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# Treatment of mild-to-moderate Major Depression

1. In treating an episode of mild to moderate major depression, what is the goal?
    - The **goal is symptom remission** and restoring baseline functioning**. Relapse appears to occur less frequently in patients whose symptoms remitted** compared to those whose symptoms responded but did not remit.
        - Response-defined as improvement of ≥50% in a clinician administered rating scale, but less than the threshold of remission
        - Remission-defined as less than or equal to the rating scale score that defines the normal range.

2. What is the general approach to treatment of a mild-to-moderate major depression episode?
    - Randomized clinical trials have found that the **combination of antidepressant and psychotherapy is more effective than either treatment alone**. Clinical trials have not established the superiority of any specific medication/psychotherapy combination.
    - A reasonable alternative to combination therapy is pharmacotherapy alone or psychotherapy alone; Antidepressants and psychotherapy have each demonstrated efficacy as monotherapy in randomized trials; Clinical trials that compared psychotherapy alone with pharmacotherapy alone found the benefits of each modality were comparable.
    - If there is more of an acute precipitant, and no prior history of Major Depression, psychotherapy alone is the preferred first choice.
    - One advantage provided by psychotherapy is that following an active course of treatment the benefits often persist and patients remain well. By contrast, the benefits of an acute course of antidepressant treatment are often lost if the drug is discontinued.

3. Which antidepressant is the most effective in treating mild to moderate major depression?
    - Multiple reviews have concluded that the **efficacy of different antidepressants is generally comparable across and within classes**. No evidence has been found that one antidepressant is superior in preventing relapse or recurrence.
        - Selective serotonin reuptake inhibitors (SSRI's)
            - Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Paroxetine (Paxil), Sertraline (Zoloft)
        - Serotonin-norepinephrine reuptake inhibitors (SNRI's)
            - Desvenalfaxine (Pristiq), Duloxetine (Cymbalta), Venlafaxine (Effexor)
        - Atypical Antidepressants
            - Bupropion (Wellbutrin), Mirtazapine (Remeron)
        - Serotonin modulators
            - Vilazodone (Viibryd), Vortioxetine (Brintellix)
        - Older, first generation anti-depressants
            - Tricyclic antidepressants (TCAs)
            - Monoamine oxidase inhibitors (MAOI's)

    - For patients with major depression whose initial treatment includes antidepressants, SSRI's are suggested based upon their efficacy, tolerability and cost. SSRI's are the most widely prescribed class of antidepressants.
        - Within the SSRI's, there is evidence that suggests Escitalopram (Lexapro) and Sertraline (Zoloft) provide the best combination of efficacy and low probability of discontinuation for any reason.
    - Reasonable alternatives to SSRI's include SNRI's, atypical antidepressants, and serotonin modulators.
        - Note: **Treatment of severe MDD, SNRI's first line choice**
    - Tricyclics and monoamine oxidase inhibitors are typically not used for initial treatment due to concerns about safety (particularly in overdose) and adverse effects.

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4. Are there factors that may provide direction in selecting an antidepressant medication?
    - Given the lack of clear superiority in efficacy among antidepressants, selecting an antidepressant is based on other factors such as:
        - Safety, side effect profile, specific depressive symptoms, co-morbid illness, concurrent medications and potential drug-drug interactions, ease of use (frequency of administration), patient preference or expectations, cost
    - Patient response to antidepressants during prior episodes & family history of response to antidepressants are often used in choosing an antidepressant. However, there is little evidence that patient outcomes are improved by selecting an antidepressant on the basis of these factors.

5. How long does a medication trial need to be to assess if it is working?
    - **Improvement is often apparent within 1-2 weeks** and early improvement may predict eventual remission. Studies show that among all patients who remitted, more than 90% were early improvers
    - An **adequate trial of an antidepressant is 6-8 weeks** (some recommend up to 12 weeks) before deciding if an antidepressant has sufficiently relieved symptoms. However, for patients who have shown little improvement after 4-6 weeks, it is reasonable to administer the next step treatment.

6. How long should the antidepressant medication be taken if it works?
    - Continuation treatment should be done for about **6 months after response** to the antidepressant medication to preserve and enhance remission and prevent relapse
    - **Maintenance treatment**
        - Time after the recovery period treatment is continued to prevent a recurrence
        - Patients **with risk factors for recurrence should receive at least 1-3 years of maintenance treatment** following continuation treatment
            - Risk factors:
                - History of childhood maltreatment/abuse
                - Early age of onset of depression (< 21 y/o)
                - Lifetime history of at least 2-3 major depression episodes
                - Persistent residual depressive symptoms (especially sleep disturbances & SI)
                - Comorbid psychiatric disorders
                - Psychosocial stressors (Ex. marital conflict, inability to work)
                - Family history of mood disorder
        - Patients with a history of **multiple ( ≥ 3), chronic ( ≥ 2 years), or severe major depressive episodes or with comorbid psychiatric and general medical disorders are encouraged to maintain treatment indefinitely**
    - For patients who respond to the combination of medication and psychotherapy, randomized trials indicate that continuation and maintenance treatment with combination treatment is superior to either pharmacotherapy alone or psychotherapy alone.

7. What is the prognosis?
    - Initial treatment of mild to moderate depression with antidepressants leads to a remission in 30-50% of patients and a response or remission in roughly 50-60% of patients.
    - Remission may be more likely if treatment commences soon after onset of symptoms

8. Is medication augmentation used when antidepressant monotherapy is not successful?
    - Yes. Some evidence suggests that the benefit of augmentation is superior to switching antidepressants. Many options are available and include:
        - **Augmenting with a second generation antipsychotic (SGA's)**
            - **Aripiprazole (Abilify) appears to be the first choice of SGA's**
            - Others options include: Brexpiprazole (Rexulti), Olanzapine (Zyprexa), Quetiapine (Seroquel), and Risperidone (Risperdal)
        - Augmenting with lithium
        - Combining with a second antidepressant
            - Uses antidepressants with distinct and different mechanism of actions
            - Avoid combinations with monoamine oxidase inhibitors (MAOI's)

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9. What psychotherapy is used to treat major depression?
    - Cognitive-Behavioral therapy (CBT)
    - Interpersonal therapy
    - Supportive psychotherapy

10. Is any type of therapy superior to the others?
    - There is no compelling evidence that one therapy type is superior to the rest
    - CBT and Interpersonal therapy are frequently selected because they have been more widely studied than other types of psychotherapy

11. Are there other recommendations for treating mild to moderate depression?
    - Relaxation and positive activities
        - Relaxation techniques-progressive muscle relaxation or relaxation imagery
        - Pursue positive activities (behavioral activation)- Encourage patients to pursue positive activities that may have ceased during depression; patients may say they will engage in those activities after they are less depressed; clinicians need to explain that engaging in these activities is a means of relieving depression
    - Exercise-suggested based on evidence from low quality randomized trials; although many studies suggest exercise is beneficial, the evidence is not compelling

## Severe Major Depression

1. What is **severe major depression**?
    - Defined as **having 7 to 9 depressive symptoms that occur nearly every day**. Patients often report suicidal ideation, typically demonstrate obvious impairment of functioning, are at higher risk of developing psychotic features and catatonic features. Sometimes/often requires psychiatric hospitalization.

2. How is severe major depression treated?
    - Combination of pharmacotherapy and psychotherapy
    - Pharmacotherapy alone
    - Electroconvulsive therapy (ECT)
        - Especially for patients who require a fast response (patients with suicidal ideation or behavior that is life threatening).
        - Randomized trials show that ECT is more efficacious that any other treatment for severe major depression

3. If pharmacotherapy is to be used how should the antidepressant be chosen?
    - A review of meta-analyses of randomized trials found that severe major depression responds better to **SNRI's** than SSRI's
    - Mirtazapine (Remeron) is a reasonable alternative
    - Tricyclics (TCA's) are also a reasonable alternative; However, TCA's are frequently avoided due to their greater safety hazards (cardiotoxicity and potential lethality with overdose)
    - For **severe major depression with psychosis**:
        - **Antidepressant plus antipsychotic**
            - More effective than antidepressant monotherapy or antipsychotic monotherapy;
            - At present it is **reasonable to use any antidepressant/antipsychotic combination** to treat major depression with psychosis.

4. What is the course of treatment for psychotic depression?
    - antidepressant plus an antipsychotic for 4-8 weeks before determining if the combination is effective
    - About 50% of patients recover within 2-3 months and the large majority of patients recover within 6-12 months
    - Social and occupational functional recovery often lags the recovery from psychotic and depressive symptoms.

- Psychotic depression is associated with significantly more recurrences of major depression (with or without psychosis) and a significantly higher mortality rate compared with non-psychotic depression. Curiously, the rate of completed suicide does not appear to differ between psychotic depression and non-psychotic depression.

5. What is the recommendation for maintenance treatment of psychotic depression?
    - Most recommend continuing the antipsychotic for 4 months of sustained recovery from the episode. Maintenance with the antidepressant should continue for a minimum of 2 years beyond recovery and possibly indefinitely.

## Few Additional Notes about Depression

Prevalence in the United States

- Sex: F : M prevalence is roughly 2:1
- Age
    - Prevalence declines in older adults as they age
    - More common in older adults with greater burden of medical illness

Risk Factors

- Genetics
    - Research currently supports the idea that depression is due to many genes with small effects
    - Genes probably contribute to the vulnerability toward depression which then requires additional non-genetic factors to produce a depressive disorder. Consistent with this is that the concordance rate for depression in monozygotic twins is about 37%
- Early life adversity
    - Early life stress such as childhood trauma
- Stressful life events
    - Increase the likelihood of suffering an episode of major depression;
- Social factors:
    - Isolation, poor social support, criticism from family members, depression in one's friends and neighbors (being around other depressed people)
    - May lead to depression onset or perpetuate depressive episodes
- General medical illnesses. Includes:
    - Neurological disorders:
    - Infection:
    - Endocrine:
    - ~~e~~ Inflammatory disorders:
    - Neoplastic:
- Medications
    - Glucocorticoids
    - Interferons