

Major Depressive Disorder

Purpose:

As part of the Mega Regulation we are required to provide quarterly education for providers. Instead of having a separate Drug Utilization Review (DUR) Committee to review the educational material we utilize the Pharmacy and Therapeutic (P&T) Committee. We are asking P&T members to review and provide feedback ON:

1. Clinical appropriateness of document.
2. Relevance to practice standards in treatment of major disorder.

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August 2019

Major Depressive Disorder

Summary:

In 2017, an estimated 17.3 million adults in the United States had at least one major depressive episode. This number represented 7.1% of all U.S. adults. The goal of this quarter's educational material* is to review major depressive disorder and discuss available treatment options.

Objective(s):

1. Define major depressive disorder (MDD).
2. Understand epidemiology of MDD and associated risk factors.
3. Understand clinical presentation and clinical course.
4. Be cognizant of best practices in the clinical assessment and treatment of patients with MDD.
5. Understand the various phases of treatment of MDD and be able to modify therapy based on level of patient response.
6. Understand the various treatment options available and be able to choose the most appropriate option given patient specific factors.
7. Understand the impact of demographic and psychosocial factors on MDD

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- Understand the various phases of treatment of MDD and be able to modify therapy based on level of patient response.
- Understand the various treatment options available and be able to choose the most appropriate option given patient specific factors.
- Understand the impact of demographic and psychosocial factors on MDD.



What is Major Depressive Disorder?

- Major depressive disorder (MDD) is defined as a depressed mood or loss of interest or pleasure in usual activities that persists over a period of at least two weeks accompanied by a constellation of depressive symptoms such as changes in eating or sleeping patterns, fatigue, difficulty concentrating, indecision, thoughts of death or suicide, or feelings of worthlessness, helplessness, or hopelessness.



Diagnosing Depression

- A clinical diagnosis of depression can be made if a patient demonstrates at 5 least of the following features over a 2-week period and represent a change from baseline and least 1 such symptom include depressed mood or loss of interest or pleasure:
 1. Depressed mood most of the day nearly every day
 2. Diminished interest in all or almost all activities most of the day nearly every day
 3. Significant changes in weight (gain or loss) or changes in appetite (increase/decrease) every day or nearly every day
 4. Insomnia or hypersomnia nearly everyday
 5. Psychomotor agitation or retardation as observed by others nearly every day
 6. Fatigue or loss of energy nearly every day
 7. Feelings of worthlessness or excessive inappropriate guilt nearly every day
 8. Diminished ability to think or concentrate or indecisiveness nearly every day
 9. Recurrent thoughts of death or suicidal ideology

Diagnosing Depression



- Additional diagnostic criteria include:
 1. The symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning.
 2. The symptoms do not meet criteria for a mixed episode.
 3. The symptoms are not due to the direct physiological effects of a substance or a general medical condition.
- Of note the DSM-5 no longer excludes those who meet the above criteria who have bereaved within the past 2 months.

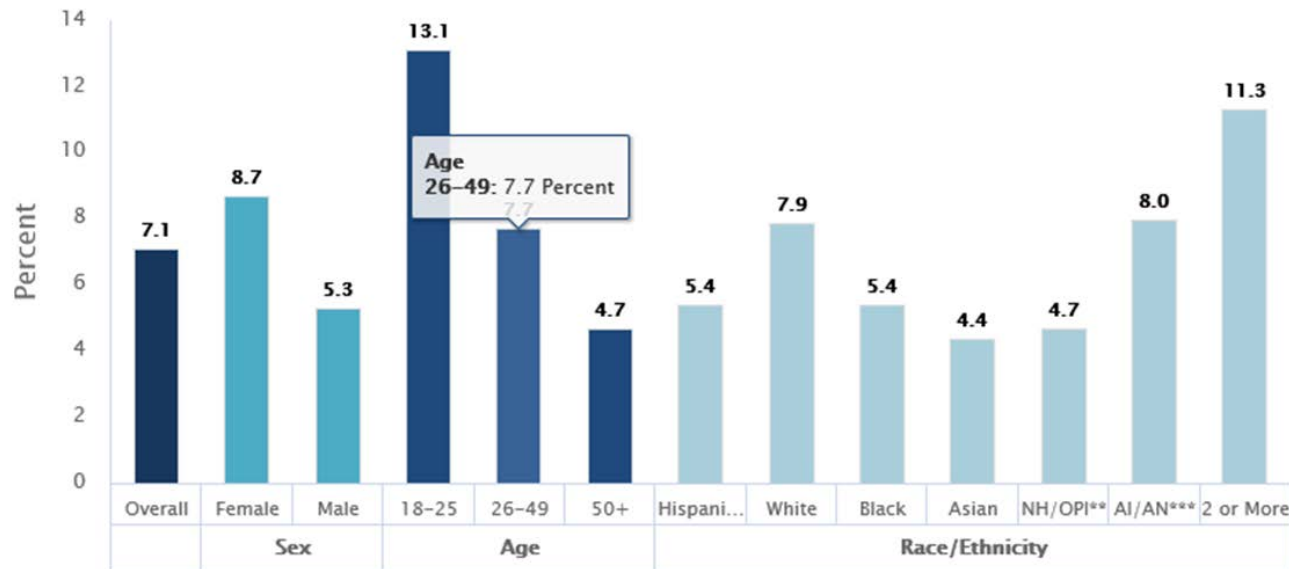


Epidemiology

- In 2017, an estimated 17.3 million adults in the United States had at least one major depressive episode. This number represented 7.1% of all U.S. adults.

Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2017) 

Data Courtesy of SAMHSA



*All other groups are non-Hispanic or Latino | **NH/OPI = Native Hawaiian / Other Pacific Islander
 | ***AI/AN = American Indian / Alaskan Native



Epidemiology

- Factors associated with prevalence of MDD include female sex, being middle-aged, being never or previously married, having low income, being unemployed, and/or being disabled.
- Of note, MDD rarely occurs alone and is often accompanied by anxiety disorders, substance abuse disorders, and impulse control disorders. Anxiety disorders are the most commonly accompanied disorder.



Background Statistics

- Findings from previous surveys have demonstrated a glaring need to change the approach by which mental health services are delivered.
 - NESARC: The average time to treatment for MDD was approximately 3 years with only 60% of sampled patients with MDD actually received treatment.
 - NCS-R: Only half of those with a major depressive episode within the previous year received treatment. Ultimately, only one-fifth of these individuals actually received adequate treatment.



Clinical Course

- Onset of MDD can occur at any age, but the average age of onset occurs in the late 20s. Symptom onset is usually insidious over the course of days to weeks, but can occur abruptly secondary to severe stress.
- Length of depressive episodes vary by individual, but the average length per episode is usually 16 weeks.
- The median time to recovery from a depressive episode if treated is 20 weeks. By contrast, untreated episodes usually last 6 months or longer.
- Episodes are recurrent in 35% of patients and are unremittent in 15% of patients. Of note, after three episodes, the risk of recurrence approaches 100% without prophylactic treatment.



Complications and Prognosis

- The most serious complication of MDD is suicide with or without homicide.
- It is prudent to understand that MDD affects not only patients, but those associated with them as well. MDD affects a patient's marital, parental, social, and vocational function, which in turn can distress others within that patient's social network. This reinforces the need to adequately treat MDD as this distress may also increase risk of depression in those associated with the patient.
- Likewise, MDD has been associated with delays in recovery for patients with other co-morbidities.
- However, if treated the prognosis is generally good as most patients respond to acute treatment and continuation treatment has been associated with lower risk and severity of relapses.



Treatment Options- Psychiatric Management

- Psychiatric management plays a pivotal role in the treatment of MDD and should be provided through all phases of treatment. Proper psychiatric management entails the following activities and interventions:
 - Establishing a therapeutic alliance.
 - Complete psychiatric assessment: This also includes an assessment of past and current substance abuse
 - Patient Safety evaluation: This extends beyond an evaluation of suicidal and/or homicidal tendencies, but also includes an evaluation of the level of self-care and care of any of the patient's dependents.
 - Establishing an appropriate treatment setting: The guiding principle is to provide the least restrictive setting for treatment that addresses both patient safety and capacity for improvement. (Acutely suicidal/homicidal patients should be hospitalized).
 - Evaluating functional impairment and quality of life: This is helpful in devising an individualized plan of treatment.

Treatment- Psychiatric Management



- Psychiatric management continued
 - Coordinating care with other clinicians.
 - Monitoring patient's psychiatric status and response to therapy.
 - Integrating patient administered rating scales into patient evaluation.
 - Enhancing treatment adherence: This includes identifying potential barriers to treatment, providing transparent communication, addressing patient fears, and providing realistic goals.
 - Performing patient and family education: This includes clarification of common misconceptions, medication consultation, and reinforcement of healthy behaviors.



Treatment- The Acute Phase

- The goal of the acute phase is to induce remission of the major depressive episode to achieve a full return to baseline.
- The acute phase usually lasts a minimum of 6-12 weeks.
- Treatment may include pharmacotherapy, depression-focused psychotherapy, a combination of pharmacotherapy and psychotherapy, electroconvulsive therapy (ECT) or other somatic therapies.
- The selection of a treatment modality is driven by clinical presentation, patient preference, prior treatment experiences, and other individualized patient factors that may arise.



Acute Phase Treatment- Pharmacotherapy

- An antidepressant is recommended for mild to moderate MDD.
- Severe cases of MDD should be treated with an antidepressant unless ECT is planned.
- Efficacy across the therapeutic classes of antidepressants is generally comparable so the selection of an agent is based on the safety and tolerability of the agent and individualized patient factors such as cost, previous experiences, and patient preference.
- In general, an optimal first line agent could include any of the following: selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion.



Acute Phase Treatment- Pharmacotherapy

- Non selective monoamine oxidase inhibitors should be restricted to use in cases refractory to other treatment modalities due to significant drug-drug interactions (DDIs) and dietary restrictions.
- Complementary and alternative therapies such as S-adenosyl methionine (SAME) or St John's Wort may be considered, but their efficacy is modest at best. With respect to St John's Wort, be aware of numerous DDIs due to hepatic enzyme induction.
- The monitoring and titration schedule is wholly patient specific, with more severe cases requiring more frequent monitoring.
- Should side effects occur, an appropriate action would be to lower antidepressant dose or to switch to another agent without such side effect(s).



Acute Phase Treatment- ECT

- ECT is a treatment of choice in the following circumstances:
 - Severe MDD that is refractory to psychotherapy and/or pharmacotherapy. (ECT is particularly ideal in patients who have functional impairment and have failed numerous medication trials)
 - MDD with psychotic or catatonic features
 - MDD with an urgent need for response (suicidal or nutritionally compromised patients)
 - Patient preference
 - Previous positive response to ECT



Acute Phase Treatment- Psychotherapy

- Depression-focused psychotherapy alone can be used as an initial treatment choice in those with mild-moderate MDD. Supported forms of psychotherapy include:
 - Cognitive behavioral therapy (CBT)
 - Interpersonal psychotherapy
 - Psychodynamic therapy
 - Problem-solving therapy
- This is the preferred treatment modality for women who are pregnant, wishing to become pregnant, or are breastfeeding depending on the degree of disease severity.
- Of note, marital and family problems are commonplace in therapy and therefore, marital and family therapy should be used as appropriate.

Acute Phase Treatment- Combination Therapy



- Psychotherapy and pharmacotherapy can be used in tandem as an initial modality for those with moderate to severe MDD and may be of use in milder cases with psychosocial or interpersonal problems, intrapsychic conflict, or a co-occurring Axis II disorder.



Acute Phase Treatment- Assessing Response

- In assessing the adequacy of response to therapy, always assure that the chosen treatment modality has been given at a sufficient dosing/frequency over enough time to discern improvement. (Onset of improvement for psychotherapy is comparatively longer). However, treatments should be modified if no benefit is seen after 1 month.
- In general, 4-8 weeks of treatment are needed before a conclusion regarding patient response can be determined.



Acute Phase Treatment – Non-responders

- If at least moderate improvement is not observed within 4-8 weeks of initiation, the diagnosis should be reappraised, side effects assessed, comorbidities reviewed, compliance assessed, and the treatment plan should be adjusted. Likewise, if pharmacotherapy was chosen, dosing and pharmacokinetic factors should also weigh into account.
- Another comprehensive review should be conducted after another 4-8 weeks of little to no response.



Acute Phase Treatment – Non-responders

- For those on an antidepressant, appropriate therapeutic adjustments can include:
 - Increasing a dose towards upward prescribing limits with consideration of side-effect burden
 - Adding psychotherapy
 - Adding another pharmacologic agent (Can be an antidepressant of another class, lithium, thyroid hormone, or a second generation antipsychotic)
 - Changing antidepressants (Can be within the same class or to a different class)
 - Patients with anxiety or insomnia may also be augmented with anxiolytics or sedative-hypnotics.
 - For those refractory to medication, ECT is the most effective treatment modality.



Acute Phase Treatment – Non-responders

- For those on psychotherapy, appropriate therapeutic adjustments can include:
 - Increasing intensity of psychotherapy
 - Changing type of psychotherapy
 - Augmenting with medication



Continuation Phase

- To reduce risk of relapse, patients who have been successfully treated with pharmacotherapy should continue on the same agents at the same dosing for 4-9 months.
- Depression-focused psychotherapy should also be utilized in the continuation phase with best evidence for CBT.
- Those who have responded to ECT should continue on pharmacotherapy with best evidence for the combination of nortriptyline and lithium. However, such patients may also be given continuation ECT, especially if the patient has had a poor response to pharmacotherapy or psychotherapy.



Maintenance Phase

- Those who have had 3 or more prior MDD episodes or have chronic MDD should proceed to the maintenance phase after the continuation phase.
- Maintenance phase therapy should be considered for those with residual symptoms, ongoing psychological stressors, have an early age of onset, or family history mood disorders as these patients are at greater risk of recurrence.
- In the maintenance phase, if pharmacotherapy was used, the full therapeutic dose previously used prior should be utilized.
- If psychotherapy was used in both the acute and continuation phases, it should still be utilized, but with consideration for fewer sessions.
- If a patient was only responsive to ECT, continuation ECT should be continued. However, continuing with vagus nerve stimulation (VNS) is also acceptable.



Discontinuation

- Upon discontinuation of pharmacotherapy, the key is to taper slowly over the course of several weeks to avoid withdrawal symptoms. A slow taper may include switching to an agent with a longer half-life to mitigate risk of withdrawal. In addition, patients should be consulted regarding the possibility of relapse, and an effective plan for such a relapse should be devised and communicated. Patients should still have routine follow up over the next several months.
- For those on psychotherapy, the issue of treatment discontinuation should be communicated far in advance of the final session, but means of discontinuation vary greatly between the types of psychotherapy.



Clinical Factors for Consideration

- Various patient specific factors can influence how patient treatment plans are individualized. It is prudent to be cognizant of such factors in the assessment of a patient and how they can alter the course of treatment.



Clinical Factors for Consideration

- Psychiatric Factors
 - Suicidal patients should be hospitalized when warranted and receive an increased intensity of treatment.
 - Patients exhibiting psychotic symptoms should receive a combination of an antipsychotic with an antidepressant.
 - Those exhibiting catatonic features should be treated with a benzodiazepine or barbiturate. Those refractory to those adjuncts should receive ECT. In addition, catatonic patients may need greater supportive care as well (Nutrition, hydration, etc...).
 - Patients who have other psychiatric disorders should also have those treated as part of the treatment plan.
 - Smokers may benefit from the selection of bupropion or nortriptyline to facilitate smoking cessation.



Clinical Factors for Consideration

- Demographic and psychosocial factors
 - In prescribing to women on contraceptives, always be cognizant for potential DDIs especially those concerning enzyme induction.
 - Perimenopausal women may benefit from the selection of an SSRI or SNRI in regards to hot flashes.
 - Both men and women should be asked regarding any sexual side effects.
 - Men should always be consulted regarding the risk of priapism associated with trazodone.



Clinical Factors for Consideration

- Demographic and psychosocial factors cont...
 - Pregnant women, those wishing to be pregnant, or those who are breast feeding should receive psychotherapy for mild-moderate MDD. Antidepressants should be considered for moderate-severe MDD and for those in remission from MDD, are on maintenance medication, or are at high risk of recurrence should the medication be discontinued.
 - Pregnant women may exhibit changes in pharmacokinetics and may require dosage titration.
 - ECT is an option for pregnant women who exhibit psychotic or catatonic features, have severe MDD, or prefer it.
 - Women during the postpartum period should be assessed for suicidal/homicidal ideation, psychotic symptoms, and the capacity to fulfill a role as a parent.



Clinical Factors for Consideration

- Demographic and psychosocial factors cont...
 - Elderly patients may require dosage adjustment for renal/hepatic impairment.
 - Family history of bipolar disorder warrants additional monitoring for a differential diagnosis.
 - Family history of recurrent MDD may justify a need for maintenance therapy.
 - Familial response a therapeutic agent may be helpful guiding treatment response.
 - Family problems may pose a barrier to therapy. Therefore, educating a patient's family regarding MDD and enlisting their support should be strongly considered.



Clinical Factors for Consideration

- Comorbidities
 - Communicate with other practitioners to recognize the potentiality of interplay with other comorbidities and to reduce risk of potential interactions.
 - A pain assessment should be performed as pain can contribute can co-occur with depression
 - Patients with cardiovascular disease (CVD) may need additional monitoring depending on the agent chosen. SNRIs and TCAs may require additional heart rate and blood pressure monitoring.
 - Be cognizant of medications with anticholinergic side effects due to increases in heart rate in those with CVD, worsening of cognition in dementia, bladder outlet obstruction in men with prostatic hypertrophy, and the precipitation/worsening of narrow angle glaucoma.



Clinical Factors for Consideration

- Comorbidities Cont...
 - Be cognizant of agents that can lower seizure threshold such as bupropion, clomipramine, and maprotiline in patients with seizure disorders.
 - Concerning patients with Parkinson's disease, serotonergic agents may worsen symptoms. By contrast, the dopaminergic effect of bupropion may improve symptoms, but may worsen psychosis. Likewise selegeline has antiparkinsonian properties, but may interact with L-dopa and other antidepressants.
 - Consider potential DDIs between anticoagulants and antidepressants in stroke patients.
 - Consider the impact of weight gain conferred by some antidepressants. If significant weight gain is experienced, consider diet, exercise, medication change, or lifestyle change.



Clinical Factors for Consideration

- Comorbidities Cont...
 - Those post bariatric surgery may require dosage titration due to altered absorption.
 - Consider the least sedating medications possible in patients with sleep apnea.
 - Consider potential for DDIs between agents such as St. John's Wort in patients actively being treated for HIV.
 - Be aware of the potentiality for exacerbations of depression symptoms due to interferon in patients undergoing treatment for hepatitis C.
 - For patients receiving tamoxifen, choose medications that have minimal effect on CYP450 2D6 metabolism.
 - For patients with chronic pain, SNRIs and TCAs may be preferable.



Pharmacology-SSRIs

| SSRI | Starting dose (mg/day) | Usual dose (mg/day) |
|-----------------------------|------------------------|---------------------|
| Citalopram | 20 | 20-60 |
| Escitalopram | 10 | 10-20 |
| Fluoxetine | 20 | 20-60 |
| Paroxetine | 20 | 20-60 |
| Paroxetine Extended Release | 12.5 | 25-75 |
| Sertraline | 50 | 50-200 |



Pharmacology-SSRIs

- Clinical Pearls:
 - Nausea, vomiting, and diarrhea are common and dose dependent, but side effects tend to dissipate over time
 - SSRIs can be activating and cause insomnia, which can be addressed with sleep hygiene or pharmacotherapy
 - Sexual dysfunction can be addressed with adjunct agents such as bupropion, buspirone, or phosphodiesterase type 5 inhibitors.
 - Long term use may lower bone density.
 - SSRIs may worsen headaches initially, but may aid headaches over time.
 - SSRIs may cause weight gain. Paroxetine has the highest incidence. Fluoxetine may cause initial weight loss that tends to normalize over time.
 - Serotonin syndrome is a serious and potentially life-threatening side effect characterized by abdominal pain, high fever, diarrhea, flushing, sweating, tremor, myoclonus, rhabdomyolysis, renal failure, and cardiovascular shock. The incidence of serotonin syndrome in SSRIs alone is low, but is of great concern when given with other serotonergic agents with emphasis on MAOIs
 - Withdrawal is least likely to occur with fluoxetine due to its long half-life, which makes it an ideal agent for tapering down prior to discontinuation.



Pharmacology-SNRIs

| SNRI | Starting dose (mg/day) | Usual dose(mg/day) |
|-------------------------------|------------------------|--------------------|
| Venlafaxine Immediate Release | 37.5 | 75-375 |
| Venlafaxine Extended Release | 37.5 | 75-375 |
| Desvenlafaxine | 50 | 50 |
| Duloxetine | 60 | 60-120 |

- Clinical pearls

- SNRIs share many of defining characteristics of SSRIs with the key difference being noradrenergic side effects such as increased heart rate, dry mouth, constipation, excess sweating, and increased blood pressure.
- SNRI induced hypertension is dose dependent and can be ameliorated with dose reduction or the addition of an antihypertensive agent.

Pharmacology-Dopamine Norepinephrine Inhibitor



| Dopamine Norepinephrine Inhibitor | Starting dose (mg/day) | Usual dose (mg/day) |
|-----------------------------------|------------------------|---------------------|
| Bupropion immediate release | 150 | 300-450 |
| Bupropion sustained release | 150 | 300-450 |
| Bupropion extended release | 150 | 300-450 |

- Clinical Pearls
 - Bupropion has no direct impact on serotonergic neurotransmission and therefore has minimal sexual side effects
 - Bupropion has dose dependent risk of seizures. Therefore, rapid titration should be avoided. IR and SR formulations should be taken in divided doses.
 - Bupropion should not be used in patients with a history seizure disorder, anorexia nervosa, or bulimia nervosa
 - Caution should be exercised in using bupropion in patients exhibiting psychotic symptoms



Pharmacology- Serotonin Modulators

| Serotonin Modulators | Starting dose (mg/day) | Usual dose (mg/day) |
|----------------------|------------------------|---------------------|
| Nefazadone | 50 | 150-300 |
| Trazadone | 150 | 150-600 |

- Clinical Pearls

- Both trazadone and nefazadone share the side effect of sedation, which may be desirable for insomniacs.
- Trazadone has key side effects in potential for ventricular arrhythmias and priapism.
- Nefazadone has been associated life-threatening hepatotoxicity.



Pharmacology-Norepinephrine-serotonin modulator

| Norepinephrine-serotonin modulator | Starting dose (mg/day) | Usual dose (mg/day) |
|------------------------------------|------------------------|---------------------|
| Mirtazepine | 15 | 15-45 |

- Clinical Pearls

- Mirtazapine is sedating and usually dosed at night
- Mirtazapine is associated with greater weight gain when compared to other non-TCA, non-MAOI-antidepressants.
- Mirtazapine may increase serum cholesterol in some patients.



Pharmacology- Tricyclics (TCAs)

| Tricyclics | Starting dose (mg/day) | Usual dose (mg/day) |
|---------------|------------------------|---------------------|
| Amitriptyline | 25-50 | 100-300 |
| Doxepin | 25-50 | 100-300 |
| Imipramine | 25-50 | 100-300 |
| Desipramine | 25-50 | 100-300 |
| Nortriptyline | 25 | 50-200 |
| Trimipramine | 25-50 | 75-300 |
| Protriptyline | 10-20 | 20-60 |
| Maprotiline | 75 | 100-225 |



Pharmacology- Tricyclics

- Clinical Pearls
 - Cardiovascular effects are a major concern with TCAs. A pre-treatment ECG is recommended for those age 50 and older with significant cardiac risk factors due to risk of arrhythmia. Exercise great caution while using with Class Ia antiarrhythmic agents and in patients with prolonged QT intervals.
 - Tachycardia and orthostatic hypotension are also classwide concerns. Nortriptyline may be more favorable concerning orthostatic hypotension
 - TCAs exhibit anticholinergic side effects. Secondary amine TCAs such as desipramine and nortriptyline are milder in this respect as opposed to tertiary amine TCAs.
 - TCAs are sedating
 - TCAs can contribute to weight gain. Amitriptyline is most contributory and less so with desipramine.
 - TCAs can cause myoclonus which may be of concern in those susceptible to seizures.



Pharmacology- Monoamine oxidase inhibitors

| MAOIs | Starting dose (mg/day) | Starting use (mg/day) |
|-----------------|------------------------|-----------------------|
| Phenelzine | 15 | 45-90 |
| Tranylcypromine | 10 | 30-60 |
| Isocarboxazid | 10-20 | 30-60 |
| Selegeline | 6 | 6-12 |

- MAOIs are generally reserved for patients refractory other treatments due to serious concerns of potential hypertensive crisis and serotonin syndrome.
- Patients on MAOIs need to be placed on a dietary restriction to avoid foods rich in tyramine to avoid hypertensive crisis. Selegeline is a selective MAO-B inhibitor and does not require such a restriction unless the dosage is 9mg/day or greater
- To avoid serotonin syndrome, a “washout period” of 2 weeks is necessary when switching both to and from an MAOI and an SSRI/SNRI. The major exception to this concerns fluoxetine. Due to its long half-life patients must wait 5 weeks when switching from fluoxetine to an MAOI.



Pharmacology- Overall Considerations

- Regardless of pharmacologic agent chosen, patients should see partial improvement within 2-4 weeks if not sooner. Patients exhibiting partial response should be titrated as tolerated until remission is achieved or the maximum allowable dosage is reached.
- It is important to recognize that in eliciting a partial response, energy tends to improve before mood, which is of great concern with respect to patients with suicidal ideation. Such patients should be monitored judiciously.
- Antidepressants typically require 4-6 weeks to elicit maximal effect.



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