GLIN IPA

2024

Clinical Care Pathway: Depression

Clinical Care Pathway: Depression

Purpose & Objective

This protocol provides evidence-based care recommendations in the screening and treatment of major depressive disorder (MDD) in the general adult and older adult populations in the primary care setting. The protocol seeks to assist in early diagnosis and effective treatment of MDD. The MDD protocol should provide primary care physicians, family nurse practitioners, and physician's assistants with a guide that is evidence-based and cost effective. This pathway and recommendations were derived from the American Academy of Family Physician (AAFP) and U.S. Preventative Services Task Force (USPSTF) references.

Goals of Care

- Alleviating functional impairments
- Improving quality of life
- Achieving symptom resolution & episode remission

Screening

- Screening Tool
  - › PHQ-2 or PHQ-9 can be used pending ability to implement & review screening tool at appointment (free screening tools available; Appendix I)
    - Patients who screen positive with a PHQ-2 should be further evaluated with the PHQ-9, other diagnostic instruments, or direct interview to determine whether they meet criteria for a depressive disorder.

Screening Tool (continued)

- › Should be provided by front-office staff in waiting room to complete prior to appointment
  - Pending office ability, the administration of the PHQ for follow up can be done using phone calls and/or a smartphone application prior to an appointment or telehealth encounter
- › It is then scored by an administrative staff or medical assistants & subsequently enter the score into the electronic health record prior to provider assessment/evaluation of patient

- Initial Screening & Frequency
  - › All patients not currently receiving treatment for depression & with no previous history of depression should be screened for depression with either PHQ-2 or PHQ-9.
    - This includes pregnant & postpartum women
  - › Screening should be repeated in those patients with past negative screening:
    - Annually with either PHQ-2 or PHQ-9, or
    - History of alcohol abuse and/or drug abuse
    - If symptoms suggest the presence of depression with PHQ-9
    - Symptoms or combination of symptoms may include psychological or somatic symptoms (Table 1)
    - Certain populations with higher risks for depression, such as those with HIV infection, may be considered for regular screening

Table 1

Psychological Symptoms	Somatic Symptoms
Depressed Mood	Loss of interest or pleasure in activities that are normally enjoyable
Loss of Interest or Pleasure	Lack of emotional reactivity to normally pleasurable surroundings & events
Decreased Energy & Fatigue	Depression worse in the morning
Reduced Concentration & Attention	Objective evidence of definite psychomotor retardation or agitation (remarked on or reported by other people)
Reduced Self-Esteem & Self-Confidence	Marked loss of libido
Disturbed Sleep	Waking up in the morning two (2) hours or more before the usual time
Diminished Appetite	Marked loss of appetite
Ideas of Guilt & Unworthiness	Weight loss (often defined as 5% or more of body weight in the past month)
Bleak & Pessimistic Views of the Future	
Ideas or Acts of Self-Harm or Suicide	

Screening Tool (continued)

- › Screening should be done using standardized screening tool at least six (6) months after an initial positive screen with PHQ-9
- › For patients scoring 'mild' on the PHQ-9, a repeat PHQ-9 should be completed as clinically indicated based on symptoms review at each appointment, or at a minimum of at least annually.
- › A positive screening of PHQ-2 or PHQ-9 would prompt moving to "Diagnosis" section below for further evaluation

- Basic assessment at initial encounter should include
  - › Mental state examination, use of standardized rating scales to rate all aspects of the illness
  - › Complete detailed history with information from all possible sources
    - In case patient has received treatment in the past, it is important to evaluate type of antidepressant used, dose of medication used, compliance with medication, reasons for poor compliance, reasons for discontinuation of medication, response to treatment, side effects experienced etc. If the medications were changed, then the reason for change is also to be evaluated.
  - › Physical exam
    - Assess for thyroid swelling, evidence of malnutrition, or any specific nutritional deficiency, & physical illness that could contribute to depressive symptoms
    - Record blood pressure (BP), weight, & BMI

Diagnosis

- Following a positive PHQ-9, establish a diagnosis according to DSM-5 criteria (Appendix II)
- Differential diagnosis by ruling out secondary depression
  - › Rule out bipolar disorder
    - Many patients with bipolar disorder present to clinicians during the depressive phase of illness & spontaneously do not report about previous hypomanic or manic episodes. Treating a patient of bipolar depression as unipolar disorder can increase the risk of antidepressant-induced switch.
    - Presence of psychotic features, marked psychomotor retardation, reverse neuro-vegetative symptoms (excessive sleep & appetite), irritability of mood, anger, family history of bipolar disorder & early age of onset signals need to evaluate for the possibility of bipolar disorder, before diagnosing unipolar depression.

Diagnosis (continued)

    - If suspicion of bipolar disorder, use standardized scale Mood Disorder Questionnaire (MDQ) to rule out bipolarity.
  - Rule out premenstrual dysphoric disorder - evaluation of history also takes into consideration the relationship of onset of depression with change in season (seasonal affective disorder), peri-partum period & phase of menstrual cycle.
  - Physical illnesses commonly associated with depression (Appendix III)
  - Assess for use of medications that may cause depression (Appendix IV)
- Basic evaluation: CBC, CMP with blood glucose, renal function tests & LFTs, fasting lipid panel (FLP), thyroid function tests with reflex to free T4, Vitamin D level & urine pregnancy test, if indicated & appropriate.
  - Neuroimaging should be considered for those with first-episode of depression seen in late or very later age, or those that have neurological signs. Initial studies to be completed with either CT or MRI.

Comprehensive Medical Evaluation

- Following diagnosis, assess disease severity & subtype.
  - Determine MDD severity from PHQ-9 (Table 2)
  - Assess specifier & subtype of depression effecting pharmacotherapy considerations (Appendix V)

Table 2

PHQ-9 Score	Depression Severity
0 – 4	None
5 – 9	Mild
10 – 14	Moderate
15 – 19	Moderately Severe
20 – 27	Severe

Comprehensive Medical Evaluation
(continued)

- Evaluate comorbid physical, psychiatric & substance use conditions
    - Thorough assessment should focus on evaluation for comorbid substance abuse/dependence. Careful history of substance intake should be documented to evaluate the relationship of depression with substance intoxication, withdrawal & abstinence.
    - Whenever required appropriate tests like, urine or blood screens (with prior consent) may be used to confirm the existence of comorbid substance abuse/dependence.
- Evaluate risk of harm to self & others
    - Careful assessment for presence of suicidal ideation & other associated factors like presence of psychotic symptoms, severe anxiety, panic attacks & alcohol or substance abuse which increases the risk of suicide need to be evaluated should be completed.
    - Evaluation to include history of past suicide attempts, including the nature of those attempts.
    - Patients also need to be asked about suicide in their family history.
    - During the mental status examinations besides enquiring about the suicidal ideations, it is also important to enquire about the degree to which the patient intends to act on the suicidal ideation & the extent to which the patient has made plans or begun to prepare for suicide. The availability of means for suicide be inquired about & a judgment may be made concerning the lethality of those means.
- Assess patient level of functioning
    - Evaluate impact on school & work performance, as applicable
    - Evaluate impact of activities of daily living (ADLs; eating, bathing, etc.)
- Assess patient socio-cultural environment & beliefs
- Assessment of caregivers burden, coping & distress, if applicable
    - Evaluate caregiver's knowledge & understanding of the illness, attitudes & beliefs regarding treatment, impact of the illness on them, & personal & social resources.
- Review current medications, compliance to regimen & any lifestyle changes including a review of the pharmacy fill history to assess for noncompliance to regimen
- Document all of the information reviewed in the patient's medical record

Referral

- Refer when indicated - determine treatment setting:
  - Patients should be treated in the setting that is most safe and effective.
  - Some patients with severe depression which may be further associated with psychotic symptoms, catatonic symptoms, poor physical health status, suicidal or homicidal behavior etc., referral to inpatient care should be offered.
  - Severely ill patients who lack adequate social support outside of a hospital setting should be admitted to a hospital whenever feasible.
  - The optimal treatment setting and the patient's ability to benefit from a different level of care may be re-evaluated on an ongoing basis throughout the course of treatment.
  - Common indications for inpatient care
    - Presence of suicidal behavior which puts the life of the patient or others at risk
    - Refusal to eat
    - Severe malnutrition
    - Catatonia
    - Presence of general medical or comorbid psychiatric conditions that make outpatient treatment unsafe of ineffective
- Refer for treatment management as detailed more below under "Management – Treatment Options" & "Management – Treatment Algorithm"
- Consider referral to pharmacy team for complex pharmacotherapy review, or to assist in facilitating initiation & adjustment of antidepressant dosages, monitoring of patient adherence to regimen, & management of adverse reactions to pharmacotherapy.
- Coordinate linkage to available resources, such as care management, group medical visits, community resource referral for closing gaps in social determinant of health gaps.
- Refer to GLIN IPA Care Management, 716.800.CARE (2273), to discuss social determinants of health.

Management – Treatment Options

Formulation of treatment plan involves deciding about treatment setting, medications and psychological treatments to be used; Table 3 outlines a summary of depression guidelines first-line treatment agents.

Table 3

Depression Severity	Proposed Treatment Actions
None – minimal	No intervention
Mild	Watchful waiting; repeat PHQ-9 at follow-up
Moderate	Treatment plan, consider counselling, follow-up and/or pharmacotherapy
Moderately Severe	Active treatment with pharmacotherapy and/or psychotherapy
Severe	Immediate initiation of pharmacotherapy &, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for psychotherapy & or collaborative management

Treatment options for management of depression can be broadly be divided into antidepressants, electroconvulsive therapy (ECT) & psychosocial interventions.

- Antidepressant Medication
  - In general all the antidepressants have been shown to have nearly equal efficacy in the management of depression.
    - Selective serotonin reuptake inhibitors (SSRIs) are considered to be the first-line antidepressants, due to the side effect & safety profile.
    - The selection of antidepressant medications may be based on patient specific & drug specific factors (Table 4).

Table 4

Patient-Specific Factors	Drug-Specific Factors
Past treatment response/tolerability	Cost
Past history of adverse drug reactions	Availability
Co-morbidity (eg. glaucoma, cardiac conditions, psychiatric disorders)	Side effect profile of therapy
Patient and/or family preference	Dosing strategy
Other medication use – drug interaction potential	Formulation – tablet vs capsule vs syrup
Patient's age	Relative toxicity – safety in overdose
Gender issues – sexual dysfunction	
Intellectual & psychological capacities	

Management – Treatment Options
(continued)

- Usually the medication must be started at lower doses & the doses must be titrated, depending on the response & the side effects experienced.
- Refer to Appendix VI for review of pharmacotherapy options, initial & target dose for depression management, & side effects when considering initial pharmacotherapy treatment.

› Antidepressant medication may be used as initial treatment modality for patients with mild, moderate, or severe depressive episode.

› In some cases, lithium may be used as an augmenting agent when patient is not responding to antidepressants.

- Lithium
  - If patient establishes care with office who is currently prescribed Lithium, consider referral to psychiatry.
  - If lithium treatment may be required for management, consider referral to psychiatry.
  - Lithium is useful in over 50% of antidepressant non-responders & is usually well tolerated. The interval before full response to adjunctive lithium is in the range of several days to three (3) weeks. If effective & well tolerated, lithium may be continued for the duration of treatment of the acute episode.

› Benzodiazepine use may be considered as adjunctive treatment during the initial phase of treatment.

- An antidepressant plus a benzodiazepine at initiation of treatment is reasonable for concomitant severe anxiety or insomnia.
- Benzodiazepines added at the beginning of pharmacotherapy using standard doses, & then gradually discontinued once the antidepressant begins to take effect.
  - Limit duration of use during acute phase, limit to lowest effective dose & shortest possible duration as clinically indicated.
- Use Cautiously or Avoid
  - Benzodiazepine use should be avoided in patients with a history of alcohol or substance abuse, or a history of problematic adherence to antidepressants, & the elderly due to enhanced sedation response.
  - Avoid using benzodiazepines on an as needed basis because this approach is often not effective; fluctuating serum concentrations, especially with short acting benzodiazepine agents (eg. alprazolam) can increase the risk of minor withdrawal reactions & reinforce psychological dependence.

Management – Treatment Options
(continued)

        - As needed dosing may interfere with cognitive-behavioral therapy (CBT), by promoting rescue medication as a coping strategy that competes with the coping skills taught in CBT.
    - Avoid co-prescribing with opioids due to increased risk of sedation & respiratory depression.
- Treatment requires monitoring for tolerance (diminished effect over time), physiologic dependence, sedation, amnestic effects, impaired psychomotor speed, & increased accidents.

› Monitoring

- Assess the response to pharmacotherapy as well as the emergence of side effects & safety, including but not limited to suicidal thoughts & behaviors, at 4-6 weeks; monitor & address suicidality & to promote treatment adherence.
- Improvement with pharmacotherapy can be observed after 4-6 weeks of treatment. If at least a moderate improvement is not observed in this time period, reappraisal & adjustment of the pharmacotherapy should be considered.

- Non-pharmacologic Management

› Exercise

- 30 minutes or more of exercise a day for 3-5 days a week.

› Sleep Hygiene

- Consider a consistent sleep schedule
- Avoid alcohol
- Reduce eliminate coffee or other caffeine, especially after lunch
- Limit use of devices with screens at least one (1) hour before bedtime
- Use blackout shades, eyes masks, ear plugs

› Stress Management

- Proper sleep hygiene
- Eating a healthy diet
- Finding a relaxing hobby
- Doing breathing exercise to lower heart rate

› Nutrition/Supplementation

- High intake of fruit, vegetables, whole grain, fish olive oil, low-fat dairy & antioxidants, low intake of red and/or processed meats

Management – Treatment Options
(continued)

› Psychoeducation
- Education concerning depression & treatments should be provided to all patients. When appropriate, education can also be provided to involved family members.
- Education regarding available treatment options will help patients make informed decisions, anticipate side effects & adhere to treatments.
- Important components of psychoeducation are:
  - Assessing the knowledge of the patient & caregivers about the etiology, treatment & prognosis of depression
  - Explain about the diagnosis & symptoms of depression
  - Explain that depression is a treatable medical disorder
  - Inform the patient & especially family about the lag period of onset of action of antidepressants.
  - Provide information about treatment including available options, their effectiveness, side effects, & duration of use
  - Discuss the importance of medication & treatment compliance
  - Provide information about possible course & long-term outcome
  - Discuss problems of substance abuse, interpersonal conflict, stress, etc. & discuss how to handle these issues
  - Enhancing adaptive coping to deal with persistent/residual symptoms
  - Discuss relapse & how to identify early signs of relapse
  - Encourage healthy lifestyles

› Psychotherapeutic Intervention
- A specific, effective psychotherapy may be considered as an initial treatment modality for patients with mild to moderate depressive disorder.
- Indication
  - Clinical features that may suggest the use of a specific psychotherapy include the presence of significant psychosocial stressors, intrapsychic conflict & interpersonal difficulties.
  - Patient's preference for psychotherapeutic approaches is an important factor that may be considered in the decision to use psychotherapy as the initial treatment modality.
  - Pregnancy, lactation, or the wish to become pregnant may also be an indication for psychotherapy as an initial treatment.
- Cognitive behavioral therapy (CBT) & interpersonal therapy are the psycho-therapeutic approaches that have the best documented efficacy in the literature for management of depression & are considered first line, when indicated.

Management – Treatment Options
(continued)

  - Various psychotherapeutic interventions may be considered based on feasibility, expertise available & affordability (Appendix VII).
- The psychiatrist providing the psychotherapy will determine the frequency of sessions for individual patients, including the specific type & goals of psychotherapy, the frequency necessary to create & maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, & the frequency necessary to monitor & address suicidality.

- ECT: refer to psychiatrist
  - › Usually reserved for pts with catatonia, suicidality, severe depression, and/or past response to ECT, augmentation, etc.
  - › May be considered in virtually all cases of moderate or severe major depression who do not respond to pharmacologic intervention
  - › Lithium should be discontinued before initiation of ECT
  - › May prolong postictal delirium & delay recovery from neuromuscular blockade
- Combination of pharmacotherapy & psychotherapy
  - › In general, the same issues that influence the choice of medication or psychotherapy when used alone should be considered when choosing treatments for patients receiving combined therapy.
- Other treatments
  - › Less commonly used treatment or treatments reserved for patients with treatment resistant depression include repetitive transcranial magnetic stimulation (rTMS), light therapy, transcranial direct stimulation, vagal nerve stimulation, deep brain stimulation (DBS), ketamine infusions & sleep deprivation treatment.
  - › Refer to psychiatry to prescribe & manage these treatments

Management – Treatment Algorithm

Phases of Illness/Treatment: management of depression can be broadly divided into three (3) phases, i.e., acute phase, continuation phase and maintenance phase.

- **Acute Phase**
  - **GOAL:** achieve remission
    - The various components of acute phase treatment are shown in Table 5 & the treatment algorithm is shown in Figure 1 (mild to moderate depression) & Figure 2 (severe depression).

Table 5

Components of Acute Phase Treatment
Comprehensive assessment
Deciding on goals of treatment
Achieving remission
Ensure safety of patient & others
Choice of treatment setting
Choosing a treatment modality – antidepressant therapy, psychotherapy, or combination
Use of adjunctive medications when indicated
Use of ECT when indicated
Psychoeducation

  - **TREATMENT:** choose between several initial treatment modalities, including pharmacotherapy, psychotherapy, the combination of medication & psychotherapy, or ECT (requires referral to psych). Selection of an initial treatment modality is usually influenced by both clinical (e.g. severity of symptoms) & other factors (e.g. patient preference).
    - Antidepressant medication – see review above on therapy selection, dose initiation, & therapy considerations
      - SSRIs, SNRIs or NDRIs (bupropion) are recommended, but the evidence base is insufficient for recommending any specific medication over another.
    - In the initial phase, depending on the symptom severity & type of symptoms, such as presence of insomnia or anxiety, benzodiazepines or other hypnotics may be used for short duration, as referenced above.
    - Failure to respond
      - If after 4-8 weeks of treatment, if no improvement is not observed, then a thorough review & reappraisal of the diagnosis, complicating conditions, & treatment plan may be conducted.

Management – Treatment Algorithm
(continued)

- Reappraisal of the treatment regimen may also include evaluation of patient adherence & pharmacokinetic/pharmacodynamic factors.
- Following this review, the treatment plan can be revised by implementing one of several therapeutic options, including maximizing the initial medication treatment, switching to another antidepressant medication, augmenting antidepressant medications with other agents/psychotherapy/ECT.
    - Switching therapy: patient can be switched to an antidepressant medication from the same pharmacologic class (e.g. SSRI to another SSRI) or to one (1) from a different pharmacologic class (e.g. SSRI to a TCA). It is suggested that when switching, a drug with a different or broader mechanism of action be chosen.
        - Consider switching to another antidepressant when:
            - It is the first antidepressant trial
            - There are poorly tolerated side effects to the initial antidepressant
            - There is no response (<25% improvement) to the initial anti-depressant
            - There is more time to wait for a therapeutic response (less severe depression, less functional impairment)
            - Patient prefers to switch to another antidepressant
        - Factors that are involved in choosing a strategy for switching antidepressants include:
            - The risk of discontinuation symptoms
            - Potential for drug interactions
            - Other antidepressant properties such as elimination half-life
            - Adverse effects
            - Pharmacodynamics
            - How quickly depression symptoms need to be controlled
        - Strategies for switching therapy include:
            - Cross-tapering
                - Standard technique, cross-tapering is consistent with multiple treatment guidelines
                - This approach can minimize the risk of drug-drug interactions, while at the same time prevent both discontinuation & depressive symptoms that may occur from abrupt drug withdrawal

Management – Treatment Algorithm
(continued)

- The dose of the current antidepressant is gradually reduced to zero, while simultaneously the new antidepressant is started & titrated up to the therapeutic range
  - Reduce the dose by the same number of milligrams (amount) each time the dose is decreased, or by the same percent (eg, 50%) each time while concurrently increasing the dose of the new treatment by the same amount each time
- Typically occurs over 1-2 weeks, but for patients who have previously demonstrated sensitivity to side effects or discontinuation symptoms, cross-tapering is extended over 3-4 weeks
- Contraindicated if patients are switched to or from a monoamine oxidase inhibitor (MAOI)

• Direct switching
- The current antidepressant is abruptly stopped & the new drug is started the next day at the equivalent dose (see Appendix VI)
- Used when switching between antidepressants that share pharmacodynamic profiles, including antidepressants within the same drug class (eg. SSRIs) or if the antidepressant to be discontinued has been used for a relatively short period of time (eg, less than 1-2 weeks)
- If discontinuing a therapy due to severe adverse reaction, wait 2-3 days before starting the new antidepressant

◦ Augmentation: This approach may be particularly helpful for patients who have had a partial response to initial antidepressant monotherapy. Options include:
- Adding a second antidepressant medication from a different pharmacologic class, or
- Adding another adjunctive medication such as lithium, psychostimulants, modafinil, thyroid hormone, an anticonvulsant, etc.
- Consider an adjunctive medication when:
  • There have been two (2) or more antidepressant trials.
  • The initiation antidepressant is well tolerated.
  • There is partial response (>25% improvement to the initial antidepressant.

Management – Treatment Algorithm
(continued)

- There is specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a therapeutic response (more severe depression, more function impairment).
- Patient prefers to add on another medication.

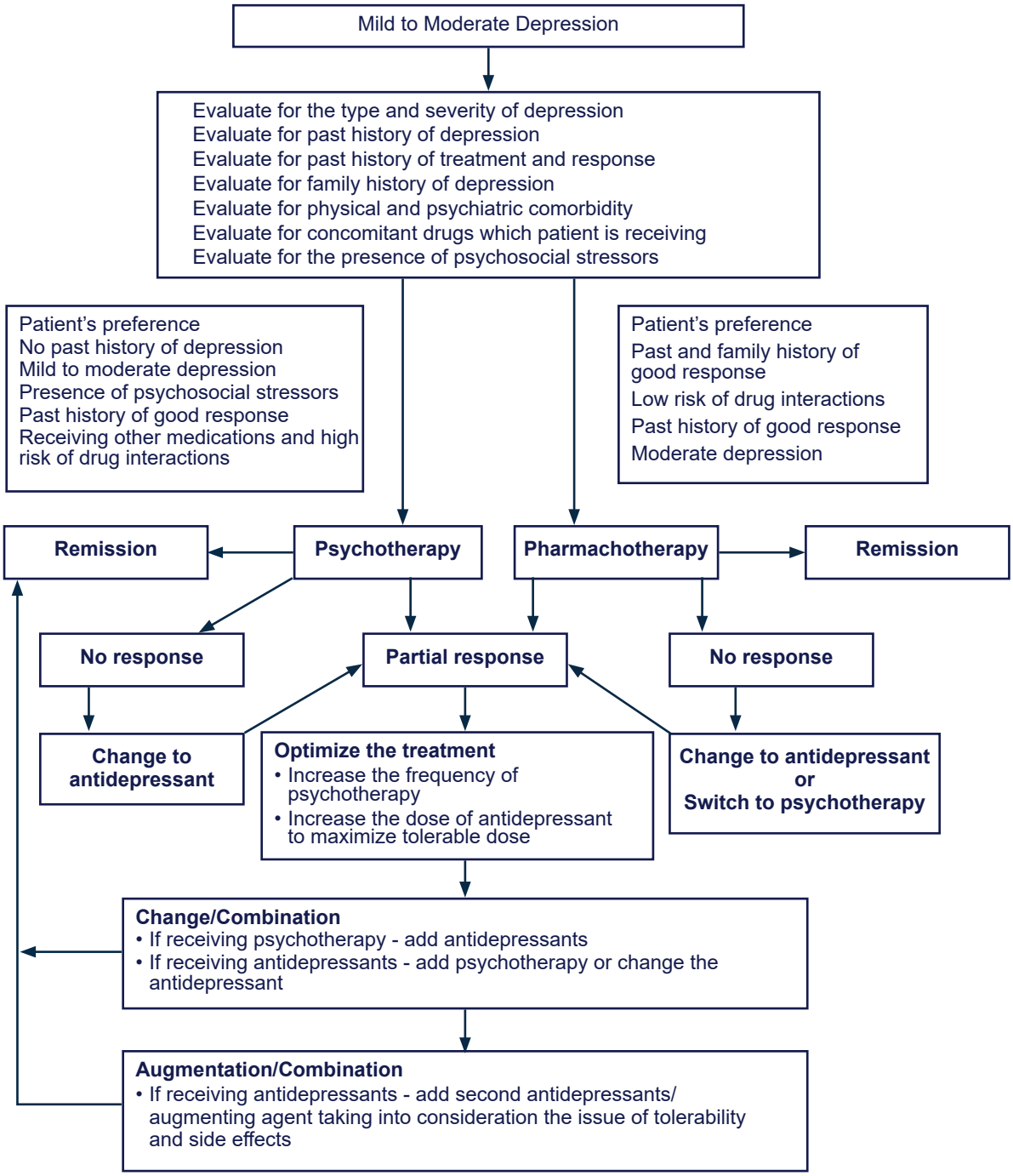
- Adding, changing, or increasing the intensity of psychotherapy may be considered for patients who do not respond to medication treatment.

- Following any change in treatment, if at least a moderate level of improvement in depressive symptoms is not seen after an additional 4–8 weeks of treatment, another thorough review need to be done.
    - This reappraisal may include verifying the patient's diagnosis & adherence; identifying & addressing clinical factors that may be preventing improvement, & identifying & addressing psychosocial issues that may be impeding recovery. If no new information is uncovered to explain the patient's lack of adequate response, depending on the severity of depression, ECT may be considered (refer to psych).

Management – Treatment Algorithm
(continued)

Figure 1

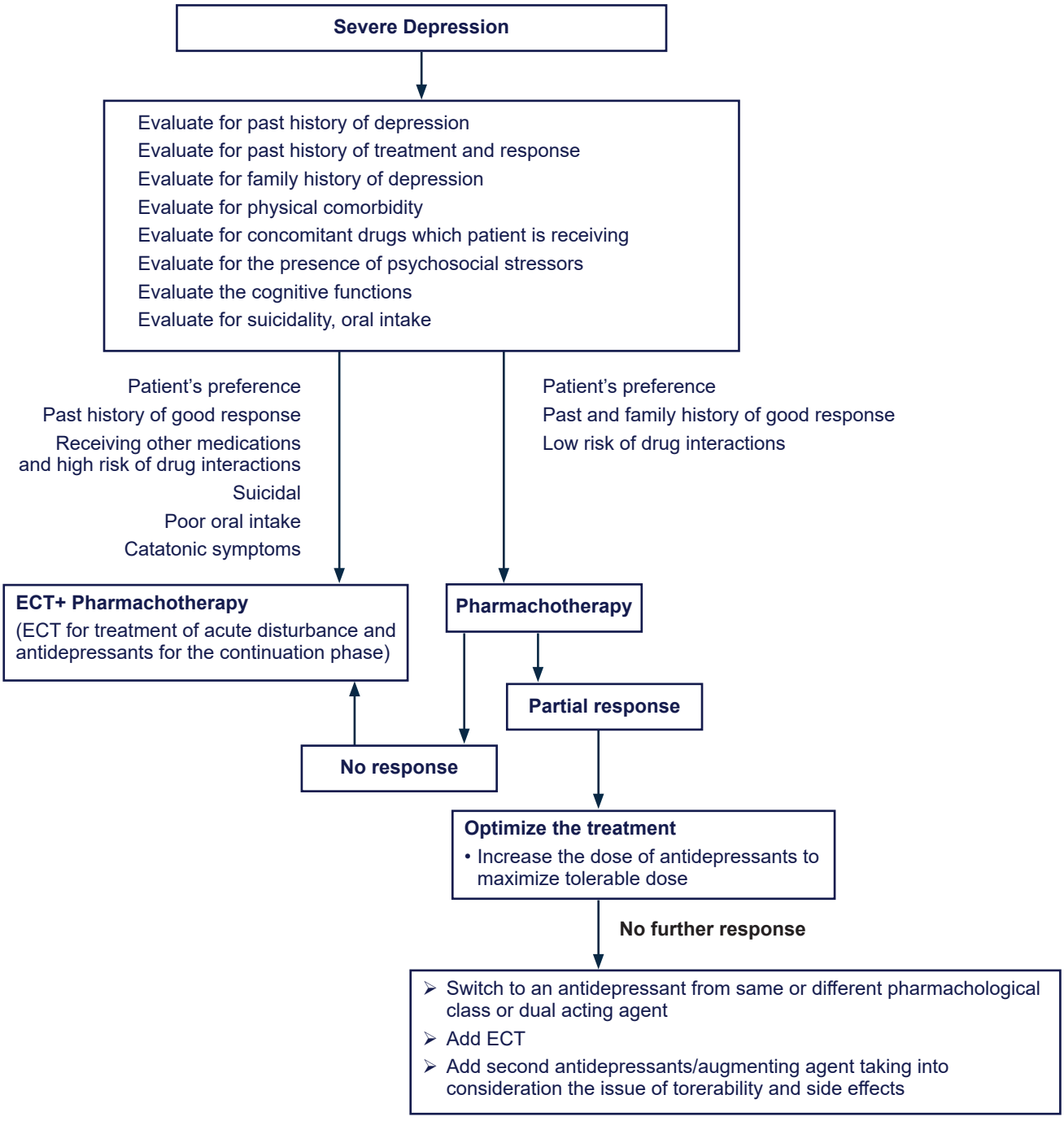
Acute Phase Management Treatment Algorithm - Mild to Moderate Depression



Management – Treatment Algorithm
(continued)

Figure 2

Acute Phase Management Treatment Algorithm - Severe Depression



Management – Treatment Algorithm
(continued)

- Choice of psychotherapy
  - Out of the various psychotherapeutic interventions used for management of depression, there is robust level of evidence for use of CBT.
  - The major determinants of type of psychotherapy are patient preference & the availability of clinicians with appropriate training & expertise in specific psychotherapeutic approaches.
    - Other clinical factors which will influence the type of psychotherapy include the severity of the depression.
    - Psychotherapy is usually recommended for patients with depression who are experiencing stressful life events, interpersonal conflicts, family conflicts, poor social support & comorbid personality issues.
  - The optimal frequency of psychotherapy may be based on specific type & goals of the psychotherapy, the frequency necessary to create & maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, & the frequency necessary to monitor & address suicidality.
    - Other factors which would also determine the frequency of psychotherapy visits include the severity of illness, the patient's cooperation with treatment, the availability of social supports, cost, geographic accessibility, & presence of comorbid general medical problems.
  - Besides the use of specific psychotherapy, all patients & their caregivers may receive psychoeducation about the illness.
  - Role of Yoga & Meditation in management of depression
    - Studies related to role of traditional therapies like meditation, yoga & other techniques have been mostly published in documents of various organizations propagating that particular technique.
    - Well-designed scientific studies to authenticate these claims need to be conducted; however, efficacy of these techniques as supportive/adjunctive therapy is widely accepted.

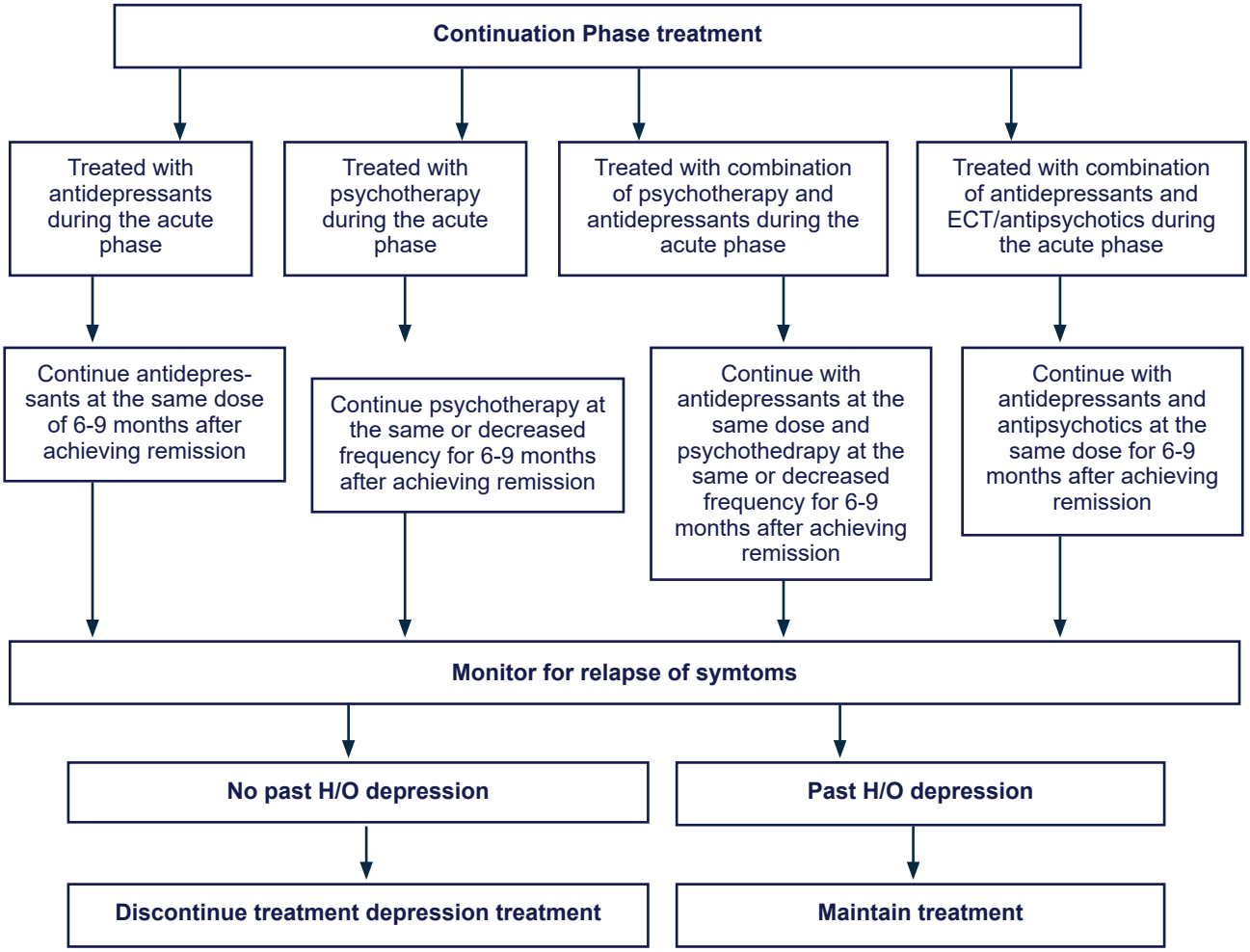
- **Continuous Phase**
  - **GOAL:** maintain the gains achieved in the acute phase of treatment & prevent relapse of symptoms. The treatment algorithm to be followed is shown in Figure 3.
  - Patients who have been treated with antidepressants in the acute phase need to be maintained on same dose of these agents for 16-24 weeks to prevent relapse (total period of 6-9 month from initiation of treatment).
  - There are evidences to support the use of specific psychotherapy in continuation phase to prevent relapse.

Management – Treatment Algorithm
(continued)

- The use of other somatic modalities (e.g. ECT) may be useful in patients where pharmacology and/or psychotherapy have failed to maintain stability in continuation phase.
- The frequency of visit during the continuation phase may be determined by patient's clinical condition as well as the specific treatment being provided.
    - Patient should be followed-up with every 6-12 weeks during continuation phase unless safety assessment dictates more regular f/u every 2- 4weeks if warranted

Figure 3

Continuation Phase Treatment Algorithm

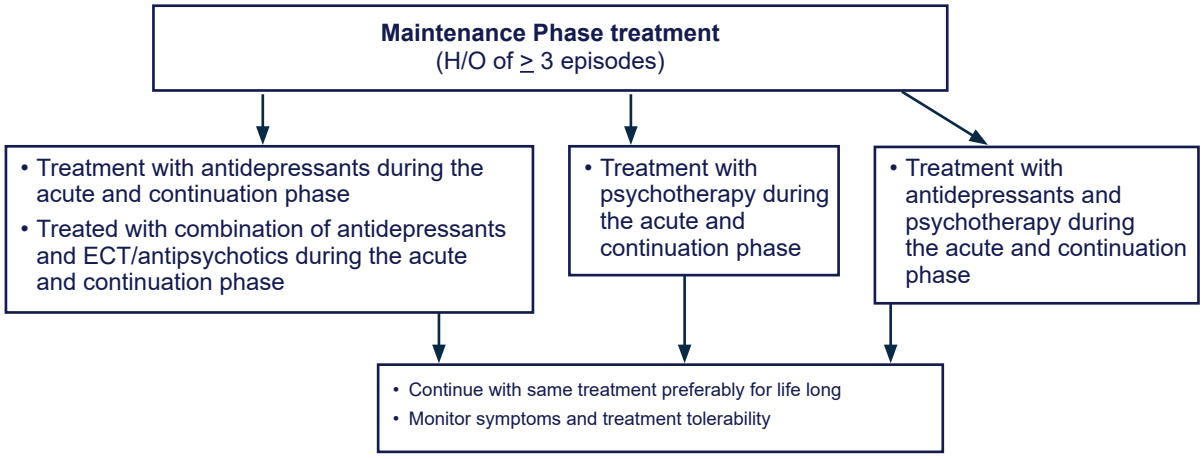


Management – Treatment Algorithm
(continued)

- **Maintenance Phase**
  - › **GOAL:** prevent recurrence of depressive episodes; on average, 50-85% of patients with a single episode of MDD have at least one more episode.
  - › This phase is usually considered when patient has recurrent depressive disorder. Therefore, maintenance phase treatment may be considered to prevent recurrence.
  - › The duration of treatment may be decided keeping in view the previous treatment history & number of depressive episodes the person has had in the past.
    - Patients who have history of three (3) or more relapses or recurrences need to be given long-term treatment.
  - › The treatment that was effective for acute & continuation phase should be used in the maintenance phase (Figure 4).
    - Same doses of antidepressants, to which the patient had responded in previous phase is considered.
    - The frequency of visit for CBT & IPT can be reduced during the maintenance phase (once a month).

Figure 4

Maintenance Phase Treatment Algorithm



- › If maintenance phase treatment is not indicated for patients who remain stable following the continuation phase, patients may be considered for discontinuation of treatment.
  - If treatment is discontinued, careful monitoring be done for relapse, & treatment to be promptly reinstituted if relapse occurs.

Management – Treatment Algorithm
(continued)

- If maintenance phase treatment is not indicated for patients who remain stable following the continuation phase, patients may be considered for discontinuation of treatment.
    - If treatment is discontinued, careful monitoring be done for relapse, & treatment to be promptly reinstituted if relapse occurs.
- The decision to discontinue maintenance treatment may be based on the same factors considered in the decision to initiate maintenance treatment, including the probability of recurrence, the frequency & severity of past episodes, the persistence of depressive symptoms after recovery, the presence of comorbid disorders, & patient preferences.
- When discontinuing therapy in the maintenance pharmacy
    - Psychotherapy: the manner in which this is done may be individualized to the patient's needs
    - Pharmacotherapy: it is best to taper the medication over the course of at least several weeks to few months (4-12 weeks, typically).
        - Such tapering allows for the detection of emerging symptoms or recurrences when patients are still partially treated & therefore can be easily returned to full therapeutic intensity.
        - Tapering can minimize the risks of antidepressant medication discontinuation syndromes.
            - Discontinuation syndromes have been found to be more frequent after discontinuation of medications with shorter half-lives, & patients maintained on short-acting agents may be given even longer, more gradual tapering.
            - Paroxetine, venlafaxine, TCAs, & MAOIs tend to have higher rates of discontinuation symptoms while bupropion-SR, citalopram, fluoxetine, mirtazapine, & sertraline have lower rates.
            - The symptoms of antidepressants discontinuation include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, & hyperarousal (agitation).
        - Discontinuation symptoms:
            - **MILD:** reassurance may be sufficient
            - **MILD to MODERATE:** short-term symptomatic treatment (analgesics, antiemetics, or anxiolytics) may be beneficial
            - **SEVERE:** antidepressant are to be reinstated & tapered off more slowly
    - After the discontinuation of active treatment, patients should be reminded of the potential for a depressive relapse. Patient should be reminded of the early signs of depression, & a plan for seeking treatment in the event of recurrence of symptoms may be formulated.

Management – Treatment Algorithm
(continued)

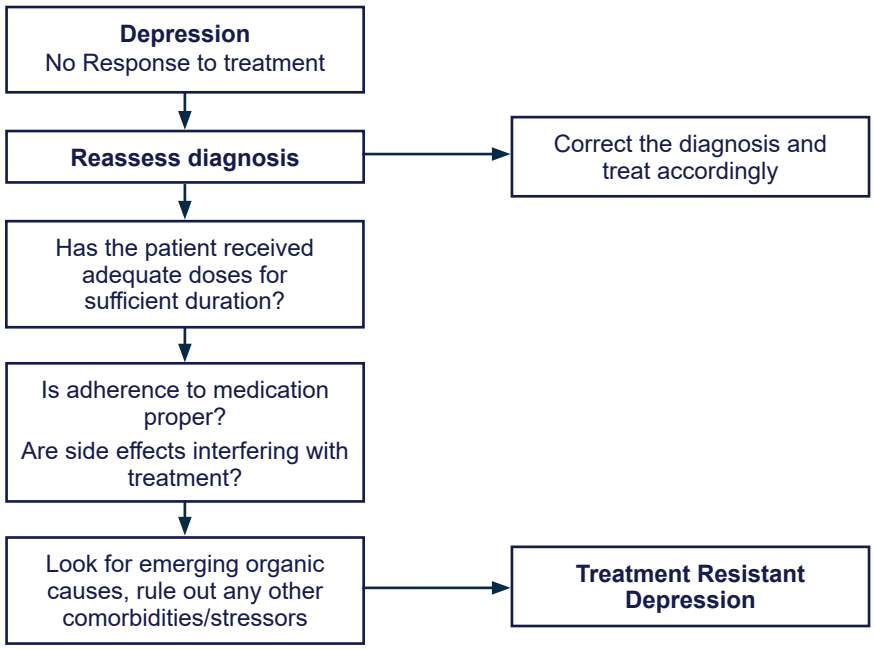
- Patients should be seen for evaluation of therapy & to be monitored every 3-6 months to identify relapse, for the first year, & then annually.

- **Relapse**
  - › If a patient suffers a relapse upon discontinuation of medication, treatments need to be promptly reinitiated. In general, the previous treatment regimen to which the patient responded in the acute & continuation phase are to be considered.

- **Treatment Resistant Depression (TRD)**
  - › Adequate treatment for at least 4-6 weeks is necessary before concluding that a patient is not responsive to a particular medication. Two (2) successive trials of medications of different categories for adequate duration is required before considering TRD.
  - › First step in care of a patient who has not responded to medication is carrying out a thorough review & reappraisal of the psychosocial & biological information base, aimed at re-verifying the diagnosis & identifying any neglected & possibly contributing factors, including the general medical problems, alcohol or substance abuse or dependence, other psychiatric disorders, & general psychosocial issues impeding recovery. Algorithm for arriving at the diagnosis of treatment resistant depression is given in Figure 5.

Figure 5

Identification of Treatment Resistant Depression



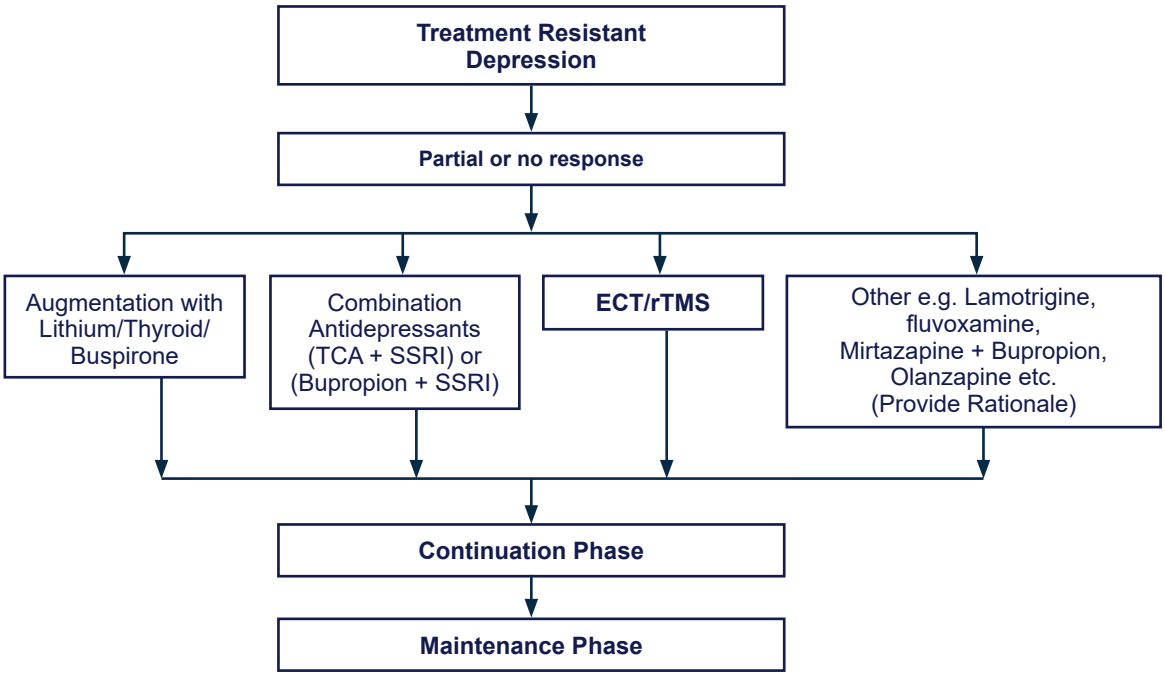
Management – Treatment Algorithm
(continued)

› Management of TRD involves addition of an adjunctive agent, combining two (2) antidepressants, addition of ECT or other somatic treatments like repetitive transcranial magnetic stimulation (rTMS). ECT & rTMS require referral to a psychiatrist for evaluation, prescription, & monitoring. Algorithm for management of TRD is given in Figure 6.

- rTMS occurs in a rhythmic & repetitive form has been put forward as a new technique to treat this debilitating illness. Current evidence suggests that rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) is a promising treatment strategy for depression, but not all patients show a positive outcome.

Figure 6

Treatment Resistant Depression Algorithm



- **Management in Special Conditions**
  - Certain clinical situations require special attention or can influence treatment decisions. Management of these situations is summarized in Appendix VIII.

Follow Up

- Patient is discharged & support staff emphasizes key education points & depression management changes. A current medication list is printed for the patient. Follow up visit is scheduled as appropriate.
- Based on patient specific factors determined by provider, patient is contacted for follow up the visit by a care team member to emphasize key points in the education provided & to ensure that barriers to achieving the depression remission are re-addressed & viable plan to address barriers is reviewed with the patient. Patient is advised of the importance regarding follow-up care & the need for monitoring.

Appendix I

The Patient Health Questionnaire-2 (PHQ-2)

Patient Name: _____ Date of Visit: _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than one-half of the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Md Care.* 2003;41:1284-1292. ©2007CQAIMH. All rights reserved. Used with permission.

The Patient Health Questionnaire-2 (PHQ-9)

Patient Name: _____ Date of Visit: _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than one-half of the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself-or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed; or the opposite-being so fidgety or restless that you have been moving around a lot more than ususal	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

10. If you checked off any problems listed above, how difficult have those problems made it for you to do your work, take care of things at home, or get along with people? ❑ Not difficult at all ❑ Somewhat difficult ❑ Very difficult ❑ Extremely difficult

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.*. 2001;6:606-613. ©CQAIMH. All rights reserved. Used with permission.

Appendix II

DSMV Criteria: Major Depressive Disorder

DSM-5 Diagnosis: Major Depressive Disorder

Major Depressive Episode:

- Five (5) (or more) of the following symptoms have been present during the same 2-week period & represent a change from previous functioning; at least one of the symptoms is either one (1) depressed mood or two (2) loss of interest or pleasure.

  Note: Do not include symptoms that are clearly attributable to another medical condition.

  - Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)
  - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation)
  - Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
  - Insomnia or hypersomnia nearly every day
  - Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
  - Fatigue or loss of energy nearly every day
  - Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
  - Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The episode is not attributable to the physiological effects of a substance or to another medical condition.

  ***Note**: The above criteria represent a major depressive episode.*
- The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- There has never been a manic episode or a hypomanic episode.

***Note**: This exclusion does not apply if all of the manic-like or hypermanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.*

Appendix III

Physical Illness Commonly Associated with Depression

Physical illnesses commonly associated with depression	
Epilepsy	Malignancy
Post-stroke	Hypothyroidism
Parkinson's Disease	Hyperthyroidism
Multiple Sclerosis	Hyperparathyroidism
Degenerative Brain Disease	Cushing's Syndrome
Alzheimer's Disease	Addison's Disease
Coronary Artery Disease	Diabetes Mellitus

Appendix IV

Medications Which May Cause or Worsen Depressive Symptoms

Medication	Description and Notes
Anticonvulsants	• Warning included broadly in FDA labeling, but not causally established
Antihypertensives ß-blockers, CCBs, α2 adrenergic agonists	• ß-Blockers & α2-agonists may worsen cardinal symptoms of depression • Hypertension medications confound correlation
Hormonal therapies GnRH antagonists, corticosteroids, clomiphene, hormonal contraceptives	• Possible alterations of MAO activity from changes in estrogen & progesterone concentrations
Interferon therapies	• Boxed warning for interferon alfa • Careful monitoring required during therapy • Symptoms usually remit quickly on medication discontinuation
Isotretinoin	• Linked to depression and other mood disturbances • Recommended monitoring in iPledge
Montelukast	• 2020: the FDA added a boxed warning in response to reports of serious adverse effects for mental health (depression, suicidality, other neuropsychiatric adverse events) • FDA recommended seeking alternatives for allergic rhinitis before initiating LTRAs
Varenicline (Chantix®)	• 2016: the FDA **removed** a boxed warning of neuropsychiatric adverse effects (EAGLES study)
Vesicular monoamine transporter 2 inhibitors (deu)tetrabenazine, valbenazine	• Boxed warning for deutetrabenazine & tetrabenazine • Observed in the setting of Huntington disease • Caused by depletion of synaptic monoamines

CCBs = calcium channel blockers; MAO = monoamine oxidase; LTRAs = leukotriene receptor antagonists

Appendix V

Depression Specifiers and Subtypes

Specifier and Criteria	Notes
With anxious features • Feeling "keyed up" or tense • Feeling often restless • Difficulty concentrating because of worry • Fear that something awful may happen • Feeling of losing control	• Prominent feature of both bipolar affective disorder & MDD • High anxiety levels are associated with higher suicide risk, longer duration of illness, & greater likelihood of treatment nonresponse
With mixed features • Elevated, expansive mood • Inflated self-esteem or grandiosity • More talkative than usual or pressure to keep talking • Flight of ideas or racing thoughts • Increase in energy or activity, decreased need for sleep • Risky behavior	• Mixed features associated with a major depressive episode are a significant risk factor for development of bipolar I or bipolar II disorder
With melancholic features • Loss of pleasure in all, or almost all, activities • Lack of response to good things happening • Depression that is regularly worse in the morning • Early morning awakening • Psychomotor changes • Significant anorexia or weight loss • Excessive or inappropriate guilt	• Psychomotor changes are almost always present & are observable by others • More common in more severe episodes • More likely to occur in patients with psychotic features
With atypical features • Significant weight gain or increase in appetite • Hypersomnia • Leaden paralysis • Long-standing pattern of interpersonal rejection sensitivity	• Hypersomnia: sleep > 10 hr/day (or an increase of ≥ 2 hr/day than when not depressed) • Leaden paralysis: feeling heavy, leaden, or weighted down, usually in arms or legs
With psychotic features • Delusions • Hallucinations	• Presence of either or both criteria merits specifier
With catatonia • Catalepsy, negativism • Waxy flexibility, posturing • Stupor, agitation • Mutism, echolalia, echopraxia • Mannerisms, stereotypies, grimacing	• Immobility & mutism are common • ≥ 3 symptoms required for diagnosis
With peripartum onset • During pregnancy, or • Within 4 weeks postpartum	• Consider wellbeing of maternal/fetal dyad in therapy selection
With seasonal pattern • Regular temporal relationship between the major depressive episodes and a particular time of the year which • Remission in other times of the year	In most cases, episodes begin in fall or winter & remit in spring Often characterized by: • Prominent changes in energy • Hypersomnia • Overeating • Weight gain • Craving for carbohydrates

Appendix VI

Pharmacotherapy Options for Management of Major Depressive Disorder

Drug	Usual starting dose per day (mg)	Usual total dose per day (mg)	Extreme daily dose range (mg)	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)											
Citalopram	20	20 to 40Δ	10 to 40Δ	0	0	1+	1+	3+Δ	1+¶	1+	3+
Escitalopram	10	10 to 20	5 to 30	0	0	1+	1+	2+	1+¶	1+	3+
Fluoxetine	20	20 to 60	10 to 80	0	0	2+	1+	1+	1+¶	0	3+
Fluvoxamine	50	100 to 200	25 to 300	0	1+	1+	1+	1+	1+¶	1+	3+
Fluvoxamine CR	100	100 to 200	100 to 300	0	1+	1+	1+	1+	1+¶	1+	3+
Paroxetine	20	20 to 40	10 to 50	1+	1+	1+	2+	0 to 1+	1+¶	2+	4+
Paroxetine CR	25	25 to 50	12.5 to 62.5	1+	1+	1+	2+	0 to 1+	1+¶	2+	4+
Sertraline	50	50 to 200	25 to 300	0	0	2+	1+	1 to 2+	2+¶◊	1+	3+
Selective norepinepherine reuptake inhibitors (SNRIs)											
Desvenlafaxine	25 to 50	50 to 100	50 to 400◊	0	0	1+	0	0	2+	Unknown	1+
Duloxetine	30 to 60	60	30 to 120§	0	0	1+	0	0	2+¶	0 to 1+	1+
Levomilnacipran	20	40 to 80	20 to 120	0†	0	0 to 1+	0 to 1+	0	2+¶	0	1+
Milnacipran	12.5	100 to 200	50 to 300	0	1+	0	0	0	2+¶	0	1+
Venlafaxine	37.5 to 75	75 to 375	75 to 375	0	1+	1+	0	1 to 2+	2+	0 to 1+	3+
Venlafaxine XR	37.5 to 75	75 to 225	75 to 375	0	1+	1+	0	1 to 2+	2+	0 to 1+	3+
Atypical Agents											
Bupropion	200	300	100 to 450	0	0	2+	0	1+	1+	0	0
Bupropion SR 12 hour	150	300	150 to 400	0	0	1+	0	1+	1+	0	0
Bupropion XL 24 hour	150	300	150 to 450	0	0	1+	0	1+	1+	0	0
Bupropion hydrobromide 24 hour	174	348	174 to 522	0	0	1+	0	1+	1+	0	0
Mirtazapine	15	15 to 45	7.5 to 60	1+	4+	0	0	1+	0	4+	1+
Serotonin modulators											
Nefazodone‡	200	300 to 600	50 to 600	1+	2+	0	1+	0	2+	0	0
Trazodone	100	200 to 400	100 to 600	0	4+	0	3+	1 to 2+	3+	1+	1+¶¶
Vilazodone	10	40	10 to 40	0	0	2+	0	0	4+ΔΔ	0	2+
Vortioxetine	10	20	5 to 2	0	0	0	0	0	3+	0	1+

Appendix VI (continued)

Drug	Usual starting dose per day (mg)	Usual total dose per day (mg)	Extreme daily dose range (mg)	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Tricyclics and tetracyclics											
Amitriptyline	25	150 to 300	10 to 300	4+	4+	0	3+	1 to 2+	1+◊◊	4+	
Amoxapine	25	200 to 300	25 to 400	2+	2+	2+	2+	1+	0◊◊	2+	
Clomipramine	25	100 to 250	25 to 300	4+	4+	1+	2+	3+	1+◊◊	4+	
Desipramine	25	150 to 300	25 to 300	1+	2+	1+	2+	1 to 2+	0◊◊	1+	
Doxepin	25	100 to 300	10 to 300	3+	3+	0	2+	3+	0◊◊	4+	
Imipramine	25	150 to 300	10 to 300	3+	3+	1+	4+	3+	1+◊◊	4+	
Maprotiline	25	100 to 225	25 to 225	2+	3+	0	2+	1+	0◊◊	2+	
Nortriptyline	25	50 to 150	10 to 200	2+	2+	0	1+	1 to 2+	0◊◊	1+	
Protriptyline	10	15 to 60	5 to 60	2+	1+	1+	2+	1+	1+◊◊	1+	
Trimipramine	25	150 to 300	25 to 300	4+	4+	1+	3+	1+	0◊◊	4+	
Monoamine oxidase inhibitors											
Isocarboxazid	10	10 to 40	10 to 60	1+	1+	2+	2+	0	1+	1+	4+
Phenelzine	15	15 to 90	7.5 to 90	1+	2+	1+	3+	0	1+	2+	4+
Selegiline transdermal	6 mg/24 hour patch	6 to 12 mg/24 hour patch	6 to 12 mg/24 hour patch	1+	0	1+	1+	0	0	0	0
Tranylcypromine	10	30 to 60	10 to 60	1+	1+	2+	2+	0	1+	1+	4+

Appendix VI (continued)

* Total daily oral doses shown in table may need to be given as two (2) or three (3) equally divided doses per day, depending on specific antidepressant & other factors.

¶ Lower doses may be useful for initiating or maintaining patients who are older or medically compromised (eg, renal or hepatic illness), or drug-sensitive patients, as well as patients with a low body mass index. High doses may be used for medications that are well tolerated but ineffective at lower doses. In patients with panic disorder, UpToDate contributors initiate treatment at one-half or less of the usual starting dose shown & titrate more gradually; refer to clinical topic on management of panic disorder.

Δ Maximum recommended dose of citalopram is 20 mg for patients >60 years of age, with significant hepatic insufficiency, or taking interacting medications that can increase citalopram levels.

◊ Although desvenlafaxine doses up to 400 mg per day have been studied, there is no evidence that doses >50 mg per day provide any additional benefit.

§ Although duloxetine doses >60 mg/day did not confer additional benefit in clinical trials, individual patients may benefit from dose escalation up to a maximum of 120 mg/day.

‡ Caution: can cause liver failure. Not available in Europe, Canada, & several other countries.

† Conservative starting doses shown in table are lower than starting doses shown in some other references.

* Relative mean QTc prolongation at therapeutic doses; arrhythmogenic potential can be significantly increased in overdose (eg, for cyclic antidepressants, bupropion, citalopram, duloxetine, venlafaxine, & some others). QTc prolongation classifications are based upon US Food & Drug Administration guidance.[6] The use of other classification criteria may lead to some agents being classified differently by other sources. Refer to UpToDate topics on acquired long QT syndrome & acute antidepressant poisonings.

¶ All SSRIs & SNRIs can cause transient nausea & gastrointestinal discomfort when starting therapy or increasing dose.

Δ Based upon reports of dose-related QTc prolongation & arrhythmia, the maximum recommended dose of citalopram is 40 mg/day in most patients; for patients at increased risk of elevated serum concentrations (eg, age >60 years, significant hepatic impairment, receiving interacting medications), the maximum daily dose is 20 mg.

◊ Sertraline is associated with higher rates of diarrhea.

§ Agomelatine may be hepatotoxic & is contraindicated in any degree of liver impairment. Transaminase monitoring is required.

¥ SNRIs do not have significant anticholinergic effects. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic stimulation) such as dry mouth & constipation, & they should be used with caution in narrow angle glaucoma. Levomilnacipran is associated with urinary hesitancy.

‡ May cause persistent dose-related increases in blood pressure (primarily diastolic) & heart rate. Monitor blood pressure regularly.

† Levomilnacipran can cause dose-dependent urinary hesitancy.

** Caution: can cause liver failure; transaminase monitoring is required. Withdrawn from market due to hepatotoxicity in many countries.

¶¶ Trazodone is associated rarely with priapism, which is considered a medical emergency. Refer to UpToDate topic on serotonin modulators.

ΔΔ Gastrointestinal effects include nausea, vomiting, & diarrhea.

◊◊ Gastrointestinal forms of anticholinergic side effects include: dry mouth, constipation, epigastric distress, decreased esophagogastric tone. Refer to "Anticholinergic" data column for frequency rankings.

Appendix VII

Types of Psychotherapy

Type of Psychotherapy	
Cognitive Behavioral Therapy (CBT)	Identifying problems, identifying cognitive distortions/errors, generating alternative thoughts, problem solving, mastery & pleasure rating, activity scheduling, anxiety management strategies – relaxation exercises
Interpersonal Therapy (IPT)	Focuses on losses, role disputes & transitions, social isolation, deficits in social skills, & other interpersonal factors that may impact the development of depression
Supportive Psychotherapy	Allowing the patient to ventilate, providing emotional support, guidance, increasing the patient's self-esteem, accepting feelings at face value, enhancing hope, enhancing adaptive coping
Behavioral Therapy (BT)	Activity scheduling, social skills training, & problem solving
Marital Therapy (MT)	Conceptualized depression as an interpersonal context such that both members of the marital dyad are included in therapy. Treatment includes behavioral exchange, communication training, problem solving, & resolution of conflict around issues such as finances, sex, affection, parenting, & intimacy.
Family Therapy	When interpersonal problems in the contact of pathological family dynamics are responsible for depression, then family therapy may be considered. It involves all the family members & includes similar principles as for martial therapy.
Brief Psychodynamic Psychotherapy (BPD)	Premise for treatment is that depressive symptoms remit as patient learns new methods to cope with inner conflicts. Several different approaches have been described.

Appendix VIII

Management Strategies in Special Situations

Special situation	Strategies
Suicidal risk	• Risk of suicide is high in patients with depression. • Suicide risk to be assessed initially and over the course of treatment. • If the patient has suicidal ideation, intention, and/or a plan, close surveillance is necessary. • Whenever possible, information about presence of suicidal ideation in patient be shared with family members and they need to be instructed for various safety measures to be taken. • The risk of suicide in some patients recovering from depression increases transiently as they develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness. However, it is not possible to predict with certainly whether a given patient will kill himself or herself. • A careful selection of antidepressants and ECT is an important decision to be taken by psychiatrist after considering all related factors. • Wherever feasible, the prescribed drugs need not be in the possession or reach of patient having suicidal intention.
Psychotic features	• Depression with psychotic features carries a higher risk of suicide than does major depression uncomplicated by psychosis. • It also constitutes a risk factor for recurrent depression. • Depression with psychotic features responds better to treatment with a combination of antidepressants and antipsychotics than to treatment with either component alone. • ECT is also highly effective in depression with psychotic features.
Atypical features	• Atypical depressive feature include severe anxiety, vegetative symptoms of reversed biological functions (i.e., increased rather than decreased sleep, appetite, and weight), marked mood reactivity, sensitivity to emotional rejection, phobic symptoms, and a sense of severe fatigue that creates a sensation of "leaden paralysis" or extreme heaviness of the arms or legs • Tricyclic antidepressants yield response rates of only 35%-50%. Response rates with MAO inhibitors are in the range of 55%-75% in patients with atypical depression. If it is determined that the patient does not wish to, cannot, or is unlikely to adhere to the dietary and drug precautions associated with MAO inhibitor treatment, the use of an alternative antidepressant is indicated. • The results of several studies suggest that SSRIS, MAOIS, and possibly bupropion maybe more effective treatment for atypical depression.
Alcohol and/or substance abuse or dependence	• Because of the frequent comorbidity of depression and alcohol or other substance abuse, efforts need to be made to obtain a detailed history of the patient's substance use. • If the patient is found to have a substance use disorder, a program to ensure abstinence may be regarded as a principle priority in the treatment. • It is also advisable, if other factors permit, to detoxify such a patient before initiating antidepressant therapy. • Benzodiazepines and other sedative hypnotics carry the potential for abuse or dependence and these may be used cautiously except as part of a detoxification regimen. • Hepatic dysfunction and hepatic enzyme induction frequently complicate pharmacotherapy of patients with alcoholism and other substance abuse; these conditions require careful monitoring of blood levels.
Depression with features of obsessive-compulsive disorder	• Clomipramine and the SSRIs have been demonstrated to be efficacious in the management of obsessive-compulsive symptoms in addition to their antidepressants efficacy.
Depression with panic and/or other anxiety disorders	• Panic disorder complicates major depression in 15%-30% of the cases. • TCAs and SSRIs may initially worsen, rather than alleviating anxiety and panic symptoms; these medications may therefore be introduced at a low dose and slowly increased when used to treat such patients. • High potency benzodiazepine like alprazolam and clonazepam may sometimes be used with benefit either in combination with antidepressants or as the sole pharmacological agent for anxiety, with or without panic, coupled with milder forms of depression.

Appendix VIII (continued)

Special situation	Strategies
Depression with cognitive dysfunction (pseudo dementia)	• Signs and symptoms of cognitive inefficiency routinely accompany major depression. • Some patients have both depression and dementia, while others have depression that causes cognitive impairment (i.e., pseudo-dementia). • Several clinical features help in differentiating pseudo-dementia from true dementia. Pseudo-demented patients generally exert relatively less effort but report more incapacity than patients with true dementia. In more advanced stage, patients with dementia typically fail to recognize their cognitive failure. • It is important that patients with major depression with cognitive disturbance are not misdiagnosed and thereby denied the antidepressant medication or ECT. • Depression related cognitive dysfunction is a reversible condition that resolves with treatment of the underlying depression.
Dementia	• Individuals suffering from dementia need to be prescribed antidepressants which have least potential of anticholinergic effect, e.g., bupropion, fluoxetine, sertraline, and, of the tricyclic agents, desipramine or nortriptyline. Alternatively, some patients do well when given stimulants in small doses. • Among SSRIs, paroxetine may be avoided. • ECT is also effective in depression superimposed on dementia, and it may be used if medications are contraindicated, not tolerated, or if immediate resolution of the major depressive disorder episode is medically indicated (such as when it interferes with the patient's acceptance of food).
Post Psychotic Depression	• Adding an antidepressant agent to the patient's antipsychotic regimen can help in managing post-psychotic depression effectively.
Depression during pregnancy or following childbirth	• Women in childbearing age may be counseled about the risk of becoming pregnant while taking psychotropic medications. • Whenever possible, a pregnancy is to be planned in consultation with psychiatrist so that medication may be discontinued before conception if feasible. • The clinicians need to carefully weigh the risks and benefits of prescribing psychotropic agents to the pregnant patient, taking into consideration the possibilities of physical (especially during the first trimester) and behavioral teratogenesis. • In patients whose safety and well-being require antidepressants medications, antidepressants may be justifiably used, after the first trimester, if possible. • ECT may be used as an alternative treatment; the current literature supports the safety for mother and fetus, as well as the effectiveness of ECT during pregnancy. • Postpartum depression is to be treated according to the same principles delineated for other depressive condition. • However, issue of breast feeding and appropriate precautions need to be explained to patient and caregivers.
Seasonal depression	• Some individuals suffer annual episode of depression whose onset is in the fall or early winter, usually at the same time each year. • The depressive episodes frequently have atypical features such as hypersomnia and overeating. • The entire range of treatments for depression may also be used to treat seasonal affective disorder, either in combination with or as an alternative to light therapy.
Depression in elderly	• Antidepressants are effective in treatment of depression in old age. • The high rates of adverse effects associated with TCAs suggest that these agents must not be used as the first line agents. • The lower rate of adverse events in the newer antidepressants (SSRIs) makes them more acceptable. However, nortriptyline has a role in severe depression in the elderly. • ECT has demonstrated efficacy in treatment of old age depression with the benefit of rapid response in the severely ill with and without psychotic symptoms.

Appendix VIII (continued)

Special situation	Strategies
Depression in children	• There are evidences that SSRIs are effective in child and adolescent depression and these are generally the first choice of drug. • The commonly used SSRIs include fluoxetine. Other newer antidepressants have not been adequately evaluated in childhood and use of all these classes of drugs may be used with careful monitoring. • Psychotherapeutic interventions like CBT and IPT have also been shown to be efficacious in children and adolescents.
Post-Stroke depression	• Post Stroke Depression is a common problem seen in at least 30-40% of survivors of intra-cerebral hemorrage. • Antidepressant drugs may be beneficial in managing depressive symptoms and allow faster Post Stroke rehabilitation. • Treatment is complicated by medical co-morbidity and by the potential for interactiuon with other co-prescribed drugs. • Fluoxetine and nortriptyline are probably the most standard and seen to be effective.
Cardiac disease	• The presence of specific cardiac conditions complicates or contraindicates certain forms of antidepressant medication therapy, notably use of TCAs. • Cardiac history is to be carefully explored before the initiation of medication treatment. Although TCAs have been used effectively to treat depression in patients with some forms of ischemic heart disease, particular care need to be taken in using TCAs in patients with a history of ventricular arrhythmia, subclinical sinus node dysfunction, conduction defects (including asymptomatic conduction defects), prolonged QT intervals, or a recent history of myocardial infarction. • SSRIs, bupropion, and ECT appear to be safer for patients with preexisting cardiac disease, although the latter may require consultation with a specialist and treatment modification before use. However, there are also reports which suggest that SSRIs can also lead to arrhythmia. • MAOIS do not adversely affect cardiac conduction, rhythm, or contraction but may induce orthostatic hypotension and also run the risk of interacting adversely with other medications that may be taken by such patients. There is anecdotal evidence that trazodone may induce ventricular arrhythmias, but this agent may be avoided in elderly because of orthostatic blood pressure decrements. • Consultation with the patient's cardiologist before and during antidepressant medication treatment may be advisable and is especially advisable during any treatment for a patient who has recently had a myocardial infarction.
Hypertension	• Antihypertensive agents and TCAs may interact to either intensify or counteract the effect of the antihypertensive therapy. • The action of antihypertensive agents that block alpha receptors (e.g., prazosin) may be intensified by antidepressant nmedications that block these same receptors, notably the TCAs and trazodone. TCAs may antagonize the therapeutic actions of guanethidine, clonidine, or α-methyldopa. • Antihypertensive, like diuretics which mainly act on kidney, may precipitate SIADH, when given along with SSRIs. • Concurrent antihypertensive treatment, especially with diuretics, increases the likihood that TCAs, trazodone, or MAOIs will induce symptomatic orthostatic hypotension. • β Blockers, especially propranolol, may be a cause of depressive disorder in some patients. • Dose-dependent elevations in blood pressure with venlafaxine are usually mild, although more severe elevations have been observed, making this agent less preferable in patients with hypertension.

Appendix VIII (continued)

Special situation	Strategies
Diabetes mellitus	• SSRIs may reduce serum glucose by up to 30% and cause appetite suppression, resulting in weight loss. • Fluoxetine may be avoided, owing to its increased potential for hypoglycaemia, particularly in patients with non-insulin dependent diabetes. If fluoxetine is prescribed, the patient should be advised of the need to monitor serum glucose levels regularly. • TCAs are more likely to impair diabetic control as they increase serum glucose levels by up to 150%, increase appetite (particularly carbohydrate craving) and reduce the metabolic rate. They are generally considered safe unless the diabetes is very poorly controlled or is associated with significant cardiac or renal disease. • Antidepressants such as amitriptyline, imipramine, duloxetine and citalopram are also used to treat painful diabetic neuropathy.
Asthma	• Antidepressant medications except MAOI may be used for patients with asthma without fear of interaction. Other antidepressant like SSRIS, TCAs, etc., may be used for patient with asthma without any apprehension about drug interaction.
Glaucoma	• Antidepressants that cause or exacerbate acute close angle glaucoma include medications with anticholinergics, serotonergic or adrenergic properties. • TCAs have the greatest anticholinergic properties. • SSRIs and SNRIs by virtue of their action on serotonin receptor can also cause mydriasis and thereby can produce papillary block. • Antidepressants lacking anticholinergic and serotonergic activity (bupropion) may be preferred. • Benzodiazepines (Diazepam) have mild anticholinergics properties.
Obstructive uropath	• Prostatism and other forms of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects. • Benzodiazepines, trazodone, and MAOIS may also retard bladder emptying. • The antidepressant medications with the least propensity to do this are SSRIs, bupropion, and desipramine.
Parkinson's disease	• Bupropion, exerts a beneficial effect on the symptoms of Parkinson's disease in some patients but may also induce psychotic symptoms, perhaps because of its agonistic action in the dopaminergic system. • MAOIS (other than selegiline, also known as L-deprenyl, a selective type B MAOI is recommended in the treatment of Parkinson's disease) may adversely interact with L-dopa products. • Selegiline loses its specificity for MAO-B in doses greater than 10 mg/day and may induce serotonin syndrome when given in higher doses in conjunction with serotonin-enhancing antidepressant medications. • There is no evidence favoring any particular antidepressant medication from the standpoint of therapeutic efficacy in patients with Parkinson's disease complicated by depressive disorder. • The theoretical benefits of the antimuscarinic effects of some of the TCAs in the treatment of patients with depressive disorder with Parkinson's disease are offset by the memory impairment that may result. • ECT exerts a transient beneficial effect on the symptoms of idiopathic Parkinson's disease in many patients. • Amoxapine, an antidepressant medication with dopamine-receptor blocking properties, may be avoided for patients who have Parkinson's disease. • Lithium may in some instances induce or exacerbate parkinsonian symptoms.

Appendix VIII (continued)

Special situation	Strategies
Malignancy	• In treatment of depression in subjects with malignancy, SSRI are considered to be the first line drugs. The advantage of SSRI is that they can act as effective adjunct analgesic drugs, especially in neuropathic pain. Disadvantages of SSRI are drug-drug interaction with drugs that are metabolized by CYP450/3A4 (e.g. cyclophosphamide, doxorubicin). Fluoxetine, may be used with caution especially is patients with hepatic insufficiency, since it has a long half-life. • TCAs are also good adjunct analgesics. But the disadvantages with TCAs are anticholinergic side effects and orthostatic hypotension. They can also worsen their side effects of drugs like opioids (e.g. constipation and dry mouth) which are often needed for pain control. • Psychostimulants, with their rapid onset of action have some advantages for depressed cancer patients in the sense of promoting a sense of well-being, decreasing fatigue, stimulating appetite, potentiating the analgesic effect of opioids and decreasing opioid induced sedation. • The goal of psychological treatment in depressed patients with cancer is to reduce emotional distress, improve morale, coping ability, self-esteem and sense of control.
Drug induced depression	• If medication induced depression is suspected, the suspected drug should be discontinued if possible and replaced with another agent less likely to induce depression. • When this is not possible or when discontinuation does not result in remission of the depressive symptoms, pharmacotherapy for the depression may be considered.
Liver disease	• Liver impairment affects basic elements of medication pharmacokinetics, from absorption to metabolism, distribution to elimination, changing drug levels, duration of action, and efficacy. • Most antidepressants are highly protein-bound- except, venlafaxine, and methylphenidate. • In liver failure, a reduction in albumin and alphal-acid-glycoprotein production, along with altered protein-binding. leads to higher levels of free pharmacologically-active drug. This is offset by a compensatory increase hepatic metabolism, and this is especially important for drugs with low intrinsic clearance. • Most antidepressants are highly lipid-soluble and require hepatic metabolism (biotransformation into more polar compounds) to allow them to be cleared from the body in urine or bile. • Antidepressants can also be divided into two (2) major categories of clearance, determined by their enzyme affinity. Flow-limited drugs have high hepatic extraction, and their hepatic clearance is dependent on the rate of delivery of the drug to the liver. TCAs undergo significant first pass metabolism of greater than 50% after oral administration. • Drugs with low hepatic-enzyme affinity (e.g., paroxetine) are metabolized more slowly, as enzyme saturation is the rate limiting step. The severity of impairment rather than the underlying aetiology is the most important factor to consider in prescribing for this group. Renal function may also be affected. • As the risk of drug toxicity increases with disease severity, lower starting and total doses of medication are recommended (starting dose -about one forth that of adults).
Renal disease	• In this group of patients, TCAs are probably safer than SSRIs. • The degree of renal impairment rather than the cause is most important • Renal impairment may be present without a raised creatinine level. TCAs metabolites are excreted by the kidneys, hence accumulation may occur. Of the SSRIs, sertraline is not recommended by its manufacturers in renal failure. • Fluoxetine, citalopram and paroxetine may be started at very low dose in patients with a glomerular filtration rate of at least > 10 ml/min. • Lithium may only be prescribed if absolutely necessary, at low doses, on alternate days, with frequent checking of serum levels.

Appendix VIII (continued)

Special situation	Strategies
Perioperative period	• TCAs may preferably be stopped prior to surgery. SSRIs and MAOI can interact with pethidine, pentazocine, and dextromethorphan, at the pharmacodynamics levels and lead to serotonin syndrome, therefore such drugs may be avoided during the perioperative period. However, SSRIs may not be discontinued in order to prevent anesthetic interactions, except when the SSRI is used in combination with aspirin or an Non-steroidal anti-inflammatory drugs and when the SSRI is used in patients over 80 years of age. In these patients, the balance of risks of withdrawal and bleeding is to be discussed with patients. Because abrupt discontinuation can cause serious withdrawal symptoms, the drugs may be gradually discontinued over few days to 2 weeks before surgery. • Lithium can contribute to hemodynamic instabilities, interfere with sodium and potassium metabolism, and the renal excretion of lithium can be reduced in presence of renal complications. The physical risk of intoxication, with its detrimental and fatal risks for the central nervous system, is unacceptable. Therefore, lithium discontinuation is recommended. Lithium can be stopped at once because no withdrawal symptoms occur. • When, postoperatively, the patient is hemodynamically stable, is able and allowed to drink, and is not on new, potentially interfering drugs, the medication may be restarted gradually.

References

1. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline.
2. Dassanayake T, Michie P, Carter G, Jones A. Effects of benzodiazepines, antidepressants & opioids on driving: a systematic review & meta-analysis of epidemiological & experimental evidence. Drug Saf 2011; 34:125.
3. DeCates A, De Gorgi R. Adjuctive benzodiazepines in depression: A clinical dilemma with no recent answers from research. BJPsych Advances. 2002:26(6), 321-326.
4. Chung H, Pietruszewski P. Clinical Staff Webinar, National Council Depression Care Collaborative. 2015.
5. Ellis P. Royal Australian & New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Australian & New Zealand clinical practice guidelines for the treatment of depression. *Aust N Z J Psychiatry*. 2004 Jun;38(6):389–407.
6. Gautam S, Jain A, Gautam M, Vahia VN, Grover S. Clinical Practice Guidelines for the Management of Depression. Indian J Psychiatry. 2017 Jan;59(Suppl 1):S34-S50. doi: 10.4103/0019-5545.196973. PMID: 28216784; PMCID: PMC5310101.
7. Instruction Manual: Instructions for Patient Health Questionnaire (PHQ) & GAD-7 Measures. Available at: https://phqscreeners.pfizer.edrupalgardens.com/sites/g/files/g10016261/f/201412/instructions.pdf. Published December 2014.
8. Kennedy SH, Lam RW, McIntyre RS, et al. CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016 Aug 2.
9. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, Parikh SV, Patten SB, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood & Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. J Affect Disord. 2009 Oct;117(Suppl 1):S26–43.
10. Depression in adults: treatment & management. London: National Institute for Health &and Care Excellence (NICE); 2022 Jun 29. (NICE Guideline, No. 222.)
11. Parikh SV, Segal ZV, Grigoriadis S, Ravindran AV, Kennedy SH, Lam RW, Patten SB Canadian Network for Mood and Anxiety Treatments (CANMAT) Canadian Network for Mood & Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. J Affect Disord. 2009 Oct;117(Suppl 1):S15–25.
12. Pinto-Meza A, Serrano-Blanco A, Penarrubia M, et al. Assessing Depression in Primary Care with the PHQ-9: Can it be Carried Out over the Telephone? JGIM, 2005, 20:738-742.
13. US Preventive Services Task Force, Screening for Depression in Adults. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/depression-in-adultsscreening1?ds=1&s=depression. Published January 2016.
14. Westra HA, Stewart SH, Conrad BE. Naturalistic manner of benzodiazepine use & cognitive behavioral therapy outcome in panic disorder with agoraphobia. J Anxiety Disord 2002; 16:233.
15. Depression Clinical Pathway — Outpatient Behavioral Health and Primary Care | Children's Hospital of Philadelphia (chop.edu)

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