

Depressive Disorders

A clinical overview

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Depressive Disorders



- What is depression?
 - Complex series of conditions
 - Physical component
 - Emotional component
 - Treatments aimed at both components



History of concept of depression



- First concept of depression: Mesopotamia, second millennium BC
- Causes: spiritual passion; demonic possession
- Problems to be addressed by priests; not “medically” oriented
 - Greeks, Romans, Babylonians, Chinese and Egyptians similar ideas
- Early Treatments include beating, starvation, physical restraint
 - Represents early stigma of mental illness

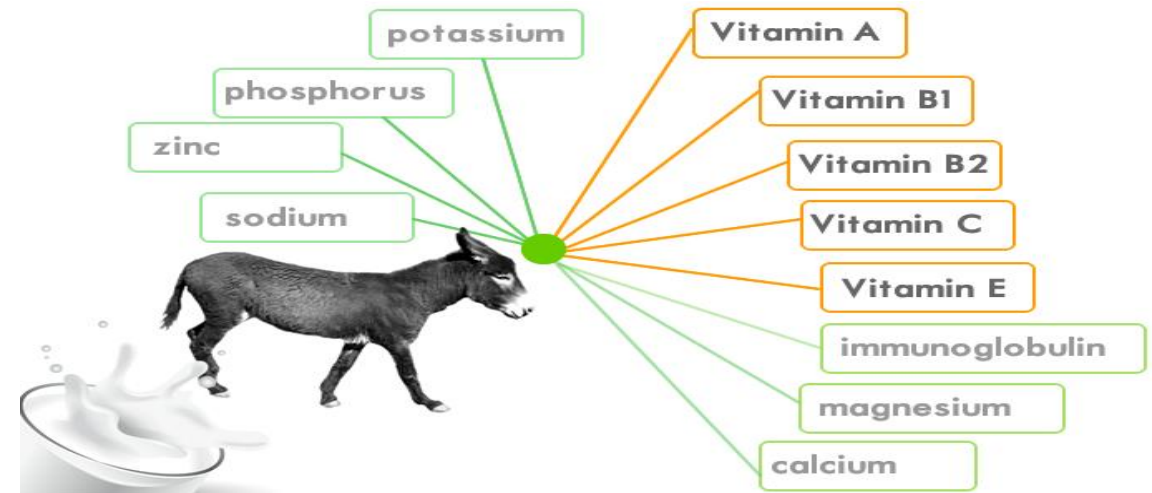


Plate 5. Bas-relief of an entrance to a small temple (Nimrud)

Progression of thought on depression



- Greeks and Romans – post CE; initial conception of depression as physical
- Notion that toxic “humors” may be harbored within body and cause mood change
- Newer Treatments
 - Gymnastics, massage, diet, baths, poppy extract and donkey milk

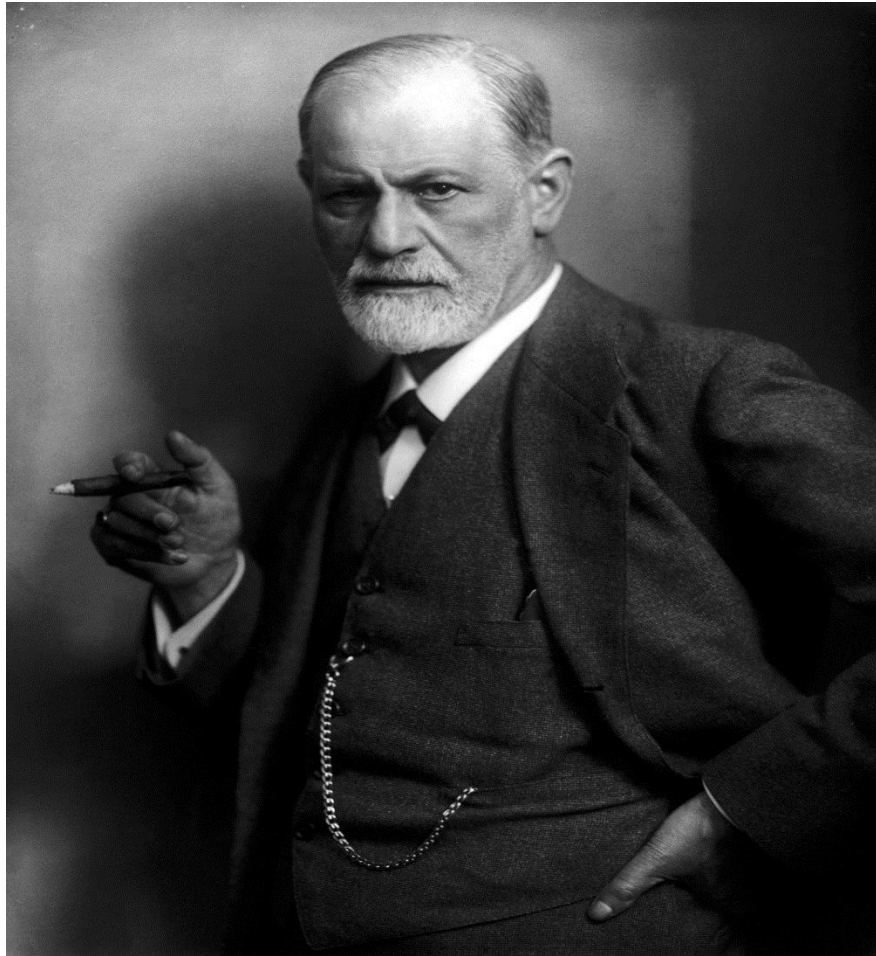


More contemporary thoughts on depression



- 1895- Emil Kraepelin differentiated manic depression from depression
 - Foundational concept that schizophrenia and mood are distinct
- 1917 - Sigmund Freud introduced concept of the “unconscious”
 - Depression was anger turned inward
 - Self loathing
 - Psychoanalysis: Form of treatment to bring unconscious thoughts and emotions to conscious awareness. Depression has “nurture” roots.





Early thoughts on depression



Freudian analysis mainstay of treatment – early 20th century

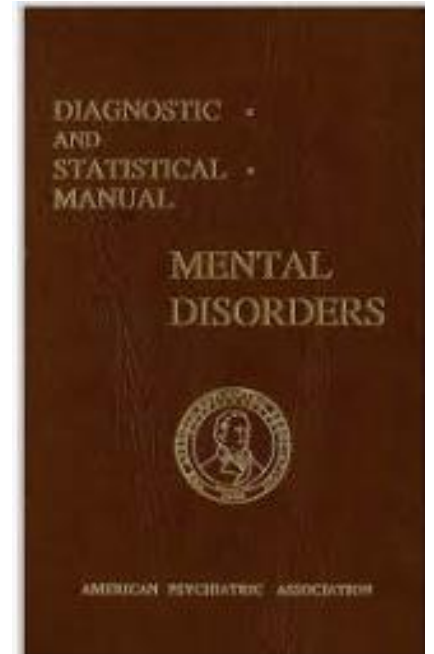
- Helpful for certain types of patients
- Lengthy and expensive
- Seen more as treatment for the elite. Not “The Peoples” therapy.
- Sigmund did not take kindly to the Prior Authorization process



Rapid changes in concept of mental illness and depression



- Post WWII- state of psychiatric diagnoses was chaotic
- DSM system introduced 1952; solve "Tower of Babel" crisis of psych
- Most profound change – 1980 DSM III
 - Change from cause bases diagnoses to measurable observation
 - Endogenous depression vs exogenous depression – eliminated
- Washington University (St. Louis); "Dust Bowl Empiricism"
- Goodwin, Guze, Winnuker , Clayton, Andreason
- Primary Principle – Psychiatric diagnoses are atheoretical





Depression and current DSM

- DSM 5 introduced 2013
- There are currently 7 specific depressive disorders
- Each disorder has unique set of criteria
- Each disorder has its own epidemiology associated with it
- Current DSM 5 represents consolidation of previous editions
 - No longer a distinct post-partum depression



DSM 5 classification of Depressive Disorders



- Major Depressive Disorder
- Persistent Depressive Disorder (dysthymia or minor depression)
- Premenstrual Dysphoric Disorder
- Substance/Medication-Induced Depressive Disorder
- Depressive Disorder due to Another Medical Condition
- Other Specified Depressive Disorder (brief depression)
- Other Unspecified Depressive Disorder



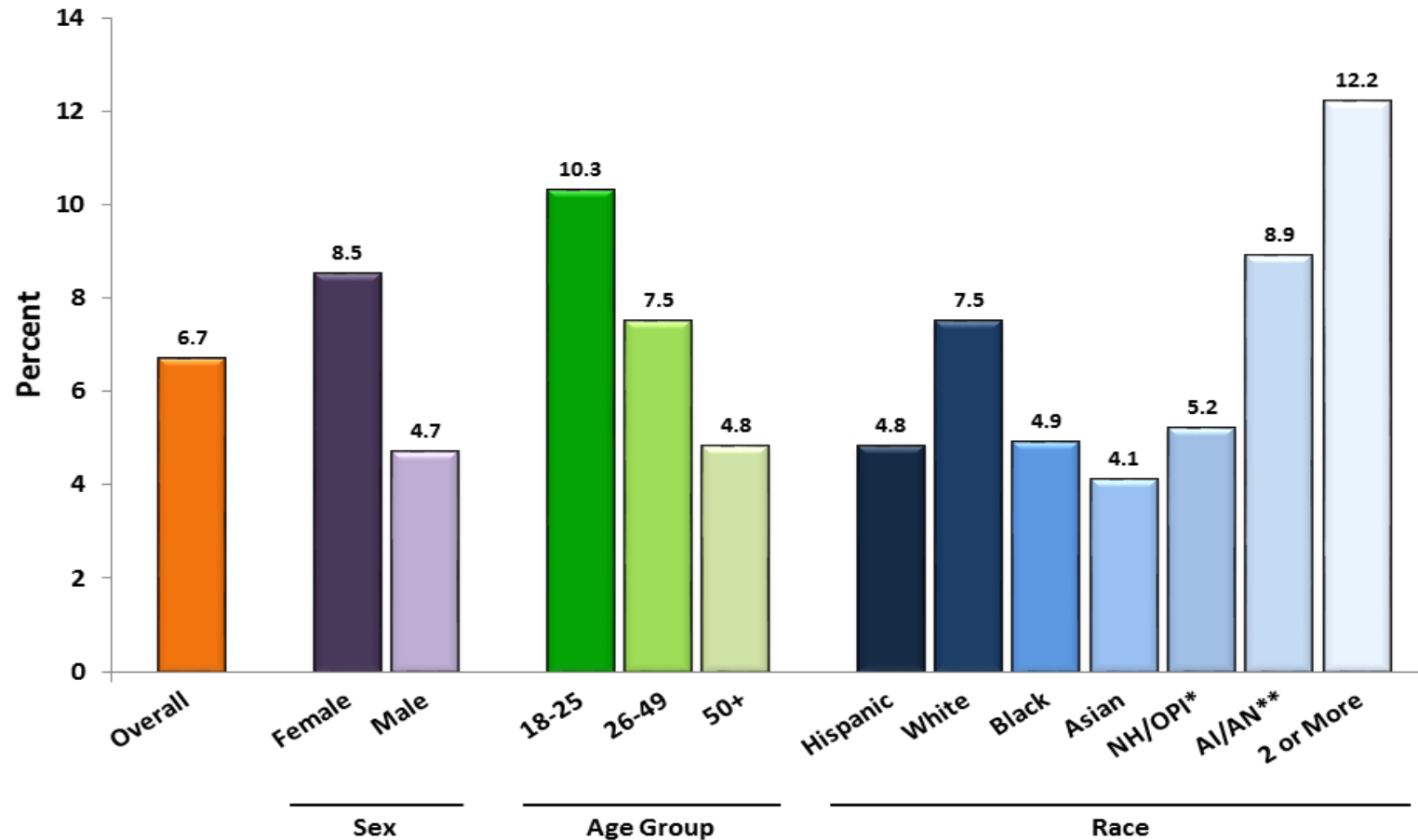
Criteria Major Depression

- Need 5 out of 9; 1 must be depressed mood or loss of pleasure
 - Depressed mood
 - Loss of pleasure
 - Weight loss
 - Insomnia
 - Suicidal
 - Poor concentration
 - Fatigue
 - Poor concentration
 - Motor agitation

Prevalence of Major Depressive Episode



12-month Prevalence of Major Depressive Episode Among U.S. Adults (2015)



Data courtesy of SAMHSA

*NH/OPI = Native Hawaiian/Other Pacific Islander
**AI/AN = American Indian/Alaska Native



Major depressive disorder: Unipolar depression

- Epidemiology
 - Sex: Twice as often in men than women
 - Age: Most common onset is between ages of 20-40
 - Lifetime prevalence: 5-12% in males; 10-25% in females
 - Annual incidence: 1.5% in entire population
 - Marital status
 - Socioeconomic status



Biology of depression

- 1950's and Introduction of Biological Psychiatry
- Iproniazid – first antidepressant
 - Accident; looking for tuberculosis cure
- Imipramine – discovered 1953
 - Accident; thought was antipsychotic
- Led to monoamine theory of depression
- 1960's – concept that depression linked to brain chemicals called monoamines
 - Monoamines released from one nerve cell, attach to adjacent nerve cell

Monoamines and depression

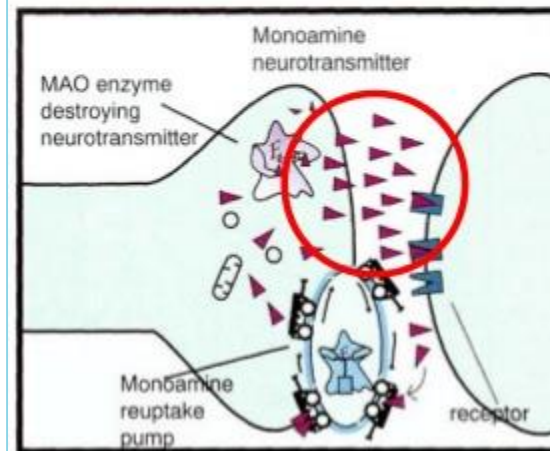


- Neurotransmitters
- Receptors
- Akin to key and lock
- Serotonin
- Norepinephrine
- Dopamine

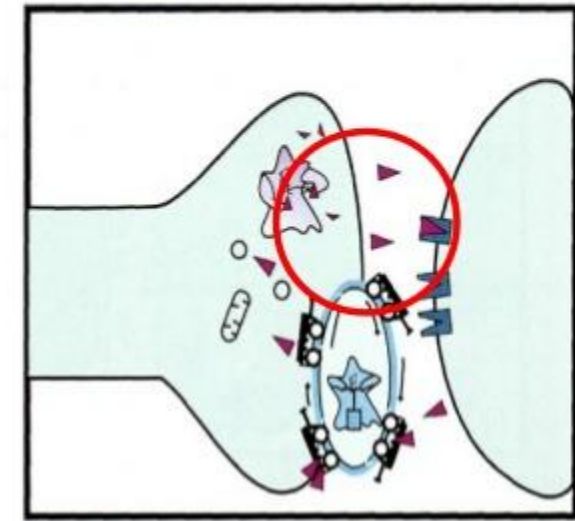
BIOCHEMICAL BASIS OF DEPRESSION

Monoamine Hypothesis: depression was due to a deficiency of monoamine neurotransmitters, notably nor-epinephrine (NE) and serotonin (5-hydroxytryptamine [5HT])

MONOAMINE HYPOTHESIS



NORMAL STATE - NO DEPRESSION

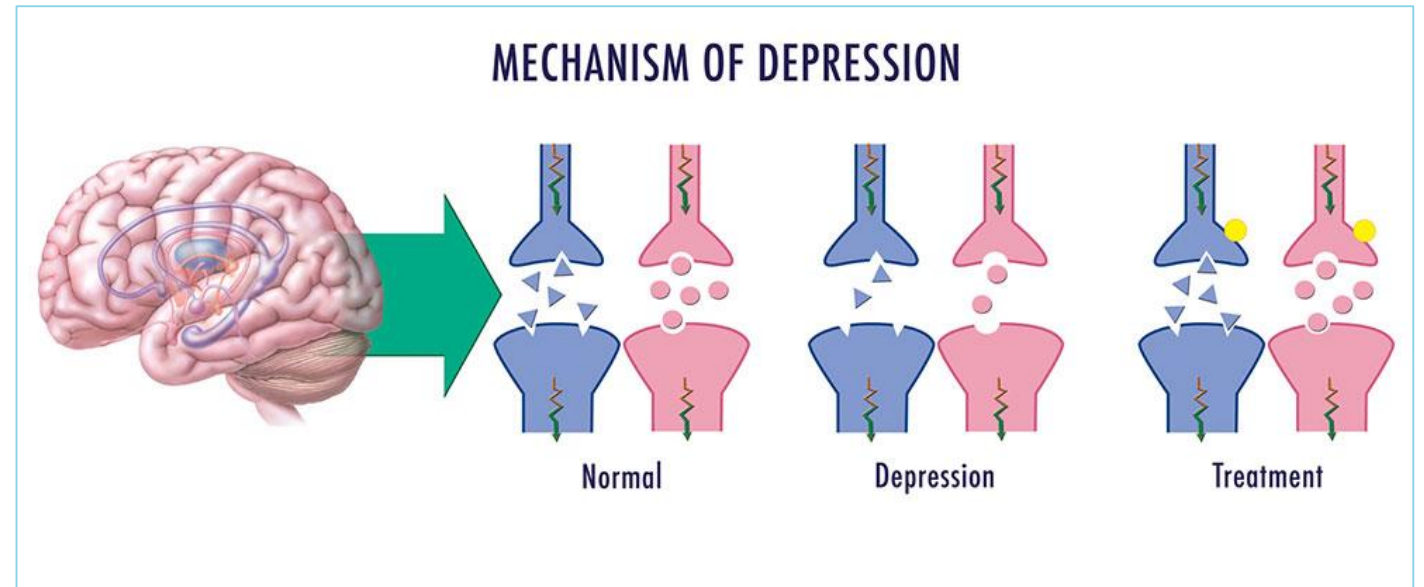


DEPRESSION: CAUSED BY NEUROTRANSMITTER DEFICIENCY

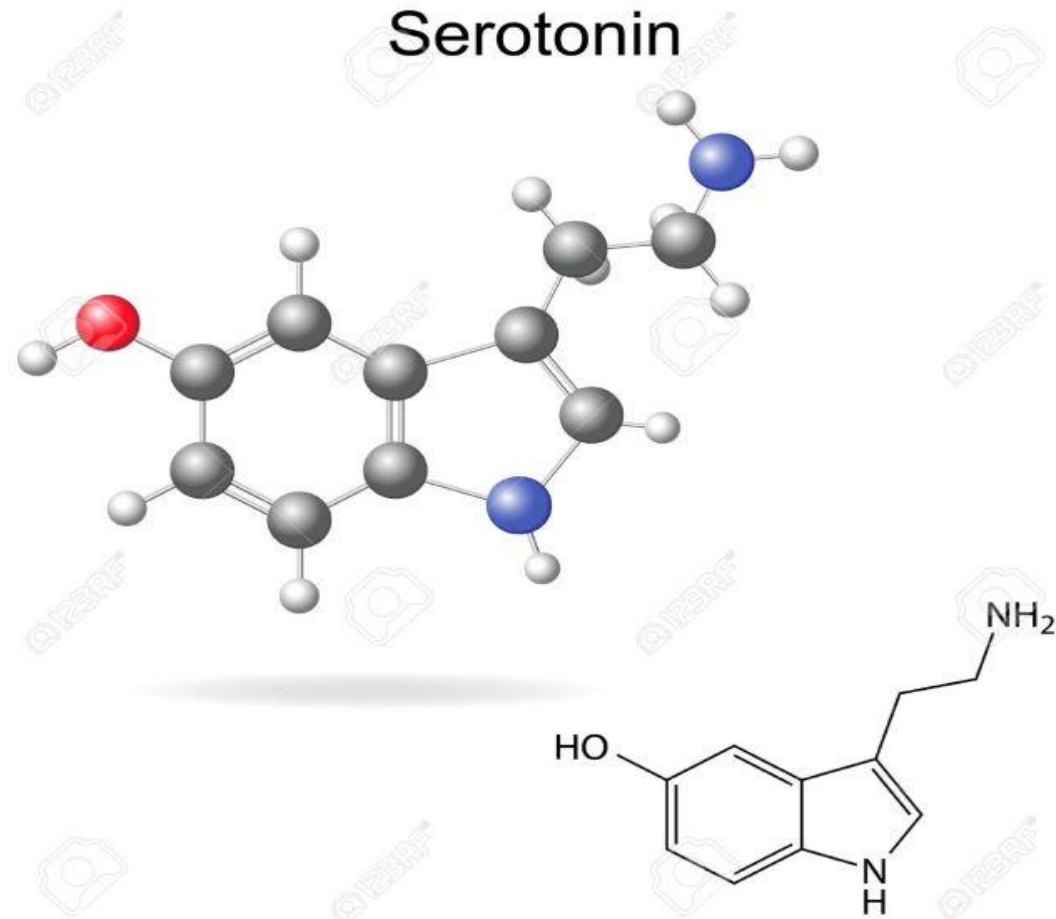
Biological theory of depression



- Normal neurotransmitter flow
- Abnormal absence of transmitter flow
- Treatment aimed at restoring normal balance



Depression—the role of serotonin



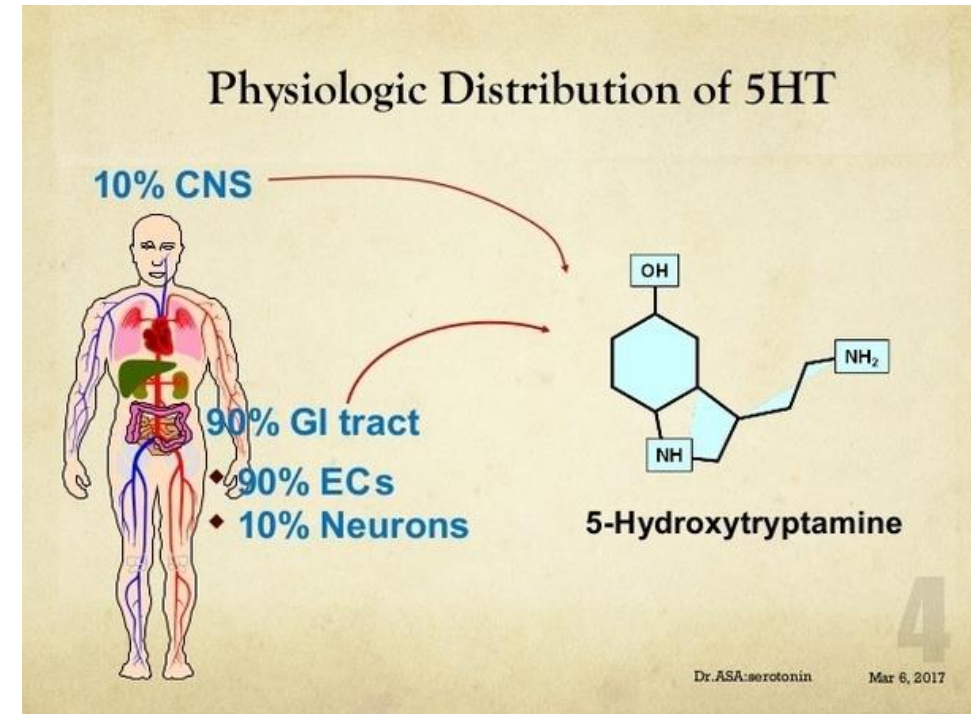
Depression—other neurotransmitters



Serotonin– most common neurotransmitter



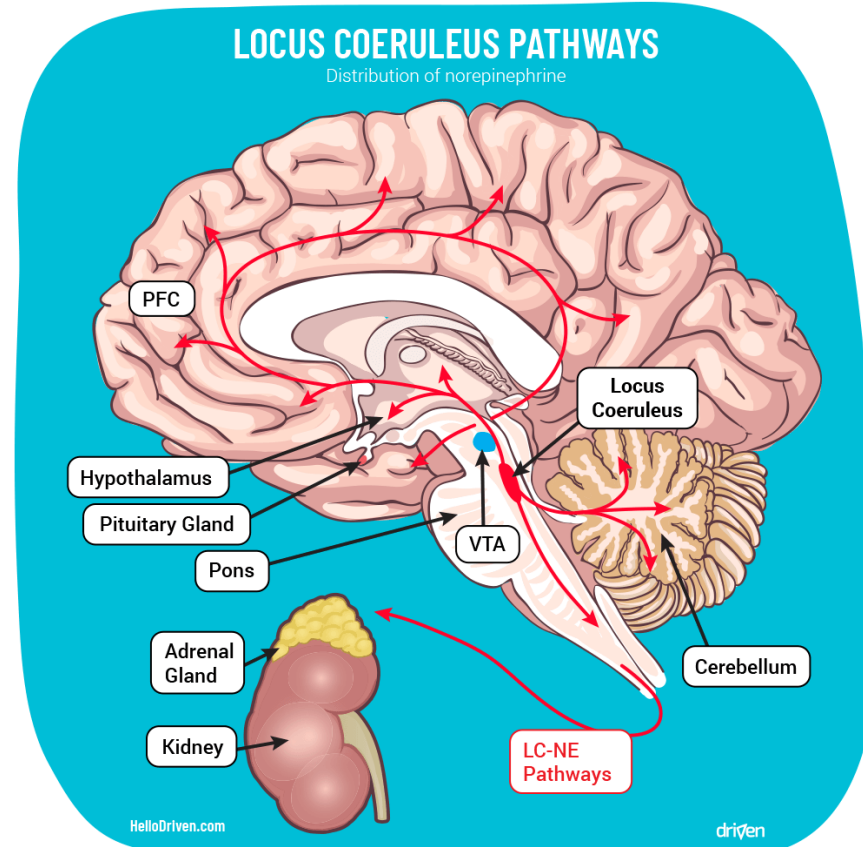
- Over 90 serotonin types of receptors
- Most serotonin receptors do not pertain to mood
- Sleep, sex, appetite, blood clotting, digestion all under prominent serotonin regulation
- In brain, most serotonin is concentrated in area called Dorsal Raphe Nucleus; synthesized from amino acid tryptophan



Norepinephrine– second most common



- Adrenaline like
- Not as widely distributed
- Plays role in anxiety
- Plays role in depression, especially agitated depression
- Located in adrenal glands also
- Synthesized from amino acid called Tyrosine

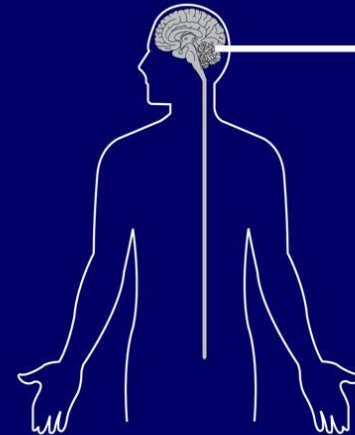


Dopamine– another big player



- Active in pleasure and reward behavior
- Enhances energy levels
- Cocaine's effect as an antidepressant is mediated via dopamine

Dopamine Alterations in Depression



During a major depressive episode secondary to MDD:

- ↓ dopamine metabolite HVA in CSF
- ↑ D₂-receptor-binding potential in striatum
- ↓ dopamine-transporter-binding potential in striatum in PET studies
- ↓ [¹⁸F]DOPA uptake in striatum

HVA = homovanillic acid; [¹⁸F]DOPA = [¹⁸F]fluorodopa.

Meyer JH et al. *Neuroreport*. 2001;12:4121-4125; Paillere Martinot ML et al. *Am J Psychiatry* 2001;158:314-316; Dunlop BW, Nemeroff CB. *Arch Gen Psych*. 2006; in press.

Psychometric tests– depression

- Beck Depression (BDI)
- HAM-D
- PHQ-2
- SCID- research



Medication treatments- depression



- SSRI – Selective Serotonin Reuptake Inhibitors
- SNRI – Serotonin Norepinephrine Reuptake Inhibitors
- Serotonergic Agents
- Tricyclics
- MAOI – Monoamine Oxidase Inhibitors
- Bupropion
- Mirtazapine



Medication treatments- depression



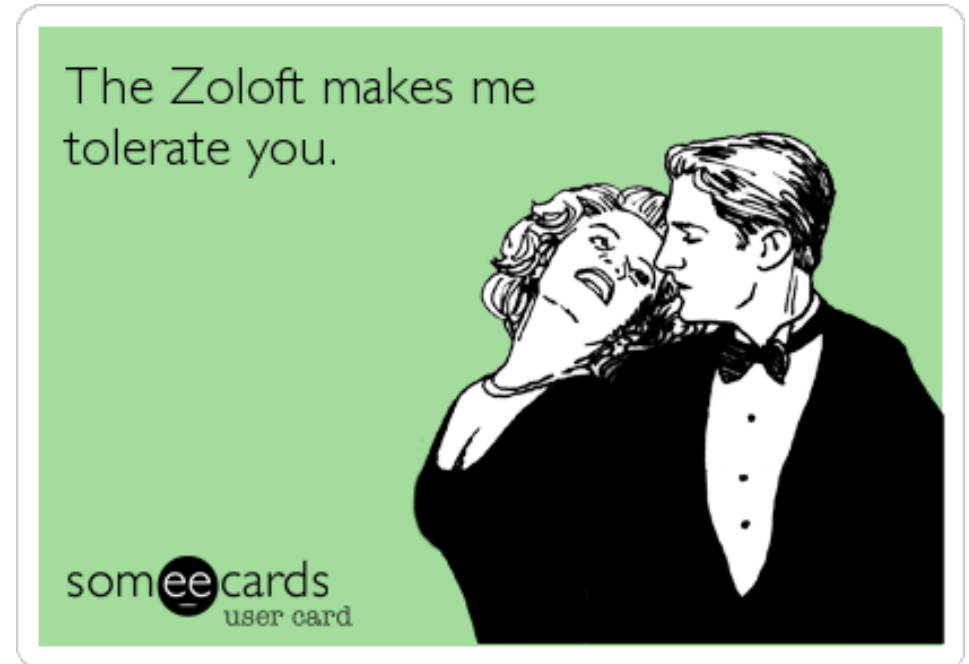
- SSRI – Selective Serotonin Reuptake Inhibitors
 - Fluoxetine (Prozac) first of these agents (1986)
 - Revolutionized depression therapy
 - Still widely used
 - Safer in overdoses
 - Long half life – stays active in body for several weeks



Medication treatments- depression



- SSRI – Selective Serotonin Reuptake Inhibitors
 - Sertraline (Zoloft) introduced 1991
 - Shorter half life
 - Less agitation
 - Excellent for anxiety and irritability
 - Fewer drug interactions





Medication treatments- depression

- SSRI – Selective Serotonin Reuptake Inhibitors
 - Paroxetine (Paxil) 1993
 - Shortest half life
 - Good for anxiety
 - Sexual side effects are problematic
 - Severe discontinuation
 - Mildly sedating

Medication treatments- depression



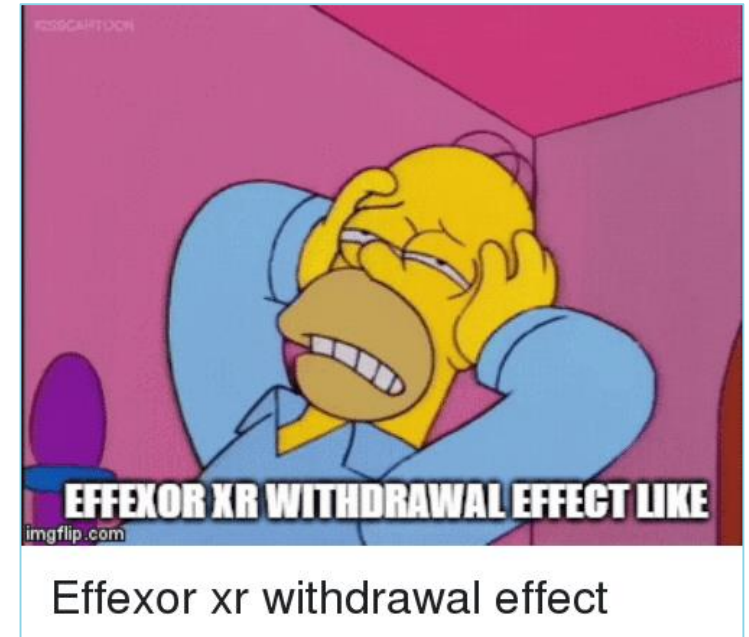
- SSRI – Selective Serotonin Reuptake Inhibitors
 - Citalopram and Escitalopram
 - Formerly Pfizer compounds
 - Heavily marketed to PCP
 - Studies least robust – approved when pharma allowed to “sunset” negative studies
 - FDA studies not designed to assess whether one antidepressant is better than another but whether a drug is effective



Medication treatments- depression



- SNRI
 - Venlafaxine (Effexor)
 - Duloxetine (Cymbalta)
 - Act like SSRI at lower doses
 - Invoke norepinephrine at higher doses
 - Venlafaxine - has severe discontinuation syndrome
 - Duloxetine – shown to be helpful in chronic pain



Medication treatments- depression



- Bupropion
 - Wellbutrin
 - Energy enhancing
 - Easily added to combinations of medications
 - Few side effects
 - Can impair sleep
 - Associated with seizures in patients with bulimia
 - Primary mechanism via dopamine



Medication treatments- depression



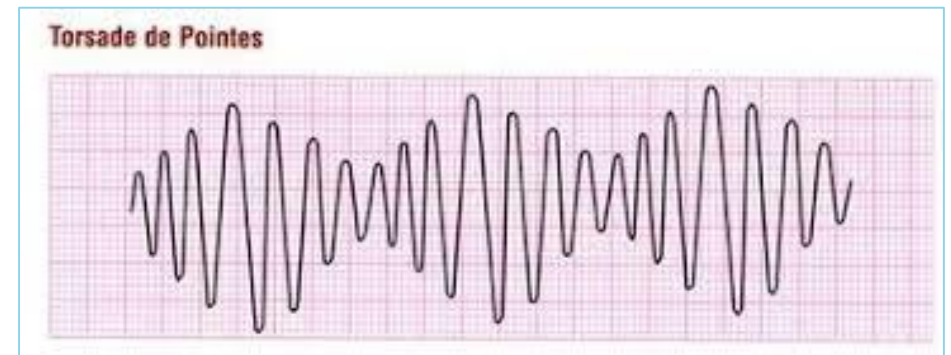
- Mirtazapine
 - Remeron
 - Unique direct effect of serotonin and norepinephrine
 - Increases appetite
 - Can be sedating
 - Useful in geriatric depression with features of anorexia



Medication treatments- depression



- Tricyclics (TCA's)
 - Had been mainstay
 - Side effects as are “dirty” drugs
 - Risky in OD – cardiac dysrhythmia and seizures
 - Low doses helpful for sleep and headache prophylaxis
 - Common agents
 - Amitriptyline; Imipramine
 - Nortriptyline; Despiramine



Medication treatments- depression



- MAOI
 - Inhibit the breakdown of all monoamines
 - Effective
 - Among earliest antidepressants
 - Not widely used due to dietary restrictions
 - Cannot consume foods with tyramine as can cause hypertensive crisis



Medication treatments- depression



- Newer antidepressants
 - Last 5 years
 - Trintellix (Vortioxetine)—supercharged SSRI
 - Vybriid (Vilazodone)—Trazodone-like but not as sedating
 - Fetzima (Levomilnacitran)—SNRI with possibly fewer side effects
 - Most health plans either not on formulary or require step therapy

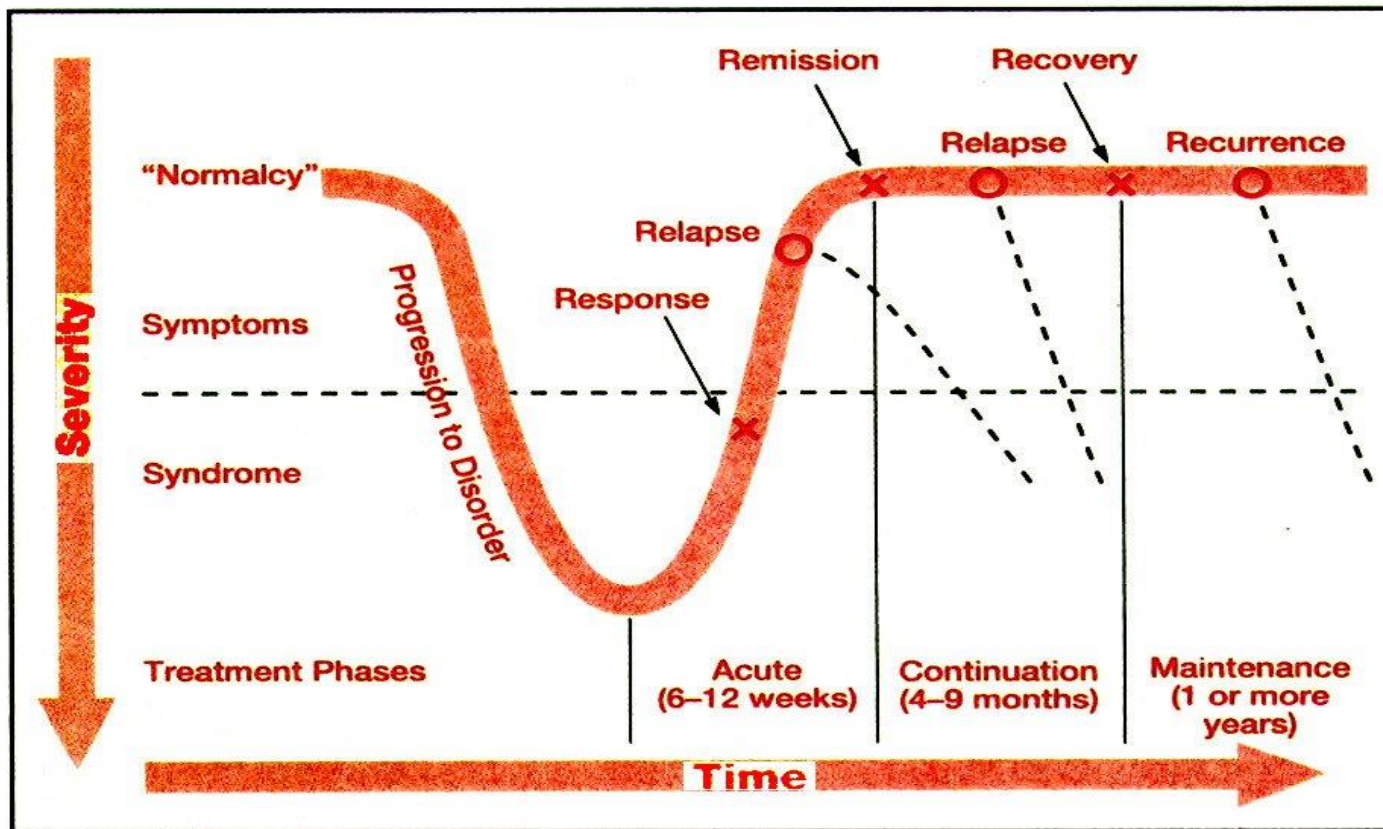


Medication treatments- depression



- Adjunctive and novel agents
 - Lithium
 - Aripiprazole/Lurasidone/Quetiapine
 - Thyroid hormone
 - Estrogen
 - Lamotrigine
 - SAM-e—regulates hormones/natural
 - Ketamine—
 - Controversial
 - Old animal sedative
 - Repair from cortisol damage

Odds
'n'
Ends



5. Phases of treatment of major depression. (Source: Kupfer DJ: Long-term treatment of depression. J Clin Psychiatry 1991; 52(Suppl 5):28-34). Copyright 1991, Physicians Postgraduate Press. Adapted and reprinted with permission.)



Non-medication biologic treatments - depression

- Electroconvulsive therapy
 - Used since 1930's
 - Controlled seizure induced under anesthesia and muscle relaxant
 - Can be performed either one sided or two sided
 - One sided may leave fewer memory problems
 - No absolute contraindications for ECT
 - Some psychiatrists quick to pull the trigger
 - Helpful for elderly with weight loss and agitation
 - Mechanism unknown—phosphoinositol in neuron membranes



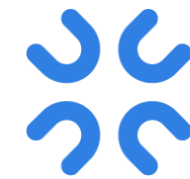


Non-medication biologic treatments - depression

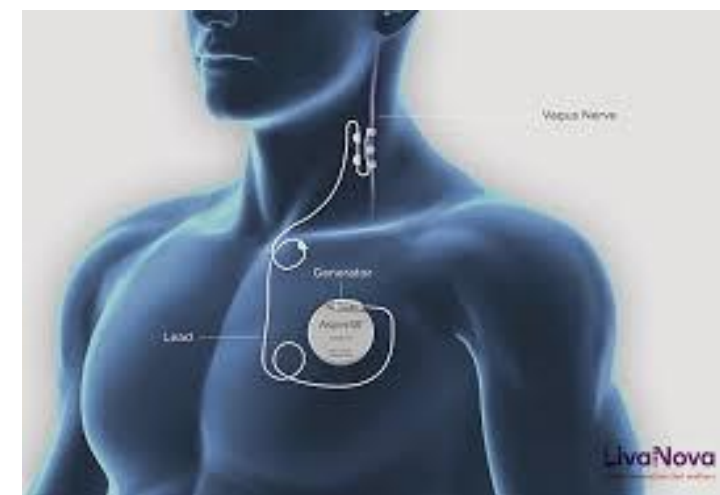
- rTMS—Reverse transcranial Magnetic Stimulation
 - Less invasive than ECT
 - Office based
 - Placing brain in magnetic field
 - Data is weak—strongest data is from Neurostar, its inventor
 - Equipment cost \$75K, so some may be anxious to reap ROI
 - Strict criteria for authorization from CMS



Non-medication biologic treatments - depression



- Vagal Nerve Stimulaton (VNS)
- Surgical procedure
- Like a pacemaker in upper chest
- Delivers pulses to vagus nerve (1-12 cranial nerves)
- Unknown reason why alleviates depression
- Many Commercial plans have authorized as last report
- New CMS NCS 18-002 provides avenue for use in MC



Psychotherapy



- Very valuable tool
- Studies show that psychotherapy together with medications yield best results
- School of therapeutic thought less important than ability to build rapport
- Some therapies more structured than others
- Types of therapy
 - Psychodynamic—requires motivation and capacity for insight
 - CBT—more like rote memorization
 - Interpersonal therapy—a riff on CBT in certain ways

