

## **CONDENSED CLINICAL PRACTICE GUIDELINE MAJOR DEPRESSIVE DISORDERS**

### **I. Key Points.**

#### **A. Definitions and scope.**

1. “Depression” in this practice guideline is consistent with the DSM-5 and encompasses both major depressive disorder (MDD) and dysthymic disorder (DD). “Youth” refers to children and adolescents ages 5 – 17; “Adults” refers to patients age 18 and older.
2. Information contained in this guideline pertains mainly to MDD. There are few clinical studies and no controlled trials for the treatment of DD in youths. Based on the limited adult literature, efficacious treatments for MDD may also be useful for the management of DD.
3. Psychiatric management consists of a broad array of interventions psychiatrists should initiate and continue to provide to patients with MDD through all phases of treatment.

#### **B. Therapeutic alliance and resiliency principles.**

1. Quality services and supports for adult and youth clients with MDD should be developed, monitored and evaluated in partnership with consumers, families and advocates.
2. The clinician should maintain a confidential relationship with the child or adolescent while developing collaborative relationships with parents, medical providers, other mental health professionals and appropriate school personnel.
3. Poor alliance or nonadherence to treatment may be caused by the depressive symptoms themselves or may represent psychological conflicts/psychopathology for which psychotherapy should be considered.

### **II. Diagnosis and Assessment.**

#### **A. Patients should receive a thorough diagnostic assessment with three primary goals.**

1. Establish the diagnosis of MDD.
2. Identify other psychiatric or general medical conditions that may require attention.
3. Develop a comprehensive treatment plan.

#### **B. General aspects of evaluation.**

1. History of present illness and current symptoms.
2. Psychiatric history including identification of past symptoms of depression.
3. General medical history and physical examination.
4. Personal history.
5. Social, occupational and family history.
6. Medication review.
7. A review of systems.
8. Psychological history and mental status examination.
9. Assessment of substance use.
10. Diagnostic tests as needed to rule out medical causes of depressive symptoms.

#### **C. Special considerations.**

1. Evaluate the safety of the patient.
  - a. Potential of harm to self or others.
  - b. Ability to care for self or dependents.
  - c. Level of self-care (i.e., nutrition, hydration).
2. Assessment of youth should routinely include screening questions about depressive symptomology. If screening indicates significant depressive symptomology, the clinician should perform a thorough evaluation to determine the presence of depressive and other comorbid psychiatric and medical disorders.
3. Evaluation should assess for the presence of ongoing or past exposure to negative events, the environment in which depression is developing, and support network.

### III. General Treatment Considerations

- A. Treatment should include an acute and continuation phase.
- B. During all treatment phases, clinicians should arrange frequent follow-up contacts that allow sufficient time to monitor the patient's clinical status, environment conditions and, if relevant, medication side effects.
- C. Each phase of treatment should include psychoeducation, supportive management, and family and school involvement.
- D. Combined therapy (psychotherapy + SSRIs) seems to work faster than monotherapy and is better for treatment-resistant cases.
- E. Integrate measurements of symptoms and progress into initial and ongoing treatment.
- F. Enhance treatment adherence by clarifying expectations for treatment, addressing lack of motivation or compliance, and encouraging dialogue about patient concerns.
- G. To consolidate responses to acute treatment and avoid relapses, treatment should always be continued for six to 12 months.
- H. If antidepressants are prescribed, careful evaluation for a possible increase in suicidal ideation and development of manic/hypomanic symptoms is necessary.
- I. Establish the appropriate setting for treatment.
  1. Psychiatrist should determine the least restrictive setting for treatment that will address safety issues and promote improvement.
  2. Identification of the setting should include consideration of symptom severity, co-occurring psychiatric or general medical conditions, available support, level of functioning, capacity for self-care, provision of feedback, and participation in treatment.
  3. Inpatient or intensive day hospital admission should be considered for several conditions.
    - a. Serious threat of harm to self/others.
    - b. Lack of adequate support outside of hospital setting.
    - c. Complicating psychiatric or medical conditions.
    - d. Poor response to outpatient treatment.
  4. Treatment setting and level of care should be reevaluated on an ongoing basis.

### IV. Clinical Factors Influencing Treatment.

- A. Psychiatric factors.
  1. Suicidality.
    - a. Consider increased intensity of treatment.

- b. Include possible hospitalization and/or combined treatment with pharmacotherapy and psychotherapy.
  - 2. Psychotic symptoms.
    - a. Combine antipsychotic and antidepressant medications or ECT.
    - b. Systematically assess cognition over the course of treatment.
  - 3. Catatonic features.
    - a. Treat with benzodiazepine or barbiturate, typically in conjunction with an antidepressant.
    - b. If symptoms persist, ECT is recommended.
  - 4. Co-occurring psychiatric disorder.
    - a. Address each disorder as part of the treatment plan.
    - b. Co-occurring anxiety may be treated adjunctively with benzodiazepines.
    - c. Co-occurring substance use disorders may be treated with a period of substance abstinence to determine whether the depressive episode is related to substance intoxication or withdrawal.
    - d. Careful selection and monitoring of medication is needed in individuals with co-occurring substance use disorders.
  - 5. Personality disorder.
    - a. Begin treatment for MDD.
    - b. Consider psychotherapeutic and adjunctive pharmacotherapeutic treatment.
- B. Demographic and psychosocial factors.
  - 1. Women — general considerations.
    - a. Evaluation should include assessment of mood changes across reproductive life history.
    - b. When prescribing medications to women who are taking contraceptives (e.g., oral, alternative), the potential effects of drug-drug interactions must be considered.
    - c. For perimenopausal women, SSRI and SNRI antidepressants are useful in improving depression and reducing somatic symptoms.
  - 2. For women who are pregnant, planning to become pregnant or breast-feeding:
    - a. For women who are currently receiving treatment for depression, a pregnancy should be planned in consultation with the treating psychiatrist. A consultation with a specialist in perinatal psychiatry may be appropriate.
    - b. Depression-focused psychotherapy alone is recommended as an initial option, particularly for mild to moderate depression.
    - c. Antidepressant medication should be considered for pregnant women who have moderate to severe major depressive disorder as well as for those who are in remission from MDD, are receiving maintenance medication and are deemed to be at high risk for a recurrence if the medication is discontinued.
    - d. When antidepressants are prescribed to pregnant women, changes in pharmacokinetics during pregnancy may require adjustments in medication doses.
    - e. ECT may be considered in treating depression during pregnancy in patients:
      - 1. Who have psychotic or catatonic features.
      - 2. Whose symptoms are severe or have not responded to medications.
      - 3. Who prefer treatment with ECT.

- f. For women who decide to nurse, the potential benefits of antidepressant medications for the mother should be balanced against the potential risks to the newborn from receiving antidepressant medications in the mother's milk.
      - g. For women who are depressed during the post-partum period:
        - 1. Evaluate for the presence of suicidal/homicidal ideas/psychotic symptoms.
        - 2. Assess parenting skills for newborn and other children in the patient's care.
    - 3. Sexual side effects of medications.
      - a. Both men and women who are taking antidepressants should be asked whether sexual side effects are occurring with these medications.
      - b. Men for whom trazodone is prescribed should be warned of the risk of priapism.
    - 4. Late-life considerations.
      - a. Treatment for depression should parallel that used in younger age groups.
      - b. In older patients, identify co-occurring general medical conditions.
      - c. Older patients may be very sensitive to medication side effects and require adjustment of medication doses for hepatic or renal dysfunction.
    - 5. Cultural considerations.
      - a. Assessment/treatment of MDD should consider the impact of language and cultural variables that may influence symptoms presentation.
      - b. When antidepressants are prescribed, the psychiatrist should recognize that ethnic groups may differ in their metabolism and response to medications.
    - 6. Family situation and history.
      - a. Family history.
        - 1. Initial evaluation should explore family history of mood disorders, suicide and recurrent MDD.
        - 2. Family history of responses to particular antidepressant medications may help in choice of a specific antidepressant for the patient.
      - b. Family situation.
        - 1. Problems within the family may influence the patient's treatment response.
        - 2. Educating the family about the nature of the disorder, enlisting the family's support and providing family therapy may be indicated.
        - 3. For patients who have experienced a recent bereavement:
          - a. Psychotherapy or antidepressant treatment should be used when the bereavement is prolonged or accompanied by significant psychopathology and functional impairment.
          - b. Support groups may be helpful for some bereaved patients.
  - C. Co-occurring general medical conditions (GMC).
    - 1. General considerations.
      - a. It is important to recognize and address the potential interplay between MDD and co-occurring GMC.
      - b. Communication with clinicians providing treatment for GMC is recommended.
      - c. Assessment should include identifying potential interactions between antidepressant medications and those used to treat GMC.
      - d. Assessment of pain is important as it can contribute to and co-occur with depression.

- e. The psychiatrist should consider the effects of psychotropic medications on the patient's GMC and the effects of interventions for GMC on the patient's psychiatric condition.
- 2. Specific medical conditions.
  - a. Pre-existing conditions.
    - 1. Treatment with specific antidepressants may suggest a need for monitoring of vital signs or cardiac rhythm in patients with hypertension or cardiac conditions.
    - 2. When using antidepressant medications with anticholinergic side effects, consider the potential for increase in heart rate in patients with cardiac disease, worsening condition in patients with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma.
    - 3. Some antidepressant drugs reduce the seizure threshold and should be used with caution in patients with pre-existing seizure disorder.
  - b. Parkinson's disease.
    - 1. Choice of an antidepressant should consider that serotonergic agents may worsen symptoms of the disease.
    - 2. Bupropion has potential dopamine agonist effects (benefitting symptoms of Parkinson's disease but potentially worsening psychosis).
    - 3. Selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents.
  - c. Stroke.
    - 1. In treating the depressive syndrome that often follows a stroke, consider the potential for interactions between antidepressants and anticoagulation medications.
  - d. Obesity and weight issues.
    - 1. Consider the health risks of obesity and the tendency of some antidepressant drugs to contribute to weight gain.
    - 2. Longitudinal monitoring of weight and calculation of body mass index (BMI) is recommended .
    - 3. If BMI increases significantly the clinician and patient should discuss potential approaches to weight control.
    - 4. If patients have undergone bariatric surgery to treat obesity, adjustment of medication formulations or doses may be required because of altered medication absorption.
  - e. Diabetes.
    - 1. Collaboration with patient's PCP is useful in monitoring diabetic control.
    - 2. Collaboration with PCP is especially important when initiating antidepressant therapy or making significant dosing adjustments.
  - f. Sleep disturbances and hygiene.
    - 1. In patients with sleep apnea, treatment choice should consider the sedative side effects of medication, with minimally sedating options chosen whenever possible.
    - 2. Sleep hygiene.

- a. The quality, amount and maintenance of sleep are essential for health and well-being. Poor sleep or sleep conditions can contribute adversely to a patient's behavioral health and treatment response.
  - b. Thorough assessment of sleep habits and attention to sleep practices are essential parts of treatment of MDD. This involves review of environmental and behavioral factors that impact the patient's sleep.
  - c. Underlying sleep disorders and sleep difficulties can be treated with therapeutic interventions and/or adjunctive medications, including both prescribed and over-the-counter products.
  - g. HIV.
    - 1. Given the significant numbers of persons with unrecognized HIV infections and the availability of effective treatment, consideration should be given to HIV risk assessment and screening.
    - 2. With patients who receive antiretroviral therapy, the potential for drug-drug interactions needs to be assessed before initiating any psychotropic medications.
  - h. Hepatitis C infection.
    - 1. Because interferon can exacerbate depressive symptoms, it is important to monitor patients carefully for worsening depressive symptoms during the course of interferon treatment.
  - i. Tamoxifen patients.
    - 1. Patients who receive tamoxifen for breast cancer or other indications should be treated with an antidepressant that has minimal effect on metabolism through the cytochrome P450 2D6 isoenzyme.
  - j. Chronic pain.
    - 1. SNRIs and TCAs may be preferable when depression occurs in the context of chronic pain.
  - k. ECT and co-occurring GMC.
    - 1. When ECT is used to treat MDD in patients with co-occurring GMC, the evaluation should identify conditions that could require modifications in ECT technique.
- D. Therapies to address non-response to treatment.
- 1. ECT.
    - a. ECT is recommended as the treatment of choice for patients with severe MDD not responsive to psychotherapeutic and/or pharmacological interventions.
    - b. ECT is recommended for patients with MDD who have associated psychotic or catatonic features, for those with an urgent need for response, and for those who prefer ECT or have had a prior positive response to ECT.
  - 2. Vagus nerve stimulation (VNS).
    - a. VNS therapy system is indicated for the adjunctive long term treatment of chronic or recurrent depression. The age indications are for patients 18 years or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatment trials.
    - b. VNS is FDA-approved for use in patients with treatment-resistant depression on the basis of its potential benefit for long-term treatment.

- c. There is no indication for the use of VNS in acute phase treatment of depression, as data showed no evidence for acute efficacy.
- d. Across all studies of VNS, treatment benefits appear to persist over time and treatment was viewed as tolerable. Side effects commonly reported were voice alteration or hoarseness, coughing, dyspnea and neck pain.
- 3. Pharmacogenomic (PGx) testing.
  - a. PGx is the study of how a person's DNA affects their response to medication.
  - b. PGx testing is utilized to assess the metabolic capacity (gene metabolic variability) of psychiatric patients. Information gleaned from testing can guide treatment decisions and improve clinical outcomes in the following ways:
    - 1. PGx can predict individuals who are more or less likely to have a favorable outcome with specific pharmacotherapies.
    - 2. PGx may be beneficial in patients who have failed to respond to multiple medication trials, secondary to side effects or lack of efficacy at recommended dosages.
  - c. One important study (cf. References) is included that has demonstrated that the clinical application of PGx testing can facilitate individualized treatment strategies for clients prone to treatment resistance or suboptimal medication efficacy.
  - d. In order for PGx testing to be of value, it must be appropriately integrated into clinical practice. At the very least, this means that when PGx testing is employed the test results should be present in the tools used for adjustment of pharmacological treatment. Therefore, any use of PGx testing (i.e., genotyping and the interpretative report) should be accompanied by a quick turnaround time.

## V. Acute Phase of Treatment.

### A. Choice of initial treatment modality.

- 1. Treatment goals should focus on remission of the major depressive episode and full return to the patient's baseline functioning level.
- 2. Selection of initial treatment modality should be influenced by clinical features and other factors such as patient preference and treatment experience.
- 3. Treatment should be integrated with psychiatric management and any other treatments being provided for other diagnoses.
- 4. Pharmacotherapy.
  - a. Antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate MDD.
  - b. Antidepressant medication should be provided for patients with severe MDD unless ECT is planned.
  - c. Initial selection of antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects by the patient, pharmacological properties of the medication, and other factors such as medication response in prior episodes, cost and patient preference.
  - d. For most patients, a SSRI, SNRI, mirtazapine or bupropion is optimal.
  - e. In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.
  - f. Complementary and alternative therapies.

1. In patients who prefer complementary and alternative therapies, SAMe or St. John's wort may be considered, although evidence for their efficacy is modest at best.
2. Despite a large number of trials examining St. John's wort, there is no consensus on its efficacy in treating MDD. St. John's wort may have better tolerability than TCAs and SSRIs, and several randomized studies have shown noninferiority relative to approved antidepressant medications.
3. Careful attention to drug-drug interactions is needed with St. John's wort.
4. Melatonin.
  - a. Melatonin is a hormone found naturally in the body and when used as a medicine is synthetically produced.
  - b. Melatonin can be helpful in correcting sleeping disorders and sleep problems. Melatonin is safe for most adults and can be prescribed for children who are under the care of a licensed practitioner.
  - c. In the presence of pregnancy, breast-feeding, hypertension, seizure disorders, diabetes, cancer and depression, melatonin should be taken only under the direction of a licensed practitioner.

g. Medication titration and monitoring.

1. Rate of antidepressant medication titrated to full therapeutic dose depends upon the patient's age, treatment setting, presence of co-occurring illnesses, concomitant pharmacotherapy and medication side effects.
2. Patients should be systematically monitored to assess response to pharmacotherapy, emergence of side effects and patient safety.
3. Frequency of monitoring should be based on symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports, and frequency and severity of side effects.
4. In the event of side effects, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect.

5. Psychotherapy.

- a. Depression-focused psychotherapy alone is recommended as an initial treatment choice for patients with mild to moderate MDD.
- b. Clinical evidence exists to support the use of CBT, interpersonal psychotherapy, psychodynamic therapy and problem-solving therapy in individual and in group formats.
- c. Use of psychotherapeutic interventions is strengthened by the presence of significant psychosocial stressors (especially marital and family problems), intrapsychic conflict, interpersonal difficulties, a co-occurring Axis II disorder, treatment availability or patient preference.
- d. In women who are pregnant, wish to become pregnant, or are breast-feeding, a depression-focused psychotherapy alone is recommended and, depending on the severity of symptoms, should be considered as an initial option.



- e. Patients should be systematically monitored to assess response to treatment and patient safety.
  - f. Frequency of sessions should be based on goals of treatment, symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports and frequency of visits necessary to ensure good therapeutic alliance and treatment adherence.
6. Psychotherapy plus antidepressant medication
- a. The combination of psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder.
  - b. Combining psychotherapy and antidepressant medication may be useful for patients with mild MDD with psychosocial or interpersonal problems, intrapsychic conflict or co-occurring Axis II disorder.
  - c. In general, the choice of an antidepressant or psychotherapy for combination treatment should be informed by the same issues as when selecting a medication or psychotherapy for use alone.
- B. Assessing treatment response.
- 1. It is necessary to establish that treatment has been administered for a sufficient duration, frequency and dose in the case of medication.
  - 2. The presence of mild residual symptoms has been shown to be a strong predictor of subsequent return to MDD. Therefore, it is important not to conclude the acute phase of treatment prematurely for partially responsive patients.
  - 3. Poor response to treatment may result from multiple factors including inaccurate diagnosis, inappropriate selection of therapeutic modalities, nonadherence to treatment, and unaddressed co-occurring medical or psychiatric disorders
  - 4. Generally, adequate treatment with antidepressant medication for at least four to six weeks is necessary before concluding a patient is not responsive or only partially responsive to a particular medication.
  - 5. For psychotherapy, treatment should be reassessed if there has not been meaningful improvement after a few months, depending on what can reasonably be expected for the treatment modality. Patients should be reassessed every three to four months to ensure adequate improvement.
- C. Strategies to address non-response.
- 1. Review interventions.
    - a. Reappraise diagnoses.
    - b. Assess side effects of medications.
    - c. Evaluate complicating co-occurring conditions.
    - d. Review psychosocial factors.
    - e. Adjust treatment plan.
    - f. Assess quality of therapeutic alliance and treatment adherence.
    - g. For psychotherapy, assess frequency of sessions and appropriateness of treatment modality.
    - h. If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest need to adjust dosages.

2. After additional one to two months of treatment, if there is minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of contributory factors and make additional changes in treatment plan.
3. Medication considerations.
  - a. For patients treated with an antidepressant, optimizing the medication dose is a good first step.
  - b. Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class.
  - c. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant.
  - d. If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotics .
4. Other options may include augmenting medication management with depression-focused psychotherapy or with other agents or changing to another non-MAOI antidepressant.
5. For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered.
6. Psychotherapy.
  - a. For patients treated with psychotherapy, consideration should be given to increasing the intensity of treatment or changing the type of therapy.
  - b. If psychotherapy is used alone, the possible need for medications in addition to or in place of psychotherapy should be assessed.
  - c. Patients with a poor history of treatment adherence or incomplete response to adequate trials of single treatment modalities may benefit from combined treatment with medication and depression-focused psychotherapy.

#### VI. Continuation Phase of Treatment.

- A. Patient should be carefully monitored for signs of possible relapse.
- B. Systematic assessment of symptoms, side effects, adherence and functional status is essential.
- C. Reducing risk of relapse.
  1. Patients who have been treated successfully with antidepressant medication in the acute phase should continue treatment with these agents for four to nine months.
  2. In general, the dose used in the acute phase should be used in the continuation phase.
  3. Depression-focused psychotherapy is recommended in this phase, with the best evidence available for CBT.
- D. Patients who respond to an acute course of ECT should receive continuation pharmacotherapy, with the best evidence available for the combination of lithium and nortriptyline.

#### VII. Maintenance Phase of Treatment.

- A. The maintenance phase seeks to reduce the risk of a recurrent depressive episode by systematic monitoring at regular intervals.
- B. This phase should include patients who have:
  1. Three or more major depressive episodes.

2. Chronic MDD.
  3. Significant risk factors for recurrence.
- C. Additional considerations that play a role in maintenance treatment and its duration.
1. Patient preference.
  2. Type of treatment received.
  3. Presence of side effects during the continuation phase.
  4. Probability of recurrence.
  5. Frequency and severity of prior depressive episodes.
  6. Persistence of depressive symptoms after recovery.
  7. Presence of co-occurring disorders.
  8. For patients with chronic and recurrent MDD or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely.
- D. Antidepressant medication that produced remission during the acute phase and maintained remission during the continuation phase should be continued at full therapeutic doses.
- E. If depression-focused psychotherapy has been used during acute and continuation phases, it should be continued with a reduced frequency of sessions.
- F. For patients who have shown a response to ECT or VNS, maintenance treatment with these modalities may be considered.

#### VIII. Discontinuation of Treatment.

- A. Pharmacotherapy considerations.
1. When medications are being discontinued it is best to taper the medication over the course of at least several weeks.
  2. Patients should be advised not to stop medications abruptly.
  3. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome.
  4. Before discontinuation of active treatment patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms.
  5. After discontinuation of medications patients should continue to be monitored over the next several months and should receive another administration of acute phase treatment if symptoms recur.
- B. Psychotherapy.
1. In psychotherapy it is important to raise the issue of treatment discontinuation well in advance of the final session, although the exact process by which this occurs will vary depending on the treatment model.

#### IX. Special Groups and Circumstances.

##### A. Youth.

1. Youth with risk factors associated with development of depressive disorders should have access to early services and interventions.
2. Education, support and case management appear to be sufficient treatment for the management of depressed youth with an *uncomplicated or brief depression or with mild psychosocial impairment*.

3. For youth who *do not respond to supportive psychotherapy or who have more complex depressions*, a trial with specific types of psychotherapy and/or antidepressants is indicated.
  4. During all treatment phases for a youth who is not responding to appropriate pharmacological and/or psychotherapeutic treatments, consider factors associated with poor response.
  5. Some youth may require maintenance treatment. To avoid recurrences, some depressed youth should be maintained in treatment for periods of time longer than six to 12 months.
  6. To improve the youth's response, caregivers should be referred for separate and concurrent counseling to address their own issues.
- B. Depressed patients with psychosis, seasonal depression and bipolar disorder may require specific somatic treatments.
- C. Treatment should include management of comorbid conditions.

## References

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