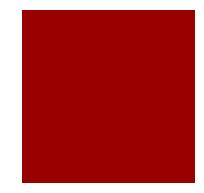
Treatment of Major Depressive Disorder

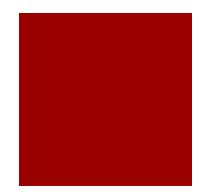
Sarah Mullowney, MD PGY3 Psychiatry Resident, University of Utah

Paula Gibbs, MD Medical Director of 5 West at UUMC Clerkship Director MS III Psychiatric Rotation Psychiatrist for Project ECHO



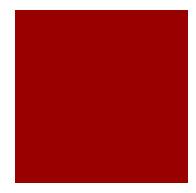
Why does depression matter?

- Affects more than 300 million people worldwide
- Leading cause of disability worldwide
- Can be associated with medical comorbidity
- Increased risk for suicide
- Treatable



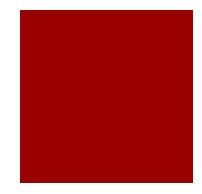
DSM-V Depressive Disorders

- Major depressive disorder
- Persistent depressive disorder
- Disruptive mood dysregulation disorder
- Premenstrual dysphoric disorder
- Substance/medication induced depressive disorder
- Depressive disorder due to another medical condition
- Unspecified depressive disorder



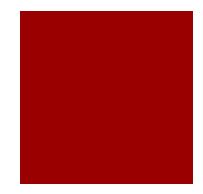
- A. Five or more of the following symptoms have been present during the same two week period and represent a change from a previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.
- Depressed mood nearly most of the day
- Markedly diminished interest or pleasure in all or nearly all activities
- Decrease or increased appetite or unintentional weight changes
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Worthless, useless, or excessively guilty feelings
- Decreased concentration or indecisiveness
- □Suicidal thoughts or recurrent thoughts of death

SIG E CAPS Sleep Interest Guilt Energy Concentration Appetite Psychomotor Suicidal thoughts



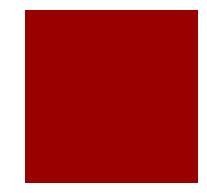
 B. These symptoms cause significant distress and impairment in social, occupational, or other areas of functioning.

 C. The episode is not attributable to the physiological effects of substance abuse or to another medical condition.

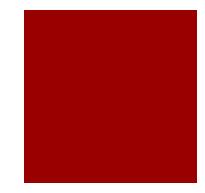


 D. the occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, delusional disorder or other psychotic disorders

 E. There has never been a manic episode or hypomanic episode

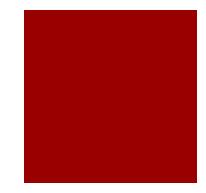


- Specify:
- With anxious distress
- With mixed features
- With melancholic features
- With atypical features
- With mood congruent psychotic features
- With mood incongruent features
- With catatonia
- With peripartum onset
- With a seasonal pattern



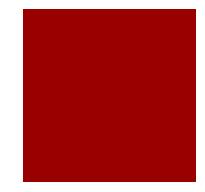
Epidemiology

- Lifetime Prevalence: 12% worldwide, 18% in the US
- Females: 10-25%
- Males: 5-12%
- Point Prevalence:
- Females 5-9%
- Males: 2-3%
- Mood disorders are highly prevalent and are among the top 10 causes of disability worldwide
- Risk factors associated with MDD: gender, stressful life events, adverse childhood experiences, certain personality traits and positive FH



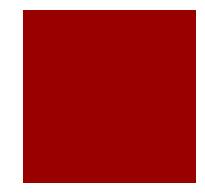
Clinical Course

- Mean age of onset: 29 years old
- Only 57% of patients with MDD seek help and mostly consult with PCPs
- Recurrent: 60-90% of MDD patients have 2 or more episode with partial or full interepisode remission
- Chronic: 20% of MDD patients have an episode of 2 years or greater in duration
- Mania: 5-10% of MDD patients have a subsequent manic or hypomanic episode(s)



Etiology of depression

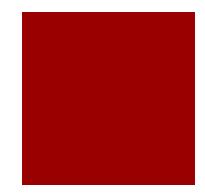
- Genetic
- Neurochemical
- Psychological traits
- Biological traits
- Environmental / Social factors



Etiology

Genetic:

- Twin studies: MZ concordance rates are in the range of 30-50% and DZ concordance rates are in the range of 12-40% (female>male twins)
- Twin adoption studies show 50-70% concordance for MDD in identical twins reared apart
- First degree relative with MDD increase the risk threefold to fourfold

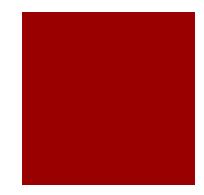


Neurochemical Basis of Depression

- Neurotransmitters implicated but not proven to have a role:
- Monoamines
 - Serotonin, Norepinephrine, Dopamine deficiencies
- GABA
- Glutamate
- HPA Axis implicated resulting in hypercortisolemia

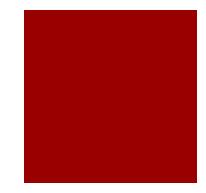
Biological Basis of Depression

- Comorbid medical problems
- Substances
- Medication



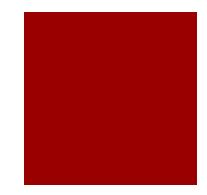
Psychological Factors

- Distorted and negative patterns of thinking
- Personality pathology
- Neuroticism
- Learned behaviors that reinforce depressive symptoms
- Self-esteem
- Management of losses and interpersonal relationships



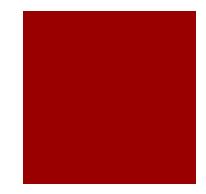
Social Basis of Depression

- Recent stressors
- Isolation
- Poor social support
- Depression in friends/family
- History of trauma, especially during childhood
- Parental loss
- Low parental warmth
- Marital problems
- History of divorce
- Low education



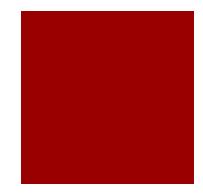
Treatment

- Psychotherapy
- Biological treatments:
- Medications
- ECT
- Vagal Nerve Stimulation
- Transcranial Magnetic Stimulation
- Combination treatment:
- Psychotherapy and biological treatment



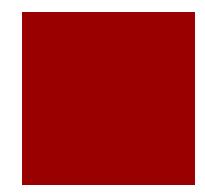
Psychotherapy

- Consensus is this is considered appropriate monotherapy for mild to moderate nonpsychotic MDD
- Can be used as an augmentation agent with more severe depression
- Proven modalities:
- Cognitive-Behavioral Therapy
- Interpersonal Psychotherapy

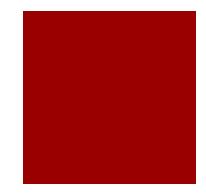


Common Medications

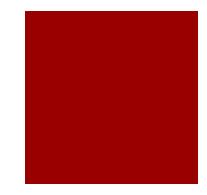
- Serotonin-Selective Reuptake Inhibitors (SSRIs)
- Serotonin/Norepinephrine-Reuptake Inhibitors (SNRIs)
- Others:
- Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)
- Mirtazapine (Remeron)



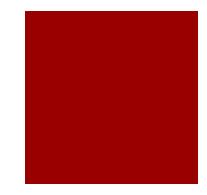
- Antidepressant Indications:
- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Panic Disorder (PD with or without agoraphobia)
- Social Anxiety Disorder
- Posttraumatic Stress Disorder (PTSD)
- Obsessive-Compulsive Disorder (OCD)
- Eating Disorder (Bulimia)
- Borderline Personality Disorder (BPD)
- NOTE: All antidepressants but Bupropion are indicated for the use in the above anxiety disorders and eating disorder (anorexia)



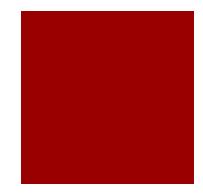
- SSRIs
 - Fluoxetine (Prozac)
 - Long half life, increased energy, generally well tolerated
 - Sertraline (Zoloft)
 - Low concentration in breastmilk, few drug interactions, generally well tolerated
 - Paroxetine (Paxil)
 - Shorter half life, more side effects, many drug interactions
 - Citalopram (Celexa)
 - Escitalopram (Lexapro)
 - Can initiate a therapeutic dose, generally well tolerated
 - Fluvoxamine (Luvox)
 - Many drug interactions, most often used in OCD
 - Vortioxetine (Trintellix)
 - Few side effects, some literature to suggest cognitive benefits
 - Expensive
 - Vilazodone (Viibryd)
 - Many side effects
 - Expensive



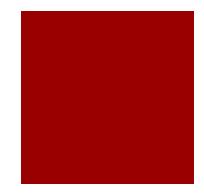
- SNRI
 - Duloxetine (Cymbalta)
 - Helpful for chronic pain
 - Venlafaxine (Effexor)
 - Increases energy
 - Hypertension, short half life = risk for discontinuation symptoms, difficult to taper to stop
 - Desvenlafaxine (Prystiq)
 - Increases energy
 - Expensive, Hypertension, short half life = risk for discontinuation symptoms, difficult to taper to stop
 - Milnacipran (Savella)
 - Indicated for chronic pain, not depression
 - Levomilnacipran (Fetzima)
 - Expensive



- Other
 - Mirtazapine (Remeron)
 - Helpful for sleep
 - Bupropion (Wellbutrin)
 - Increases energy, helps with smoking cessation, can improve concentration (ADHD)
 - Mild antidepressant, can make anxiety worse, lowers seizure threshold
 - Trazodone (Desyrel)
 - Nefazodone (Serzone)

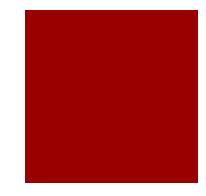


- Tricyclic Antidepressants
 - Amitryptiline (Elavil)
 - Helpful for sleep and chronic pain
 - Nortryptiline (Pamelor)
 - Clomipramine (Anafranil)
 - Most serotonergic, can be helpful for OCD
 - Desipramine (Norpramin)
 - Doxepin (Silenor)
 - Imipramine (Tofranil)



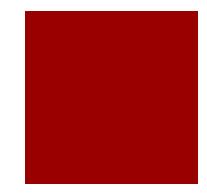
MAOI

- Isocarboxazid (Marplan)
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Selegeline (Eldepryl, Zelapar)
- Selegeline transdermal (Emsam)

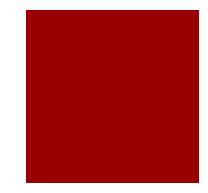


Antidepressant Prescribing

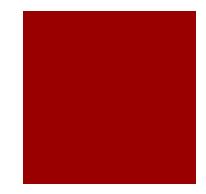
- Antidepressant List
- University of Washington AIMS Center Prescriber's Cheat Sheet



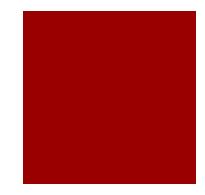
- Common SRI/SNRI side effects;
- Nausea, diarrhea, dry mouth
- Anxiety, insomnia, tremor/jitteriness
- Fatigue, drowsiness, excessive sweating
- Sexual dysfunction (decreased libido, delayed arousal, anorgasmia)
- Apathy, emotional blunting
- Weight gain (Paroxetine)
- Hypertension (Venlafaxine)



- Uncommon SSRI/SNRI side effects:
- Bruxism
- Akathisia
- Bruising/bleeding
- Arthralgias
- Suicidal ideation associated in the first several weeks of treatment and thereafter SI declining

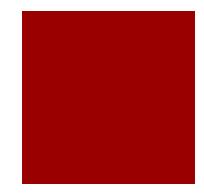


- Bupropion:
- All those of SRIs except sexual dysfunction
- Constipation
- Weight loss
- Seizures especially in OD
- Mirtazapine:
- All those associated with SRIs except sexual dysfunction
- Increased appetite and weight gain
- Hypotension
- Urinary frequency

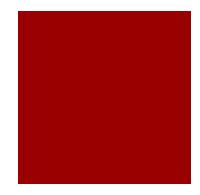


- SRI/SNRI Discontinuation Syndrome:
- Symptoms associated with the abrupt discontinuation of SRI/SNRI
- Dizziness
- Insomnia
- Nervousness/anxiety
- Irritability/agitation
- Nausea
- "Zappies"
- Those medications with the shortest half life have a greater risk
- Recommend taper off these medication to prevent

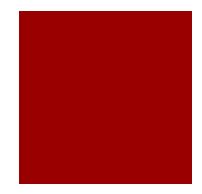
- SSRIs and half-life:
- Fluoxetine (Prozac): 1-4 days
- Paroxetine (Paxil): 20 hours
- Sertraline (Zoloft): 26 hours
- Citalopram (Celexa): 33 hours
- Escitalopram (Lexapro): 33 hours
- Fluvoxamine (Luvox): 16 hours
- Vilazodone (Viibryd): 25 hours



- SNRIs and half life:
- Venlafaxine (Effexor, Effexor XR): 5 hours and 11 hours
- Duloxetine (Cymbalta): 12 hours
- Desvenlafaxine (Pristiq): 11 hours
- Levomilnacipran (Fetzima): 12 hours
- Others:
- Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL): 12 hours
- Mirtazapine (Remeron) 20-40 hours

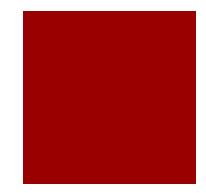


- Benefits of using non-TCA/MAOI Antidepressants:
- Once daily dosing (except IR/SR Bupropion and IR Venlafaxine)
- Low side effects and dropout rates
- Low toxicity in OD
- Effective in the treatment of different depressive subtypes
- Effective in the treatment of comorbid anxiety disorders (except Bupropion)



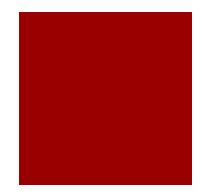
Drug/Drug Interactions

- Use drug interaction checking tools
- Many psychiatric medications are metabolized through the Cytochrome P450 system
 - CYP 3A4
 - CYP 2D6
 - CYP 2C19
- Can also act as inducers/inhibitors of these enzymes
- Bupropion, sertraline, and trazodone have minimal CYP interactions



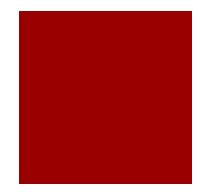
Drug-Drug Interactions

- Fluoxetine and paroxetine are CYP 2D6 inhibitors.
- TCAs, antipsychotics, and antidepressants are often metabolized through CYP 2D6 and CYP2C19
- Fluvoxamine inhibitor of CYPs (1A2, 2C19, 3A4)
- Nefazodone Inhibitor of CYP3A4
- Azoles (fluconazole) inhibitor of CYP3A4
- St. John's Wort inducer of CYP3A4
- Carbamazepine, Phenytoin, Phenobarbital inducer of CYP3A4
- Rifampin inducer of CYP3A4



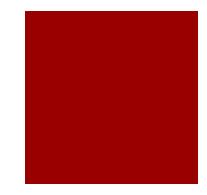
Drug-Drug Interactions

- What will happen if...
- Alprazolam (CYP3A4 substrate) + Fluvoxamine (CYP3A4 inhibitor)
- Clozapine (CYP1A2 substrate) + smoking (CYP1A2 inducer)
- Lithium + Ibuprofen
- Diazepam (CYP3A4 substrate) + grapefruit juice (CYP3A4 inhibitor)
- Amitriptyline (CYP2D6 substrate) + paroxetine (CYP2D6 inhibitor)



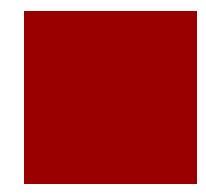
ECT

- Used for treatment resistant depression, psychotic depression, treatment resistant bipolar disorder, catatonia, or if suicidal risk is deemed to be high even in an inpatient setting
- 80-95% effective
- Expensive
- Side effects are the side effects of seizures (HA, N,V, lethargy, short term memory loss) and general anesthesia



Clinical Pearls

- Do not under dose medications:
- Titrate to the therapeutic dose
- Slow titrations with patients with severe comorbid anxiety
- Once at the therapeutic dose, if there is no response by 4-6 weeks:
- Augment with second antidepressants outside the class, buspirone, Lithium, Atypical antipsychotics, Cytomel
- Or switch to an antidepressant from another class



Clinical Pearls

- Use placebo effect to therapeutic advantage.
- Length of depressive episode can indicate how well pt will respond to treatment
- If the patient fails multiple trials of medications at the therapeutic dose and/or augmentation strategies:
- Consider compliance issues
- Add psychotherapy
- Reconsider the diagnosis (Bipolar disorder or personality disorder)
- Consider psychiatrist referral
- Consider interventional treatments: ketamine/ECT/TMS
- After remission is obtained, treatment should be continued at least 6 months, ideally 12 months, to limit risk of relapse

Questions?

