Treatment of Major Depressive Disorder

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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

Diagnostic Criteria DSM V

- 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

Diagnostic Criteria DSM V

- 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.

Diagnostic Criteria DSM V

- 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

Diagnostic Criteria DSM V

- 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 non-psychotic 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)

Medications

- 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)

Medications

- 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

Medications

- 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

Medications

- 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)

Medications

- 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)

Medications

- 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

Side Effects

- 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)

Side Effects

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

Side Effects

- 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

Side Effects

- 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

Medications

- 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

Medications

- 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

Medications

- 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?