Major Depressive Disorder: Neuropsychiatry and Psychopharmacology

Overview

• 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

- **‘Turns out I wasn’t depressed, I just needed to be wound.’”**

- **Other**
  - 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 α
- 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 supression!
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

- Parietal lobe: Sensory Perception, Cognition
- Frontal lobe: Personality, Emotions, Judgement, Reasoning
- Prefrontal area
- Broca's area (in left hemisphere): Language (Semantic) Processing, Memory/Limbic
- Temporal lobe: Visual Processing, Auditory Processing
- Auditory association (including Wernicke's area, in left hemisphere)
- Sensory/motor area
- Frontal eye field
ANATOMY OF A TEENAGER'S BRAIN

THE BIRDS AND THE BEES LOBE

MEMORY FOR MUSIC

REBELLION CENTER

SUPER TURBO REBELLION CENTER

CENTER OF UNIVERSE CENTER

"COOL" GAUGE

SLANG DECODER

JUDGEMENT GLAND

MEMORY FOR CHORES, HOMEWORK, ETC.

LOVE FOR PARENTS

DISPLAY PARSON

DISPAIN PARSON

ALL THE ANSWERS

SELF IMAGE

FITTING-IN GLAND

INTERNET/PHONE ADDICTIONS

CAR KEYS CRAVING

EYES PRESSURE RESISTANCE

ABILITY TO BE SEEN IN PUBLIC WITH PARENTS

PRONE TO BRUISING

EVERY EPISODE OF THE SIMPSONS

INDESTRUCTIBILITY CORTEX

SLAM DOOR REFLEX

MARK PARISI

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In MDD, some areas of the brain are hypoactive and others are hyperactive.
When there is an appropriate amount of monoamine neurotransmitter activity, neuronal activity throughout the brain functions normally.

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

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

### What is Depression?

#### Etiology of Primary Depression

**Monoamine Neurotransmitters**

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

**Symptoms**

- Concentration
- Pleasure/interests
- Psychomotor fatigue (mental)
- Guilt
- Suicidality
- Worthlessness
- Mood
- Sleep
- Appetite
- Psychomotor fatigue (physical)

**Regions implicated in MDD**

- Prefrontal Cortex
- Amygdala
- Striatum
- Thalamus
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 assess for depression?

Screening tools

• Phq: Patient Health Questionnaire – free in 30 languages
  [www.phqscreeners.com/](http://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 assess for depression?

Biologically:

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

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

- **Review Meds**
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

“My therapy is quite simple: I wag my tail and lick your face until you feel good about yourself again.”
Treatment: Antidepressants

- **SSRIs (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
  - **Pristique (desvenlafaxine)**
    - Energy
  - **Strattera (atamoxetine)**
    - 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 inhibit
  - 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

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<th>Age Range (Years)</th>
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- Childhood enuresis
- MDD
- OCD

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

- Charateristics 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

Patient

Higher Energy
Anxious
Irritable/agitated
Annoyed/annoying
Increased sleeping

Lower Energy
Sad
Withdrawn
Apathetic
Disinterested
Increase sleep

Medication

Higher Energy
Fluoxetine
Venlafaxine

Medium Energy
Zoloft

Lower Energy
Escitalopram
Choosing a Medicine: ENERGY
Goldilocks Approach

**Patient**
- Higher Energy
  - Anxious
  - Irritable/agitated
  - Annoyed/annoying
  - Increased sleeping
- Lower Energy
  - Sad
  - Withdrawn
  - Apathetic
  - Disinterested
  - Decreased sleeping

**Medication**
- Lower Energy
  - Escitalopram
- Medium Energy
  - Zoloft
- Higher Energy
  - Fluoxetine
  - Venlafaxine
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

"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**
  - Bupropion (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**

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- **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
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 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)
**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%