  - May be effective for suppressing melatonin



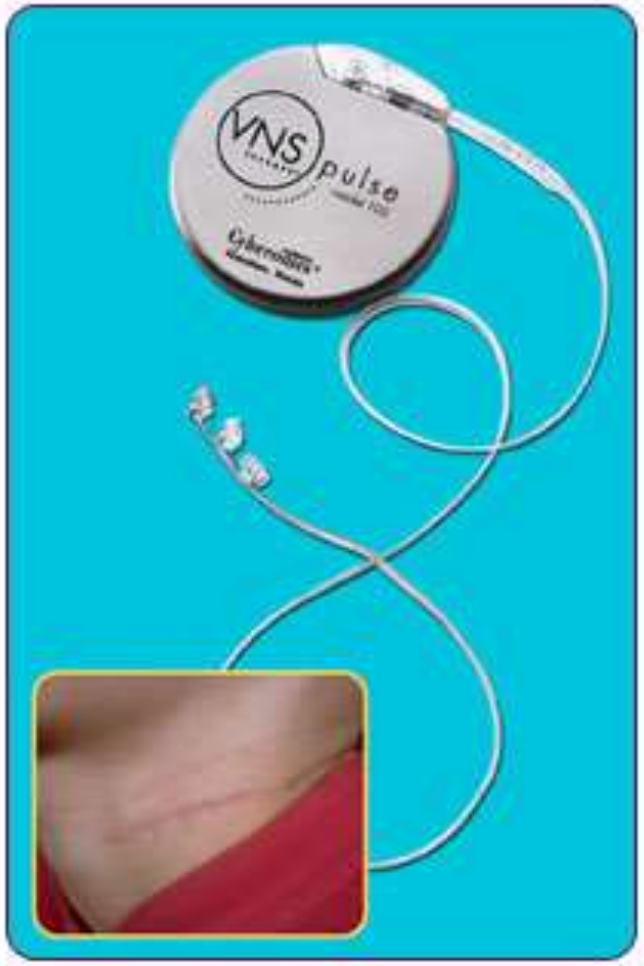
Vagal Nerve Stimulation

- Implantable Vagal Nerve Stimulation Therapy System* (VNS) approved to treat chronic depression (7/05)
- 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
- Mechanism unclear although apparently affects some same NT that drugs work on
- Not proven to be useful in acute phase of depression
- No fully controlled trials
- Cost of $25,000

*Cyberonics

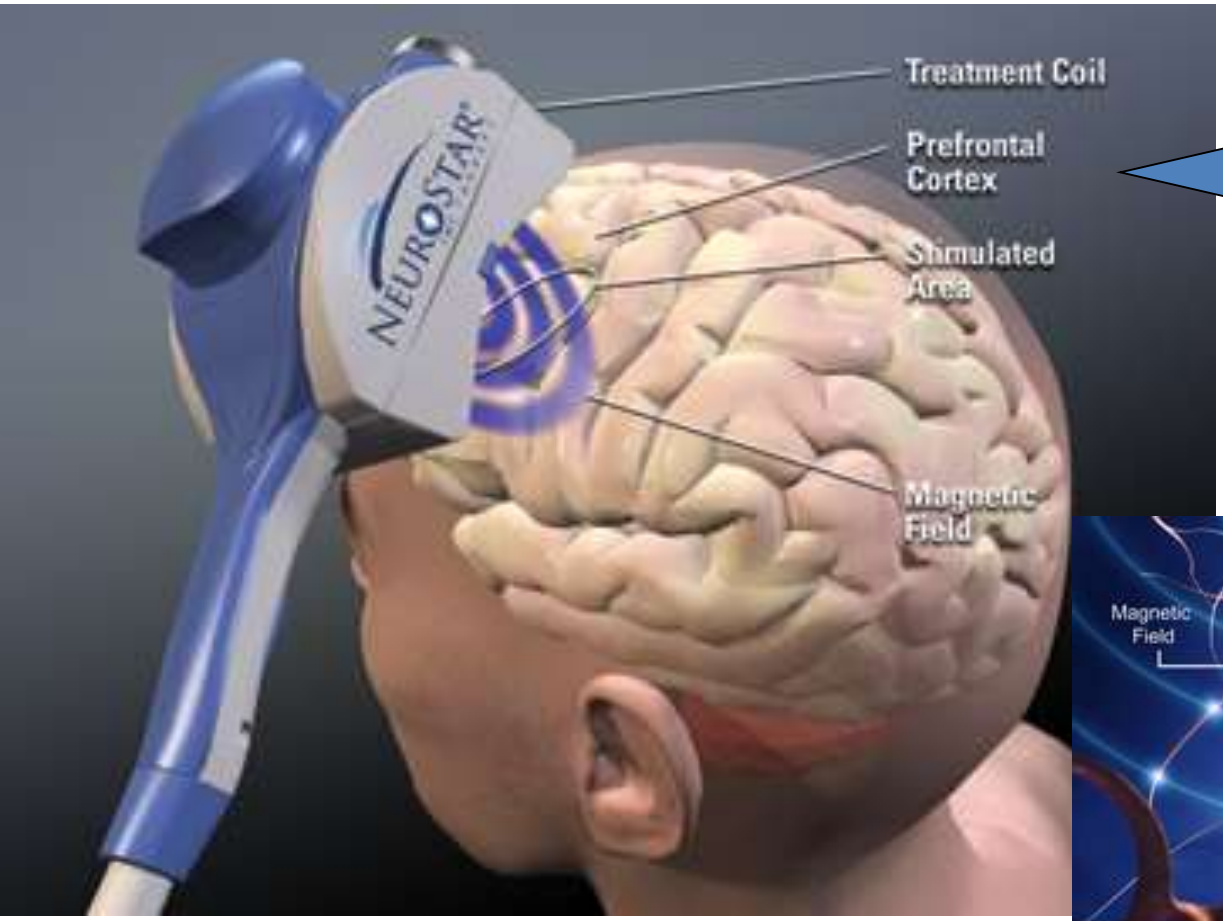
Vagal Nerve Stimulation

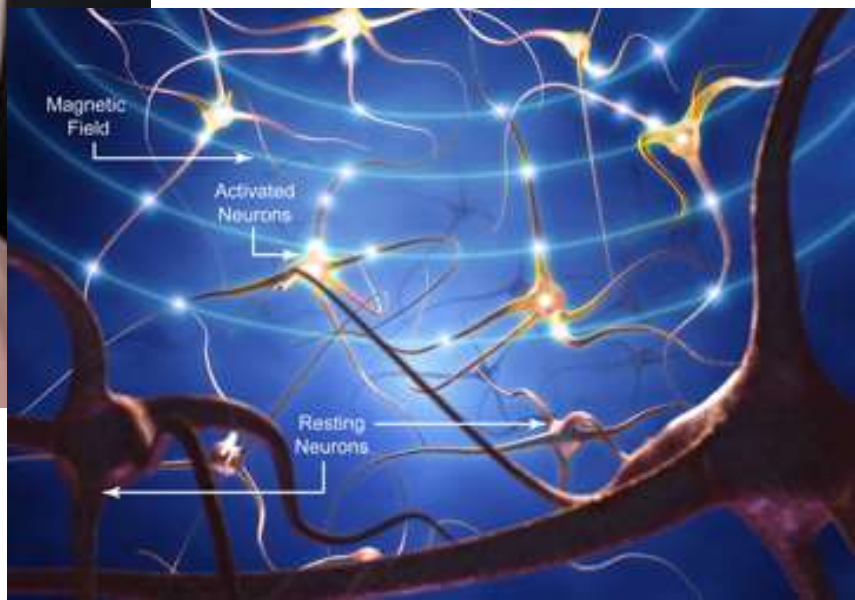
- Therapy is delivered by pulse generator (like a pacemaker) and thin, flexible wires that send mild pulses to the vagus nerve in the left side of the neck
- The vagus nerve delivers these pulses to areas of the brain involved in regulation of mood
- VNS targets specific areas of the brain that affect 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
- Previous indication for VNS is epilepsy but has been approved for treatment-resistant depression in Europe and Canada since 2001



3 months post procedure

Repetitive Transcranial Magnetic Stimulation (rTMS)





rTMS

- Administers repetitive subconvulsive magnetic stimulation to the dorsolateral prefrontal cortex
- Better cognitive side effect profile than ECT but may work less well in certain types of depression
- Negative predictors of response
  - Elderly, med resistance, longer duration of illness, MDD with psychotic/melancholic features
- Adverse effects
  - Tinnitus, headache, facial twitches: response to analgesics
- Rare adverse effects
  - Mania and seizures
    - Incidence of seizures <1%
    - Lower with lower frequency 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

Cranial Electrotherapy Stimulator

- May help with epression, 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