

Major Depressive Disorder: Neuropsychiatry and Psychopharmacology

Overview

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- What is Depression?
 - Diagnosis & Etiology
- How do I Assess for Depression?
 - The tools
- Treatment
 - Medication:
 - *How do I choose?
 - and beyond

What is Depression?

Diagnosis of Major Depressive Disorder

- Either or Both 1 and 2
 1. Mood: sad – dysphoria
 2. Anhedonia – lack of pleasure/interest
- Four or more
 - Neurovegetative
 - Appetite/wt change
 - Disturbed sleep
 - Psychomotor agitation/retardation
 - Low NRG
 - Poor concentration
 - Thought Content
 - Guilt/worthless
 - SI
- Function: dysfunctional
- Duration: Two weeks
- Exclusion:
 - Not due to GMC or Substance abuse
 - No Manic History
- Severity
 - Mild
 - Moderate
 - Severe with or without psychosis
- Longitudinal
 - Full or partial remission
 - Chronic
 - Interepisode recovery
- Features
 - Psychotic
 - Melancholic
 - Catatonic
 - Atypical
 - Post Partum onset
 - Season onset
 - Premenstrual Dysphoric d/o
 - MDD NOS

What is Depression?

Secondary Depression: Medical Etiology

- Endocrine
 - Thyroid
 - Cushing's
- Neurologic
 - MS
 - Epilepsy
 - Parkinson's: 40%
 - Huntington's
 - Alzheimer's: 20-50%
- Cardiac
 - Stroke: 30-60%
 - MI
 - CHD: 8-44%
- Cancer: 1-40%
 - Brain Tumors
 - Pancreatic
 - Paraneoplastic
- Hematology
 - Anemia
- Immune
 - AIDs
 - SLE
- Head Injury
- ID
 - UTI
 - Pneumonia
- GI (brain-gut)
 - Vitamin Deficiency
 - Vit D, B12, Mg



What is Depression?

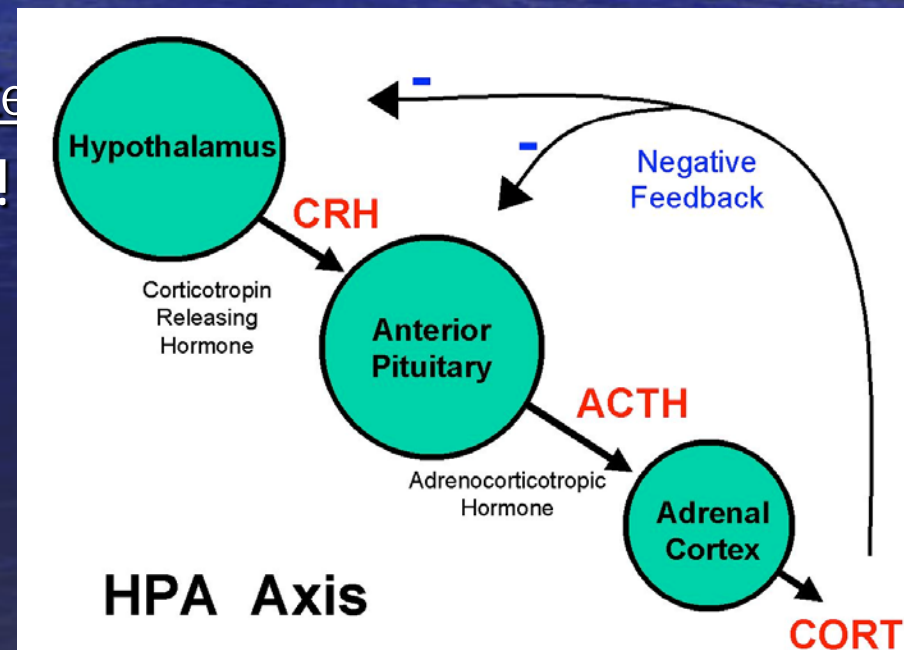
Secondary Depression: Medication Etiology

- Acyclovir
- Anabolic steroids
- ACE inhibitors
- Anticonvulsants
- Baclofen
- Barbiturates
- Benzodiazepines
- B-Blockers
- Bromocriptine
- Calcium channel blockers
- Ciprofloxacin
- Clonidine
- Corticosteroids
- Digitalis
- Disulfiram
- Estrogen
- Guanethidine
- H₂ receptor blockers
- Interferon a
- Interleukin-2

What is Depression?

Etiology of Primary Depression

- Genetics: 2-3x with relative
 - Twins 50% monozygotic (20% dizygotic)
- Hypothalamic-Pituitary-Adrenal Axis Dysregulation:
 - Overactivity
 - High Cortisol
 - Depression is a high stress state
 - Negative Feedback Impaired!
 - Dexamethasone Suppression test (DST) – non suppression!



What is Depression?

Etiology of Primary Depression

- Neurotransmitters:

Monoamine Theory of Depression

- Serotonin - Low

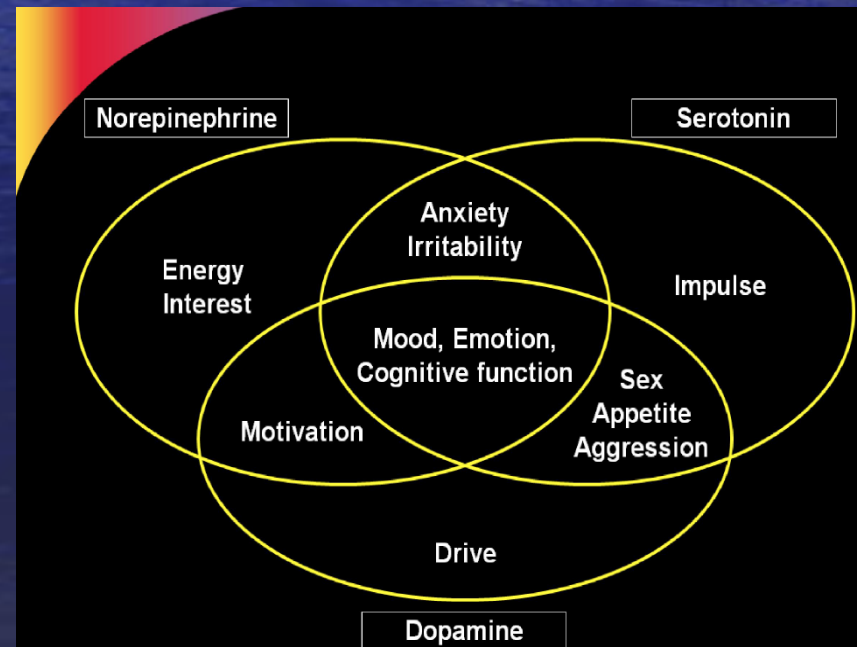
- Low P11 in depression: intracellular protein that recruits 5HT1b receptors to neuronal surfaces. All AD and ECT (TMS?) increase P11! Common pathway?

- Low CSF serotonin
 - seen in pts after suicide

- Norepinephrine - Low

- Dopamine – variable

- BDNF, etc

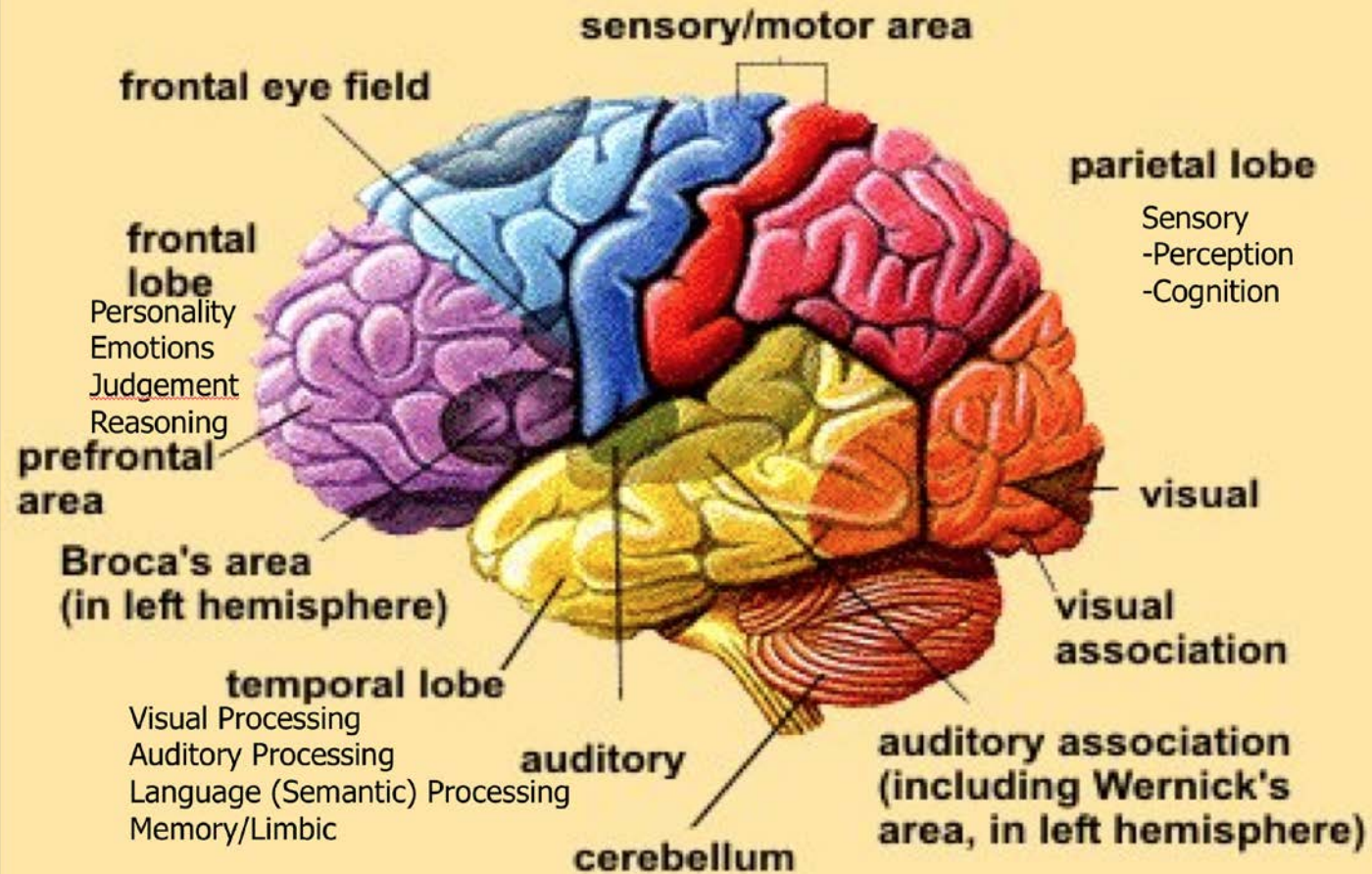


What is Depression?

Etiology of Primary Depression

- Brain Disease!
 - Neuroanatomy
 - Function

The Lobes of the Brain

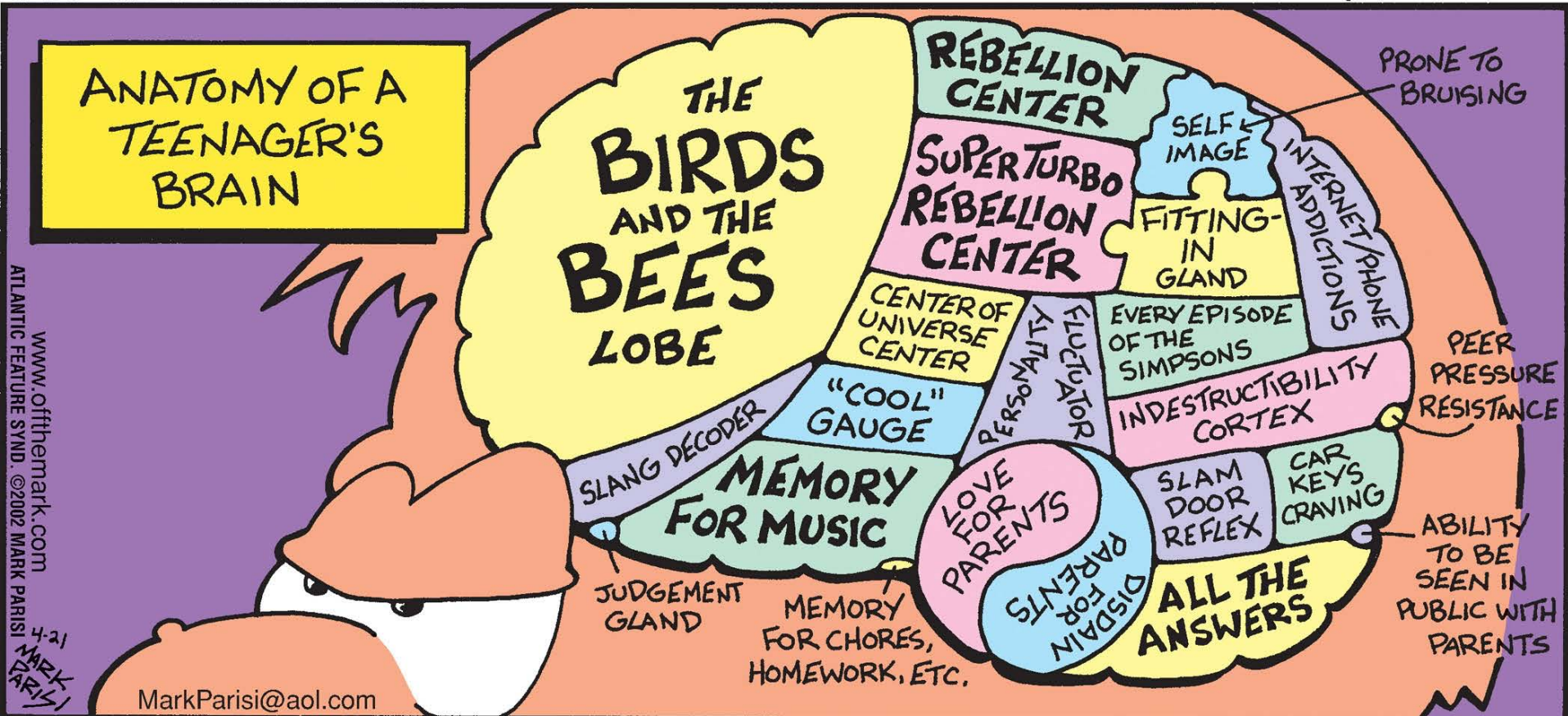


Functional Neuroanatomy Teenagers

off the mark.com

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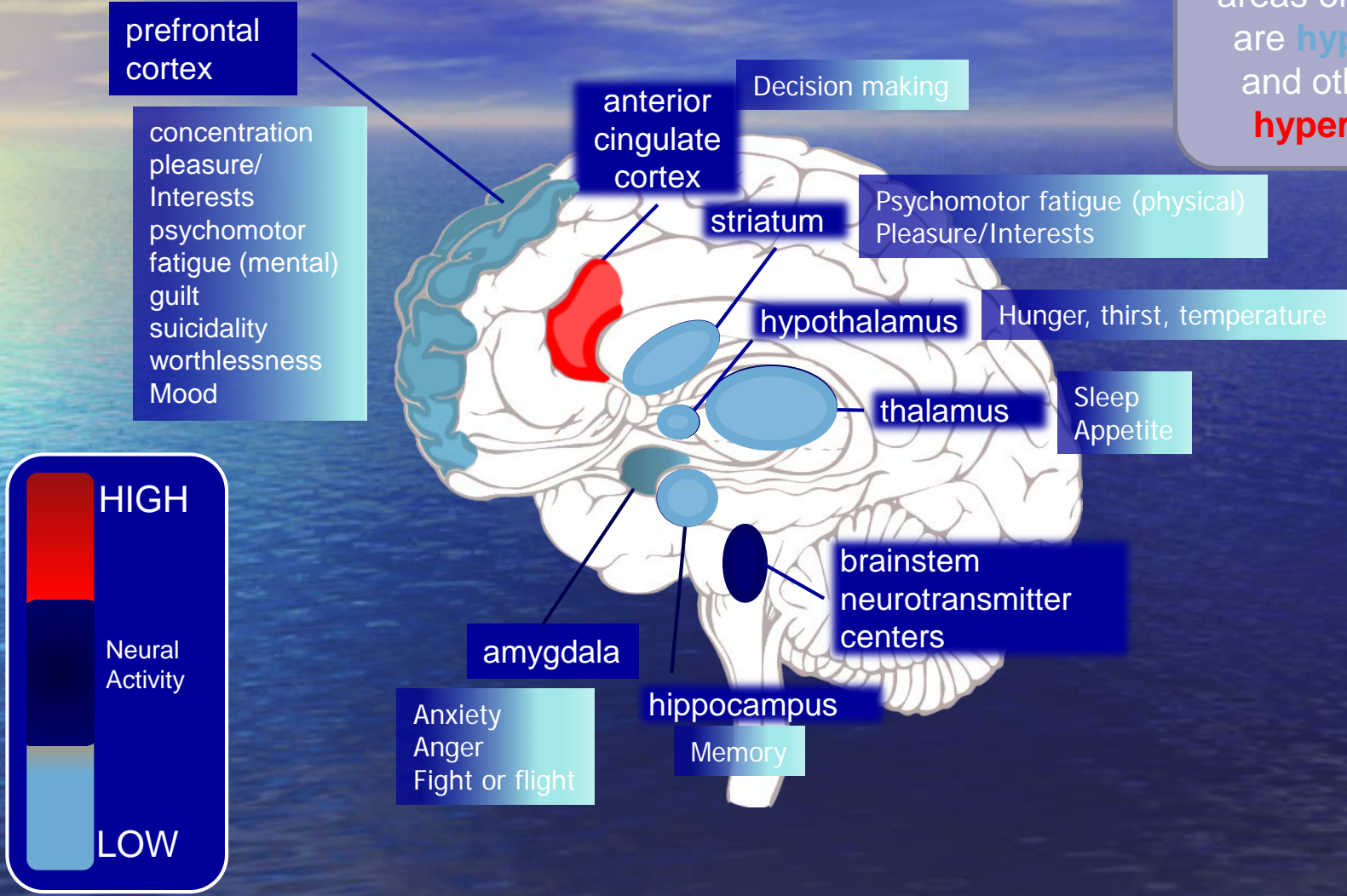
by Mark Parisi



What is Depression?

Etiology of Primary Depression

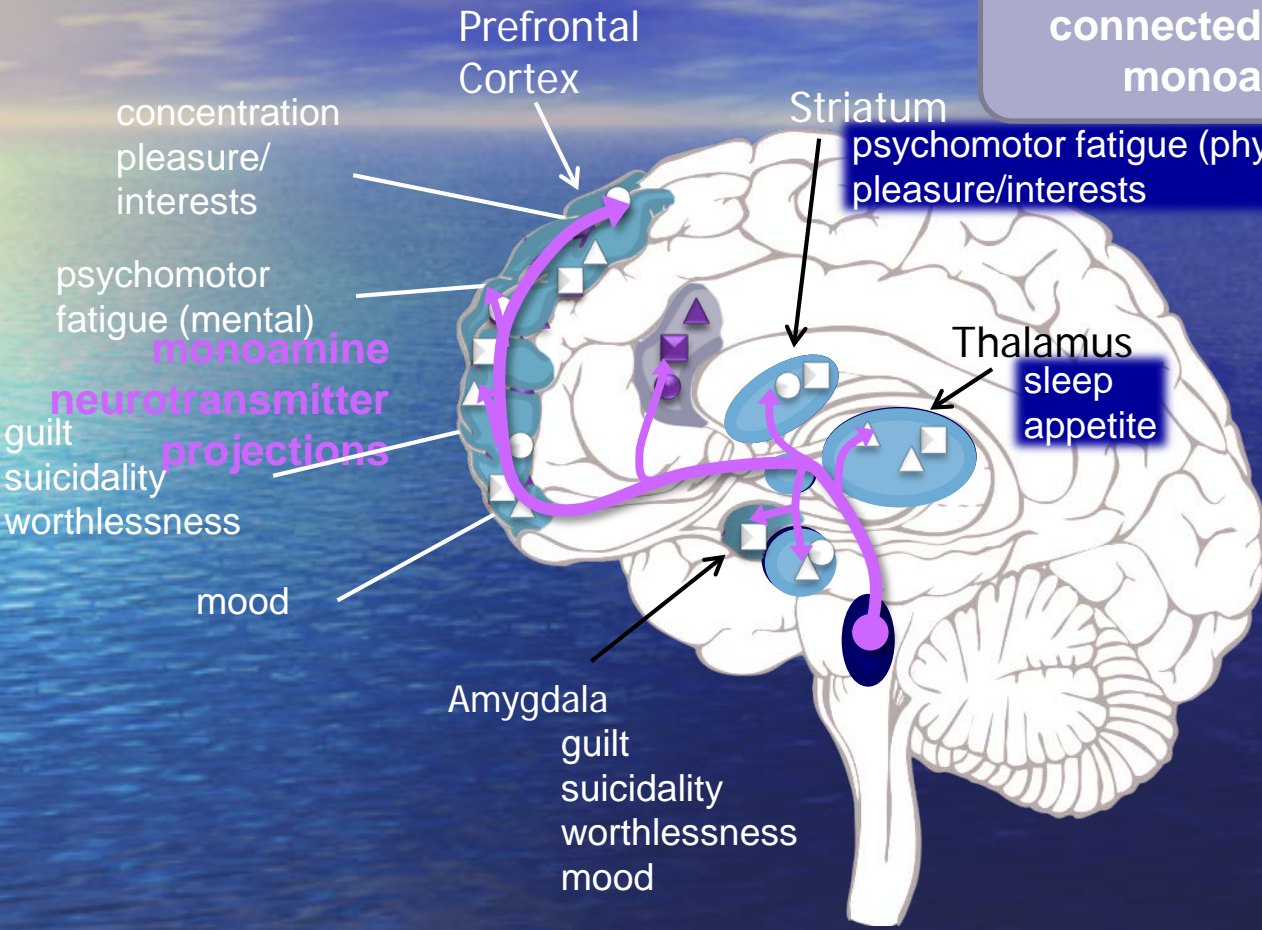
In MDD, some areas of the brain are **hypoactive** and others are **hyperactive**.



What is Depression?

Etiology of Primary Depression

Regions implicated in MDD are connected to the brainstem via monoaminergic circuits



- Monoamine dysfunction is linked to MDD
- Malfunctioning circuits lead to specific symptoms

Monoamine Neurotransmitters

- Serotonin (5-HT)
- Dopamine (DA)
- ▲ Norepinephrine (NE)

How do I assess for depression?

Listen and Ask

Descriptions of depression: patient/parent report

- Irritable and aggressive
- Somatic complaints: Headache/aches & pains
- Sleep problems: initial – middle - terminal
- Just don't feel like doing anything – no longer interested, Withdrawn
- Not interested in romantic relationships/decreased sex drive
- Crying spells without reason
- down/blue/worthless/hopeless
- Anxious/worried
- Attention issues: ADHD misdiagnosed
- Like a weight on my shoulder

Most Important Description: **CHANGE** *That is persistent*

1 question: "What has changed" behaviorally or Emotionally?

How do I asses for depression?

Screening tools

- Phq: Patient Health Questionnaire – free in 30 languages
www.phqscreeners.com/
 - Phq 2 – limited screener (first 2 question of Phq 9 – if positive, move to Phq 9)
 - Phq 9 – MDD sensitivity and specificity of 88% in primary care setting
 - GAD 7 – anxiety
 - Full Phq – multiple disorders (including somatoform)
- ADHD: Vanderbilt screening tool
- Mchat: Modified Checklist for Autism in Toddlers
 - M-chat.org

How do I asses for depression?

Biologically:

- Physical Exam

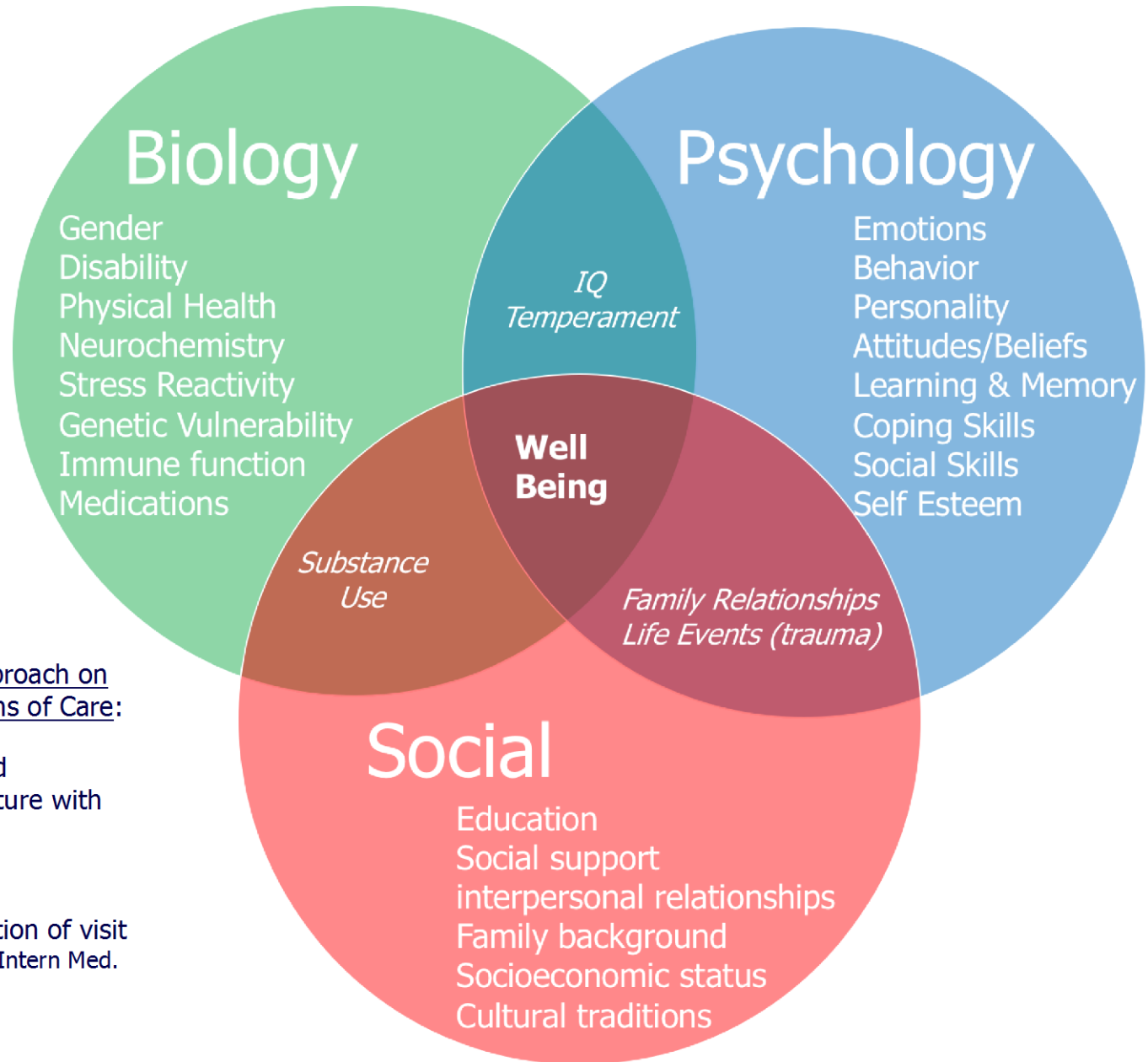
- CV: murmurs, Peripheral
- Neuro:
 - Frontal release signs
 - Neurodegenerative
 - Focal Signs – Neurovascular
- Endocrine: goiter, skin, hair, BP

- Review Meds

- Laboratory/Studies

- CBC, CMP
- TSH/FT4
- B12/Folate
- Vitamin D
- RPR, HIV
- Urine Tox, UA
- EKG
- Sleep Study
- MRI/CT

Bio-Psycho-Social Approach to Health



Effect of a Biopsychosocial Approach on Patient Satisfaction and Patterns of Care:

Results:

- Patient satisfaction improved
- Reduce health care expenditure with fewer labs ordered
- Reduced number of medications prescribed
- No significant increase duration of visit

Alon P A Margalit, MD, PhD, J Gen Intern Med.

2004 May; 19(5 Pt 2): 485-491

Treatment Basics: BIO-PSYCHO-SOCIAL

- Social
 - Relationships, family, friends, clubs, events, religion,
- Psychological
 - Stressors
 - Psychotherapy
- Biological
 - Diet, Vitamins (D, B12)
 - Physiologic: thyroid, etc.
 - Medication
 - Neuromodulation
 - Alternatives: acupuncture, others (careful!)

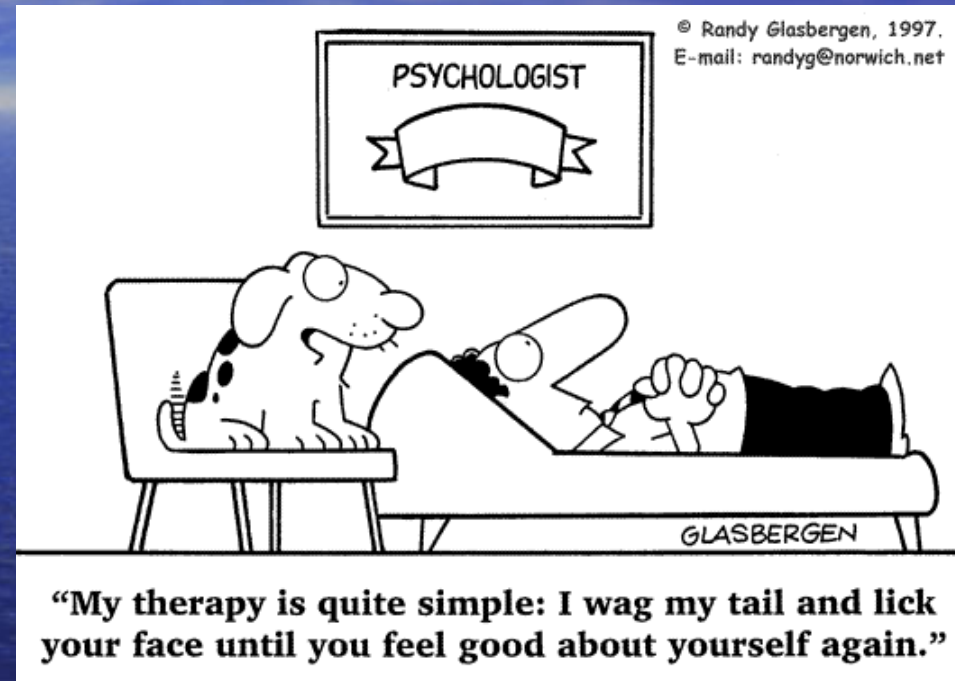


- Exercise – The Antidepressant
 - BDNF (brain derived neurotrophic factor)
 - Stimulates pluripotent brain cells in ventricles to differentiate and direct migration in brain
 - SSRI’s, SNRI’s and **EXERCISE** turn on/stimulate BDNF directed migration to hippocampus and mood centers!!!
 - Amount: 20-30min x 3days a week (AAP)
 - Types: non impact aerobic (AAP):
 - Bicycle, swim, elliptical/ski, Rowing!

Treatment: Therapies

Evidence Based Therapies:

- Cognitive Behavioral Therapy
 - Dialectic Behavior Therapy
- Interpersonal Therapy
- Psychodynamic Therapy (psychoanalytic)
- Group Therapy
- Family/Couples Therapy
- Play Therapy
 - Children use toys/games express feelings and communicate
- Expressive Therapy: Art/Music/Dance
- Animal/Equine Assisted Therapy
- EMDR = Eye Movement desensitization and Reprocessing
 - INDICATIONS! PTSD



Treatment: Antidepressants

- SSRI's (Serotonin)
 - fluoxetine (Prozac)
 - Stim, PMDD, 21 days
 - sertraline (Zoloft)
 - GI se, few Rx-Rx, neutral nrg
 - escitalpram (Lexapro)
 - Anxiety, social anxiety, fast(?), withdrawal syndrome risk, headache
 - citalopram (Celexa) –
 - QT issues, sedating, GI
 - paroxetine (Paxil)
 - Sedating (anxiety and insomnia), anxiety/social anxiety, Short Half Life (hard to get off), worst se (sedation, wt gain, sex, dysf, antichol)
 - fluvoxamine (Luvox)
 - OCD, anxiety, ruminations, short half life

Treatment: Antidepressants

- SNRI's (Norepinephrine)
 - Effexor (venlafaxine)
 - BP, Hot flashes tx, stimulating
 - Cymbalta (duloxetine)
 - Pain (neuro?), Dosing 60-120mg
 - Pristiq (desvenlafaxine)
 - Energy
 - Strattera (atomoxetine)
 - Doesn't help depression, but can cause mania

Treatment: Atypical Antidepressants

- Wellbutrin (bupropion)
 - DA and NE
 - Depression
 - Not anxiety
 - Augmenting - poop out
 - Side Effects: Agitation, Insomnia, Increase risk of seizures, energy
 - Black Box: sz in eating disorder
 - Increase risk of binge episodes
- Trazodone
 - 5-HT receptor antagonist
 - MDD, Sleep
 - Dual metabolism
 - Side Effect: Priapism
- Remeron (mirtazapine)
 - NE and 5-HT₂,₃ antagonist
 - Alpha 2 adrenergic presynaptic antagonist inc release presynaptic monoamines
 - H₁ antagonist
 - Sedation and wt gain
 - Atypical depressions
 - Augmentation
- Buspirone
 - Serotonin 1A partial agonist serotonin stabilizer
 - Anxiety + Treatment resistant depression
 - Effects: immediate/LT

Treatment: Tricyclic Antidepressants

- Uses: melancholic mdd, refractory depression, pain, fibromyalgia, migraine, ADHD, anxiety, panic, OCD
- Mechanism: 5HT and NE Reuptake inhib
 - Anticholinergic, antimuscarinic, alpha1 block (BP), antihistaminic
- Tertiary TCA' s: more sedating
 - Imipramine, amitriptiline
 - Clomipramine (most serotonergic, OCD gold standard)
 - Doxepin (most antihistaminic – sedating)
 - Amytriptiline (sleep)
- Secondary TCA' s: more selective for NE, fewer se
 - Nortriptiline (therapeutic window)
 - Desipramine

Treatment: Tricyclic Antidepressants

- Tricyclic
 - Anticholinergic side effects
 - Constipation, urinary retention
 - CV: increased PR, QRS, QTc intervals and AV block
 - Overdose: lethal
 - Quinidine like conduction delay → prolonged QT → VT, torsades de point

Black Box Warning for Antidepressants

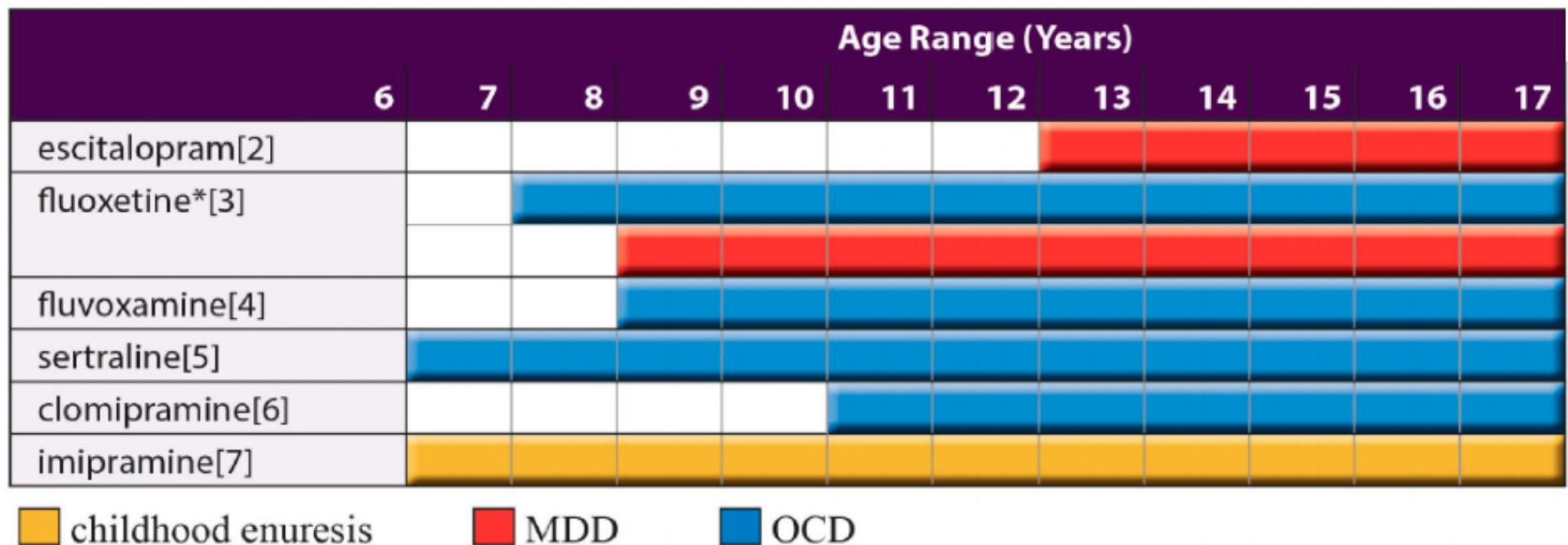
- FDA: 2004 SSRI's and broadened to all antidepressants in 2007
 - Black box warning for antidepressants
 - Increased risk of “*suicidal behavior*” = thoughts/actions = “suicidality”
 - **NOT** increase risk of suicide (completion)
- Basis of warning
 - Review of studies with 4400 youth on antidepressants
 - All short term studies – only up to 4 months
 - “Suicidal Behavior” –
 - NO ONE COMPLETED SUICIDE
 - Rates 4% on antidepressants...2% on placebo! Statistical risk
- Consequences of warning
 - Antidepressant use went down
 - Completed suicide rates increased
- Subsequent information
 - Longer term larger studies have shown decrease in completed suicides in patients taking antidepressants

Treatment: Choosing a medication

- FDA

❖ Paediatric

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Antidepressant Medications



*Fluoxetine is FDA approved for the treatment of MDD in pediatric patients up to 18 years old.

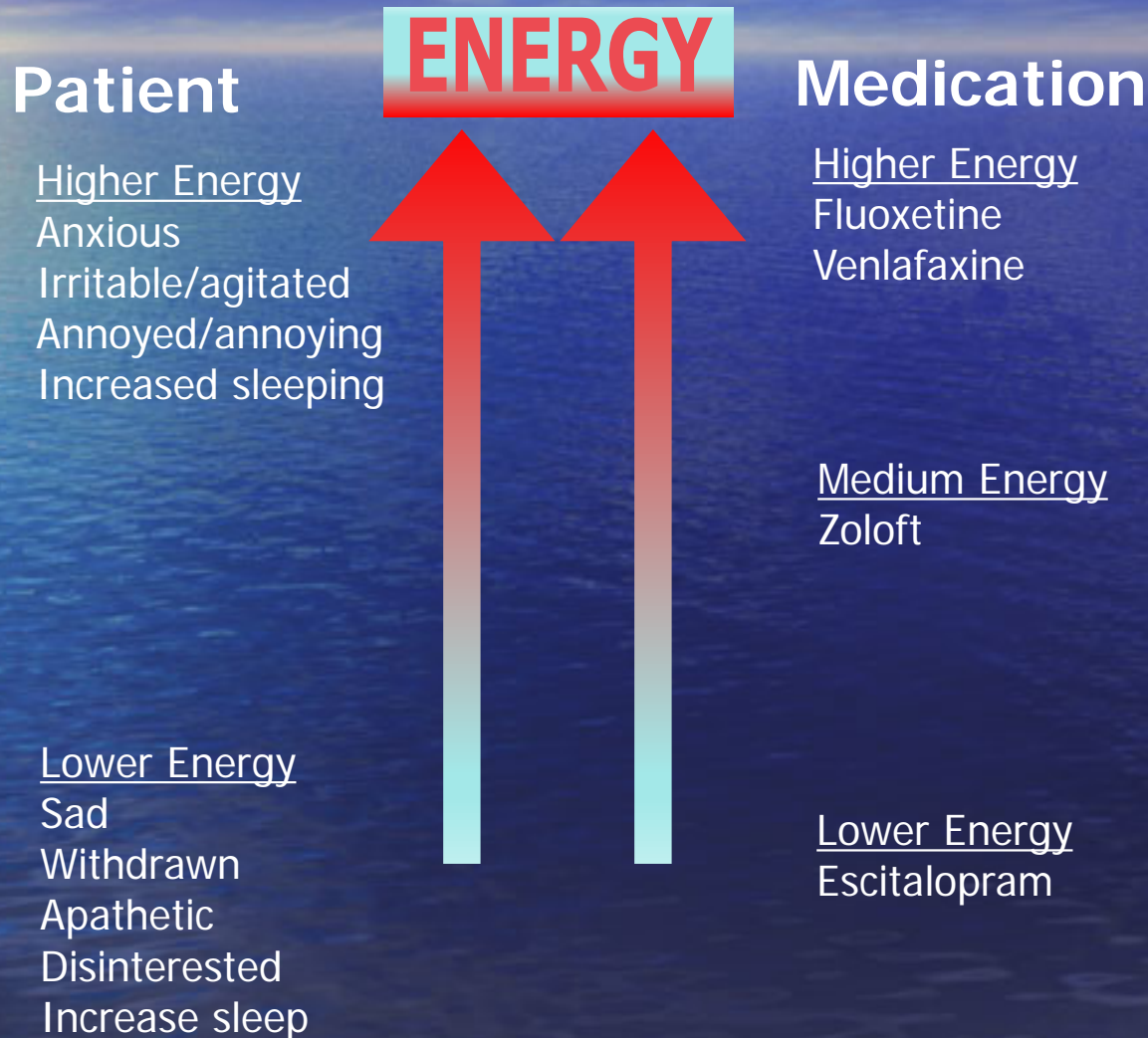
- Characteristics of the medication:

- Pharmacokinetics: $T_{1/2}$ - fluoxetine
- Pharmacodynamics: Rx-Rx interactions - sertraline

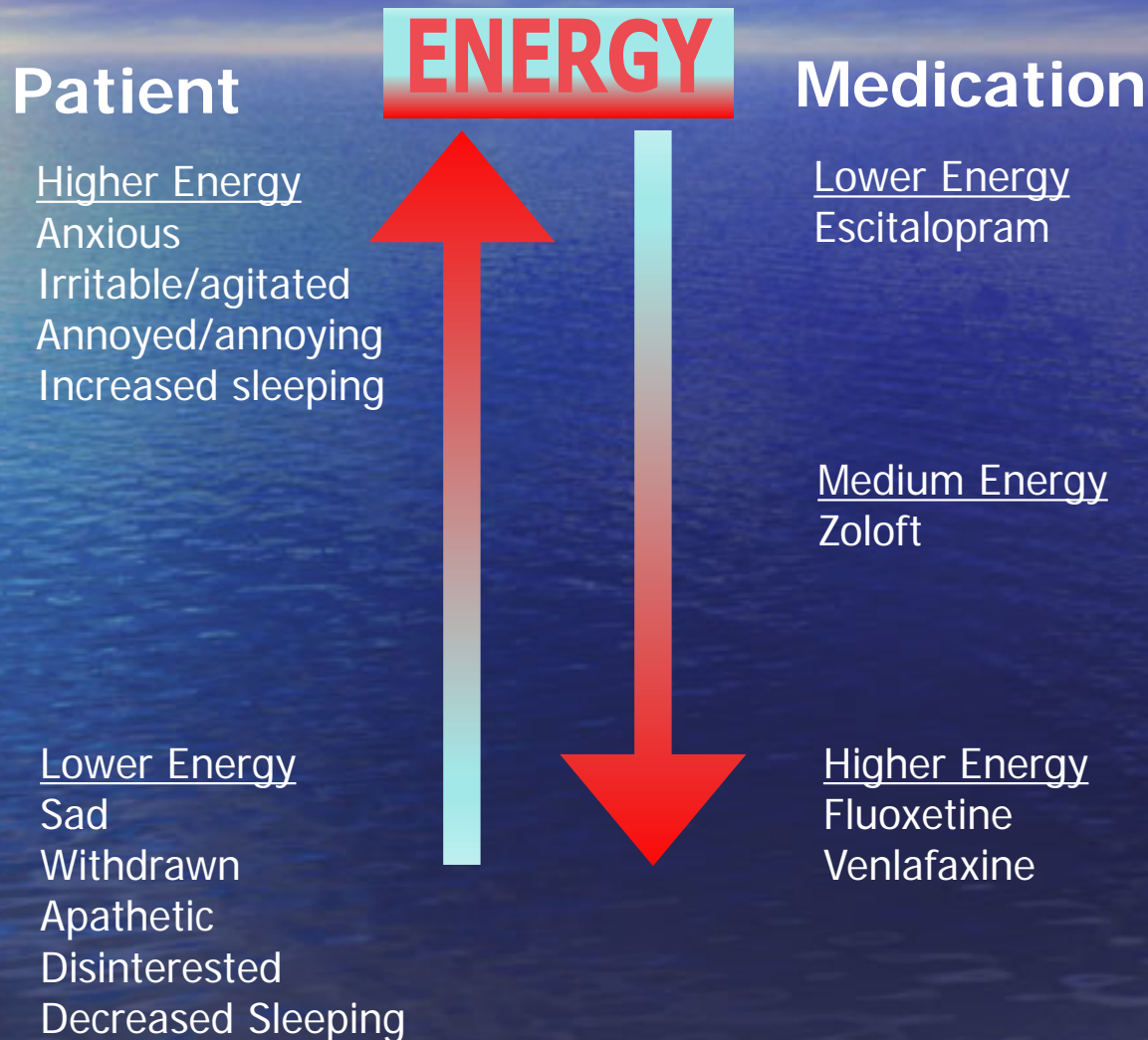
Choosing a medication

- Other uses for medication: Diagnosis
 - PMDD - fluoxetine
 - Anxiety – escitalopram, paroxetine
 - OCD - fluvoxamine
 - ADHD – TCA
 - PTSD – sertraline, citalopram
- Side Effects: Use them to your advantage
 - Urinary retention: tx Eneuresis – TCA
 - Increase appetite: tx Poor appetite - remeron
 - Fatigue: tx Sleep – TCA, escitalopram
 - Analgesic: tx Pain – duloxetine, TCA
 - Energy: low-high-med

Choosing a Medicine: **ENERGY** Goldilocks Approach



Choosing a Medicine: **ENERGY** Goldilocks Approach



Reasons Medications Don't Work

1. Not on a high enough dose
2. Not on medication long enough
3. Not taking medication
4. Not treating the problem
 - When did it start?
 - **What happened right before it started
 - Bio-Psycho-Social

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" My parents are divorced, both remarried, I have six new siblings, one bathroom, a new school, and I'm doing very nicely, thank you. "

Augmentation Strategy

- Antidepressant
 - Bupropriion (Wellbutrin)
 - Remeron
 - Buspirone
- Atypical Antipsyhotics
 - aripiprazole (Abilify)
 - brexpiprazole (Rexulti)
 - quetiapine (Seroquel)
- Salt: Lithium
- Thyroid Hormone
- Anticonvulsants
 - Depakote (valproate)
 - Lamictal (lamotrigine)
 - Tegretol (carbamazepine)
 - Trileptal (oxcarbazepine)

Augmentation Strategies

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Atypical Antipsychotics



■ schizophrenia ■ bipolar I disorder: manic or mixed ■ irritability with autistic disorder

* Risperidone should not be used by patients older than age 16 who have been diagnosed with irritability with autistic disorder.

Beyond Antidepressants: Treatment When Standard Medicine Fails or is NOT an Option

NEUROMODULATION

Neuromodulation:

- * stimulation of various nerves in the CNS, PNS, autonomic nervous system, or deep cell nuclei of the brain that lead to the "modulation" of its activity.
- * therapeutic alteration of activity through stimulation or medication via various implanted devices.

TMS: Transcranial Magnetic Stimulation

ECT: Electroconvulsive Therapy
Anesthesia
1/10,000 death rate
Side Effect: memory loss

DBS: Deep Brain Stimulation
Brain Surgery

VNS: Vagus Nerve Stimulation

Ketamine

COMPLEMENTARY TREATMENTS

- Light therapy
- Omegas 3 fatty acids
- SAM-e
- St. John's Wort



THE END

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The End

LIGHT THERAPY

- For seasonal depression but also data for nonseasonal depression and perhaps as adjunctive tx
- Bigger is better (covers larger area of retina)
- 10,000 lux and 12 inches distance
- 40 minutes per day or less, preferably in the morning
- Monitor for hypomania

Omega 3 Fatty Acids

- Omega-3 fatty acids do *something*, at least in some people
- Best evidence for augmentation and mild to moderate depression – NOT severe
- Combo of EPA + DHA in 2:1 or 3:2 ratio
- 1-2 total grams per day
- Risks are minimal
- heart benefit
- (maybe for arthritis)
- Fish burps can be managed easily
- Can take up to 1-2 months to see benefit

S-Adenosyl-L-Methionine (SAM-e)

- MDD: monotherapy and adjunctive
 - (SAM-e) > placebo and = TCAs in MDD both for monotherapy and adjunctive tx
- Generally well tolerated, fewer side effects than TCAs
- Dosing:
 - PO (1600 mg/d)

SAM-E

- **Mechanism:** the methyl group donor for a number of substrates, most notably for phospholipids, DNA, RNA, neurotransmitters, and proteins.
 - methylating plasma phospholipids, SAM-e may alter the fluidity of the neuronal membrane
 - SAM-e may exert antidepressant effects via DNA methylation by influencing the transcription of DNA.
 - An increase in SAM-e may result in increased synthesis of the neurotransmitters thought to be deficient in patients with MDD
 - **Side Effects:** GI symptoms, headaches, anxiety, irritability, fatigue, and sedation. No significant changes in weight or increases in the severity of sexual dysfunction

St Johns Wort

- Active components: hypericin and/or hyperforin
- Both may inhibit the reuptake of serotonin, norepinephrine, and dopamine
- Other neurochemical effects have been suggested as well
- Usual dose is 300 mg TID
- 30 randomized, double blind controlled trials have shown antidepressant efficacy, but most of these were published in European journals. U.S. trials have been mixed. Recent meta-analyses less positive.

St. John's Wort

- Fewer side effects than meds?
- Risk of mania, serotonin syndrome, GI, photosensitivity
- MAOI like interactions
- P450 3A4 inducer

Major Depressive Disorder

- Epidemiology

- Lifetime Prevalance of 16-19%

- Major depression affects an estimated 2.5% of children and 8.3% of U.S. adolescents. These rates account for approximately 2.6 million youth ages 6 - 17

- Age of Onset 29

- Female:Male = 1.4:1

- Suicide 10-15%

- Comorbidity: Triad

- MDD

- Anxiety – 59%

- Substance Abuse – 24%