



EVIDENCE-BASED BEST PRACTICES FOR THE TREATMENT OF NON-PSYCHOTIC MAJOR DEPRESSIVE DISORDER IN PRIMARY CARE IN SOUTH CAROLINA

Key Messages for Management of Major Depressive Disorder (MDD)

1. Adequate trial of an antidepressant consists of BOTH an adequate dose and duration.
2. Rating scales, such as the Patient Health Questionnaire (PHQ-9), are useful to assess symptom severity before initiating medication and at regular intervals to assess patient response.
3. Treat to remission, not just partial response, and inform patients that remission is the goal of treatment.
4. Total duration of treatment should last 9-12 months for the first episode of depression, and potentially indefinitely for severe or recurrent episodes.

BACKGROUND

A panel of 4 psychiatrists and 5 clinical pharmacists from different geographic regions of the state was created to consensually agree on evidence-based best practices for the treatment of major depression in South Carolina. The panel recommended detailed treatment algorithms as the core of their best practices. **The evidenced-based materials and algorithms developed and implemented in the Texas Medication Algorithm Project (TMAP) were the panel's primary source of information.** Supplemental information included specific recommendations from a review of primary literature and clinical opinion from the SCORxE mental health panel members. Modifications were made (with permission) to the TMAP content and algorithms as necessary for the SCORxE project, based on the panel's consensus or vote. This document highlights the major elements of the SCORxE mental health panel's best practices report. Evidence-based additions/revisions were made by primary care physicians to focus on treatment of non-psychotic major depressive disorder (MDD) in primary care.

The information contained in this summary is intended to supplement the knowledge of clinicians regarding best practices and drug therapy to treat major depression in primary care patients ages ≥ 18 years. This information is advisory only and is not intended to replace sound clinical judgment, nor should it be regarded as a substitute for individualized diagnosis and treatment. Special considerations are needed when treating some populations such as the elderly, pregnant or breast-feeding women, and patients with certain medical conditions (e.g., cardiac disease, liver and renal impairment).

The following symbols, in parentheses following statements, indicate the level of evidence for the statements, with Level a, Level b and Level c representing the TMAP authors' assessment, and Level d representing recommendations from the SCORxE mental health panel that differ from TMAP:

(Level a) - Strong empirical trials using randomization and blinding

(Level b) - Open label trials, cohort studies, case series and retrospective analysis

(Level c) - Few case reports and/or consensus among the TMAP panel, as well as advocate and consumer input

(Level d) - Consensus among SCORxE mental health panel

MAJOR DEPRESSIVE DISORDER TREATMENT AT-A-GLANCE

- Pharmacotherapy and evidence-based psychotherapy (EBPT) are effective treatment options for the treatment of non-psychotic MDD. Pharmacotherapy is the principal treatment of MDD and other types of depression in primary care.
- There are three phases of treatment:
 - Acute: an adequate antidepressant trial is a period of 6 to 12 weeks for each medication, including a minimum of 6 weeks at a maximum tolerated dose (Level d).
 - Continuation: patients who received pharmacotherapy during the acute phase treatment should continue their medication for AT LEAST 6 to 9 months after symptom remission at the same dose that produced therapeutic response.^{1,2}
 - Maintenance: if maintenance treatment is indicated based on risk factors for recurrence, medication should be prescribed for a duration ranging between 1 year and lifetime at the same dose that produced symptom remission.^{1,2}
- Use an adequate trial of an antidepressant, consisting of BOTH an adequate dose and duration.
 - All classes of antidepressant medications are equally efficacious (Level a).³
 - Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion SR or XL (BUP), and mirtazapine (MRT) are recommended as initial therapy based on ease of dosing, tolerability and safety profile.³
 - 50-70% of patients in research-based, efficacy trials respond to an initial agent, and 50% of non-responders respond to an alternative agent.^{4,5,6}
- The ultimate goals of treatment are to achieve remission, return to full psychosocial functioning, and prevent relapses and recurrences of depression.^{1,2}
 - Patient education is critical to adherence and treatment success.^{1,2}
 - Patients experiencing 2 or more major depressive episodes may benefit from lifelong antidepressant medication, depending on the clinical situation.^{1,2}
 - Case management by nurses and close collaboration between primary care providers and mental health specialists generally result in better patient outcomes.⁷
- Measurement-based care (MBC) promotes the use of rating scales to assess symptom severity before initiating medication, and at regular intervals to assess patient response.^{1,2}
 - Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study show that the use of MBC leads to improved remission rates for patients with chronic depression.^{8,9}
 - The use of brief depression screening instruments in primary care patients is supported by the United States Preventive Services Task Force.¹⁰
 - An example of a symptom based rating scale is the 9-item Patient Health Questionnaire (PHQ-9, see Figure 1). Remission is achieved with resolution of symptoms (PHQ-9 score < 5).¹¹
- Screening for suicide is important at initial presentation and during ongoing care (see *Assessment for Suicidality* section).
- Patients starting a new medication or changing medications should be seen regularly to monitor for symptom improvement, worsening of symptoms, and side effects.^{1,2}
 - There is no evidence to support recommendations on monitoring frequency.
 - TMAP recommends visits at 2, 4, 6, 9 and 12 weeks when initiating treatment.^{1,2}
 - Patients with suicidal ideation or severe functional impairment, at the discretion of their physician, may require more frequent visits.¹²
 - Additional contact by telephone may be appropriate between face-to-face visits.

DIAGNOSTIC CRITERIA

Major Depression

Patients experiencing depressed mood or markedly diminished interest or pleasure in activities (anhedonia) during the same 2-week period accompanied by at least four additional symptoms of depression listed below:¹³

- 1) Significant weight loss when not dieting, or weight gain
- 2) Insomnia or hypersomnia
- 3) Psychomotor agitation or retardation
- 4) Fatigue or loss of energy
- 5) Feelings of worthlessness or excessive or inappropriate guilt
- 6) Diminished ability to think or concentrate
- 7) Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt

These symptoms should represent a change from previous functioning and should occur all day or almost all day.

Bipolar Disorder and Cyclothymia

Bipolar disorder is a recurrent mood disorder featuring one or more episodes of mania or mixed episodes of mania and depression.¹³ Cyclothymia is characterized by the presence of many periods with hypomanic symptoms and many periods with depressive symptoms that do not meet criteria for a major depressive episode for at least 2 years.¹³

MAJOR DEPRESSIVE DISORDER ALGORITHM

Initial Psychiatric and Medical Evaluation

A thorough psychiatric evaluation, general medical history, comprehensive physical assessment and diagnostic tests should be performed and a diagnosis of MDD made prior to engagement of a patient into the medication treatment algorithm.^{1,2} Depending on the treatment history, severity of symptoms, clinical features and comorbid conditions (medical as well as psychiatric), patients may enter the algorithm at different stages.^{1,2} Thorough and ongoing diagnostic re-evaluation and confirmation for MDD, with special attention and screening for bipolar depression after two failed treatment stages, are recommended.^{1,2} In addition, the clinician should carefully assess for medical and psychiatric comorbidities, including substance abuse, after treatment failures.^{1,2}

Assessment for Suicidality

Identification and prevention of suicidality is critical. Approximately 45% of completed suicides occurred in patients who had contacted their primary care physician in the month preceding the act.¹⁴ There are several protocols for assessing suicide risk. A simple and validated protocol involves using a two stage process.¹⁵ The first stage involves screening for suicidal ideation with item 9 of the PHQ-9 (see Figure 1) – “Over the last 2 weeks, how often have you been bothered by thoughts that you would have been better off dead or of hurting yourself in some way?” If the patient denies these thoughts, then they should be considered low risk for suicide and no further acute assessment is necessary. If the patient endorses these thoughts, they should be asked, “Are you having thoughts of harming yourself in some way?” If the response is negative, then they should be considered low risk and no further acute assessment is necessary.

Patients endorsing active suicide ideation should undergo the second stage of assessment to investigate: severity, nature and frequency of thoughts of self-harm; attempts at self-harm in the past month or previously; specificity of current plans and capacity to implement them; strength of death wishes; intensity of hopelessness; and impulse control and availability of preventive deterrents.¹⁵ Patients endorsing active thoughts of self-harm without an articulated plan should receive same day evaluation by a mental health specialist.¹² Patients with a specific plan for self-harm require immediate assessment for safety and should be transported to an emergency room.¹²

Measurement-Based Care

Measurement-based care (MBC) promotes the use of rating scales or questionnaires to measure symptoms, side effects and adherence at every visit as well as guide tactics to modify dosage and treatment duration. Currently, most clinicians do not routinely use specific measures of depressive symptoms at patient visits. Rather, they tend to use global measures instead of specific symptoms measures.^{1,2} Results from the STAR*D study show that the use of MBC leads to improved remission rates for patients with chronic depression.^{8,9}

An example of a symptom based rating scale is the PHQ-9 (Figure 1).¹¹ The PHQ-9 is a brief questionnaire that scores each of the nine Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for depression as "0" (not at all) to "3" (nearly every day).^{11,13} PHQ-9 scores ≥ 10 have a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.¹¹

The use of brief screening instruments to screen for depression in primary care patients is supported by the United States Preventive Services Task Force.¹⁰

Description of Stages, Tactics and Critical Decision Points (CDPs)

Each stage of the MDD Algorithm (Figure 2) represents a trial of a different antidepressant. The algorithm's strategies are the medication options that clinicians and patients choose from within each stage. While medications are the algorithm's "strategies", specific recommendations concerning medication use (e.g., dose titration, measurement of treatment response, trial duration) are the algorithm's "tactics". In clinical practice, variations from these detailed recommendations may be necessary.^{1,2}

A critical decision point (CDP), is the point in the course of the medication trial when the clinician decides whether to continue the present medication regimen, adjust the medication dose, or move on to another medication (the next stage of the algorithm). The same CDP time intervals are recommended for Stages 1 through 3 (Figure 3).^{1,2}

At each CDP, clinical rating scales are very valuable to assess the patient's level of response to the antidepressant. The clinician can then make a therapeutic decision based on the results of the clinical rating scales, patient self-report and ratings of 'other symptoms'. When addressing goals of treatment for an individual patient, clinicians should consider initial response and resolution of symptoms (i.e., remission).^{1,2}

Visit Frequency

Frequency of patient visits is largely dependent on the individual patient situation. There is no evidence to support recommendations on monitoring frequency. In general, significantly symptomatic patients being started on a new medication or changing medications should be seen every 2 weeks until the clinician feels comfortable with the patient's clinical status. More frequent visits allow for monitoring of worsening of symptoms, treatment emergent suicidal ideation, other side effects, as well as dosage titration or other tactical interventions.^{1,2}

TMAP recommends visits at 2, 4, 6, 9 and 12 weeks when initiating treatment.^{1,2} The Food and Drug Administration (FDA) recommends at least weekly face-to-face contact during the first 4 weeks of treatment, then every other week for 4 weeks, then at 12 weeks, and as clinically indicated. These visits do not necessarily need to be with the physician, but can be with other trained clinical personnel. Additional contact by telephone may be appropriate between face-to-face visits.

MEDICATIONS AND DOSING

Choice of Antidepressant Medication & Medication Dosing

Choice of treatment should be guided by the patient's prior response to treatment, tolerability, psychiatric and medical comorbidity, concurrent medications, family history of response, as well as patient preference. Patient education and family involvement play critical roles in ensuring patient adherence to treatment.^{1,2}

Table 1 summarizes the usual initiation and maintenance dosing of antidepressant medication to treat non-psychotic MDD (Level d).

Decision to Change Treatment

A change of medication should be considered if symptom worsening occurs. A dose increase or an augmentation strategy should be considered if a patient responds partially to medication during the first 6 to 8 weeks of therapy (Level d). Consider a change in algorithm stage if improvement is minimal (less than 20% decrease on a rating scale such as PHQ-9) at 6 to 10 weeks (Level d).

Combining Antidepressants for Treatment of Depression

Due to the potential for drug interactions, antidepressant combination treatment should be used carefully, and patients monitored closely. In theory, the goal of combination antidepressant regimens is to combine medications to enhance clinical response. Combination therapy may occur in Stage 3 of the algorithm. Medications should be initiated simultaneously at a low dose, then gradually titrated upward to a therapeutically recommended dose. If a tricyclic antidepressant (TCA) is being used in combination treatment, TCA plasma levels should be monitored (see Table 1).^{1,2}

Because there is a risk of developing serotonin syndrome with combination antidepressant therapy, patients should be monitored for signs of confusion, disorientation, agitation, restlessness, diaphoresis, diarrhea, ataxia, and hyperreflexia.^{1,2}

Treatment of Depression Using Augmentation Therapy

When an antidepressant medication elicits only partial response, augmentation agents can potentiate an improved response and achieve a higher recovery rate, thus preventing the necessity of discontinuing the initial antidepressant.^{1,2} Treatment strategies in Stages 1 augmentation and 2 augmentation consist of the addition of buspirone (BUS), bupropion SR or XL (BUP), mirtazapine (MRT), or liothyronine (T₃) to a SSRI or SNRI (see Figure 2) (Level b).^{1,2}

Medication Switching or Discontinuation

If the first antidepressant is being discontinued due to intolerance following a brief exposure (less than 7 days), it can be stopped and the second drug started.^{1,2} If the first drug is being discontinued due to symptomatic breakthrough or inadequate response after a longer exposure (greater than 7 days), then it should be tapered and the second drug started gradually.^{1,2}

Serotonin discontinuation syndrome can occur following abrupt cessation of antidepressant therapy, particularly for those antidepressants with short half-lives (e.g., fluvoxamine, paroxetine, venlafaxine). The syndrome is characterized by disequilibrium, electric shock sensations (most common with paroxetine), general somatic complaints, sleep disturbance, and gastrointestinal symptoms. This syndrome is more likely with length of therapy greater than 5 weeks or high doses of medications. Onset is usually from 1 day to 1 week and can last up to 3 weeks. Initiating a medication taper does not always prevent its occurrence but may minimize severity.^{1,2}

Any antidepressant that has anticholinergic side effects (e.g., TCAs) can cause cholinergic rebound upon abrupt discontinuation.^{1,2}

Evaluation of Side Effects

The side effect profiles (Tables 3-5) of the antidepressants and augmentation agents vary from medication to medication. In general, side effects should be addressed first by dose reduction or medication switching before considering pharmacological intervention. Pharmacological intervention may increase the risk of drug interactions and additional adverse effects, thus decreasing patient adherence.^{1,2}

DURATION OF TREATMENT

Total duration of therapy, including acute and continuation phase treatment, should last AT LEAST 9 to 12 months for the first episode, and potentially longer based on risk factors for recurrence.^{1,2} All patients experiencing three or more episodes of major depression should continue maintenance antidepressant treatment indefinitely.^{1,2,16} Maintenance therapy should also be considered for patients experiencing two episodes of major depression with complicating factors (e.g., rapid recurrence of episodes, severe episodes, age greater than 60 at first episode, or family history of mood disorders).^{1,2,16} Additionally, maintenance therapy should be considered for other patients at high risk for recurrent depression, such as: patients with double depression (major depression and dysthymia), chronic depression, comorbid anxiety disorders, or serious personality disorder.^{1,2,16} Patients with substance abuse, dissociative or eating disorders, or those with ongoing stressors may also require long-term medication treatment.^{1,2}

EVALUATION OF PATIENT RESPONSE

Symptom Evaluation

Remission, partial response, and non-response should be based on objective data (i.e., rating scales). When addressing goals of treatment for an individual patient, clinicians should consider initial response and resolution of symptoms, and continue to evaluate for residual symptoms.^{1,2}

Evaluation of Non-Response or Breakthrough Symptoms

Patients who do not respond to antidepressants or experience an exacerbation of depressive symptoms should first be assessed for complicating phenomena. First and foremost, the adequacy of patient medication adherence should be assessed, as the challenges associated with antidepressant persistence and adherence are well documented. Second, patients should be assessed for the occurrence of co-occurring general medical or psychiatric disorders, including substance abuse. After these considerations have been ruled out, the clinician can address treatment of the breakthrough depressive symptoms.^{1,2} Subsyndromal symptoms, or those not meeting DSM-IV-TR criteria for MDD, should be addressed with dose titration, augmentation strategies, or the addition of EBPT.^{1,2,13} Symptom exacerbation meeting DSM-IV-TR criteria for a MDD episode should be addressed by the next appropriate stage of the MDD algorithm or with EBPT.^{1,2}

REFERRAL TO A PSYCHIATRIST

Consider referring the following patients to a psychiatrist (Level d):

- Patients with psychotic depression
- Depressed patients with active suicidal intent and/or plan
- Patients who do not respond to adequate dosage of two antidepressants for appropriate duration of treatment
- Patients with suspected or confirmed bipolar disorder
- Patients with cyclothymia
- Patients with active substance use disorders
- Patients with severe personality disorders
- Patients with severe psychosocial impairment (e.g., in bed most of day, not dressing or bathing)

SCORxE Mental Health Panel Members (and Disclosures for Pharmaceutical Industry Relationships)

Sandra Counts, Pharm.D. (None), **Shannon J Drayton**, Pharm.D. (None), **Kelly Jones**, Pharm.D. (None), **Markus Kruesi**, M.D. (None), **Deborah Leverette**, M.D. (Speaker's Bureau: Wyeth Pharmaceuticals, Eli Lilly & Company, Forest Pharmaceuticals, Inc.), **Robert Malcolm**, M.D. (Speaker's Bureau and Research Grant: Cephalon; Speaker's Bureau and Consultant: Sepracor, Inc.), **Joseph McElwee**, M.D. (None), **John Voris**, Pharm.D. (Speaker's Bureau: AstraZeneca), **C. Wayne Weart**, Pharm.D.* (Speaker's Bureau and Consultant: Pfizer, Merck; Speaker's Bureau: Novartis, Sanofi-Aventis). *No ties to pharmaceutical companies for mental health related drugs at this time.

Figure 1. Patient Health Questionnaire (PHQ-9) and Scoring Instructions

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have.

Over the last 2 weeks, how often have you been bothered by:		Not at all 0	Several days 1	More than half the days 2	Nearly every day 3
1.	Little interest or pleasure in doing things				
2.	Feeling down, depressed, or hopeless				
3.	Trouble falling or staying asleep, or sleeping too much				
4.	Feeling tired or having little energy				
5.	Poor appetite or overeating				
6.	Feeling bad about yourself - or that you are a failure or have let yourself or your family down				
7.	Trouble concentrating on things, such as reading the newspaper or watching television				
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 usual				
9.	Thought that you would have been better off dead or of hurting yourself in some way				
Subtotals					
TOTAL SCORE					

If you checked off any problems on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

_____ Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult

Instructions for Use (for doctor or healthcare professional only)

ASSESSMENT for initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the two right columns (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

3. Consider Major Depressive Disorder

- If there are at least 5 ✓s in the two right columns (one of which corresponds to Question #1 or #2).

Consider Other Depressive Disorder

- If there are 2 to 4 ✓s in the two right columns (one of which corresponds to Question #1 or #2).

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

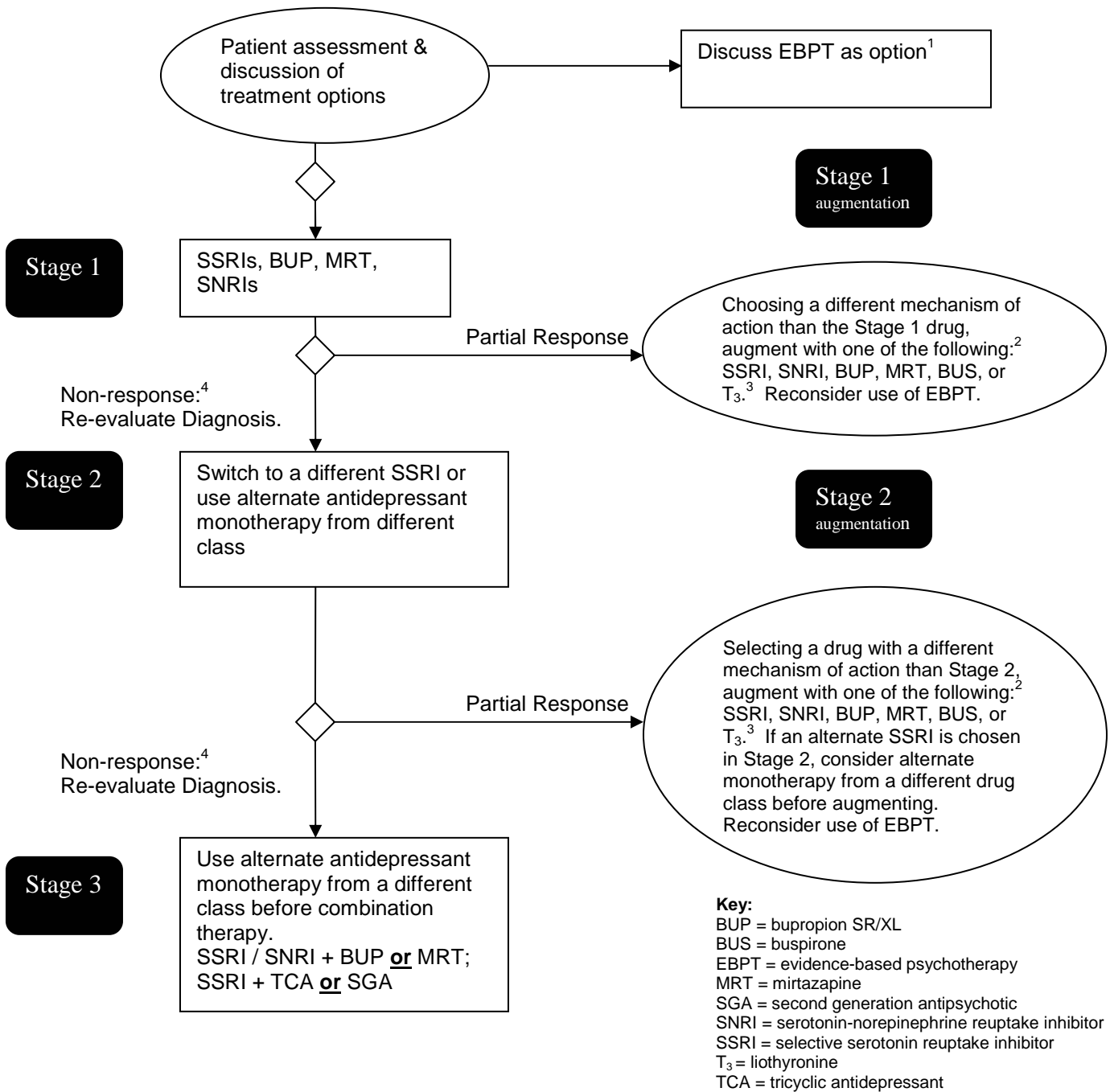
To MONITOR SEVERITY OVER TIME for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (e.g., every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Not at all = 0; Several days = 1; More than half the days = 2; and Nearly every day = 3.
3. Add together column scores to get a TOTAL score.
4. Interpretation of TOTAL score:
5. Results may be included in patients' files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

<u>Total Score</u>	<u>Depression Severity</u>
0-4	None
5-9	Mild
10-14	Moderate
15-19	Moderately severe
20-27	Severe

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Figure 2. ALGORITHM FOR THE TREATMENT OF NON-PSYCHOTIC MAJOR DEPRESSIVE DISORDER IN PRIMARY CARE

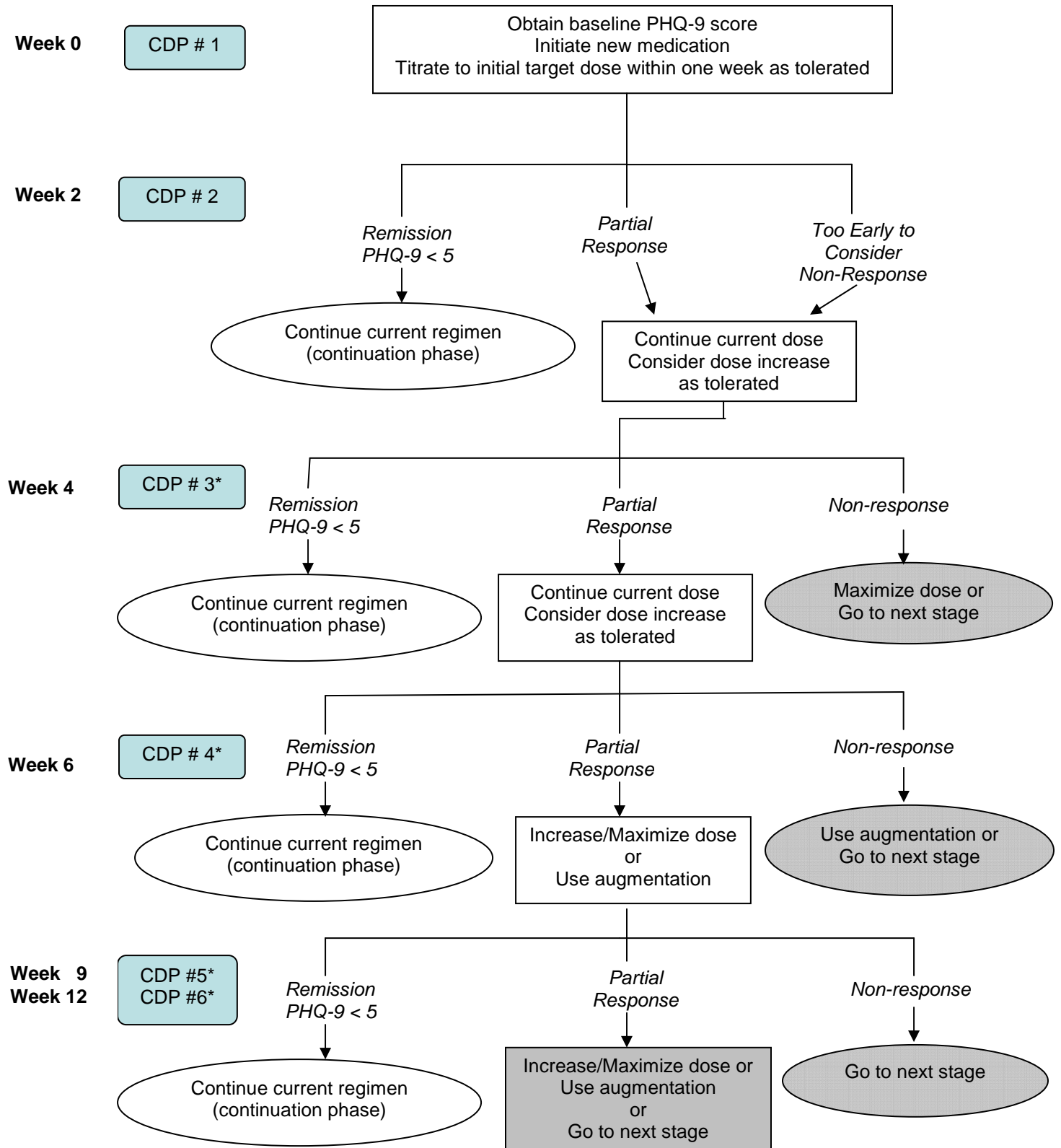


For further management of a non-responsive patient, refer to a psychiatrist or see the complete treatment algorithm in the Best Practices Report available at <http://www.sccp.sc.edu/SCORxE>.

¹ EBPT is an option before starting or in combination with pharmacotherapy at any stage in the algorithm.
² In general, SSRIs and SNRIs are not used together because of their similar mechanisms of action.
³ Use with extreme caution in patients with cardiovascular or coronary artery disease.
⁴ When reassessing diagnosis due to non-response, consider comorbid disease states and non-adherence. Reach target dose and duration of medication before documenting treatment failure.

Adapted from personal communication with M. Lynn Crismon, Pharm.D., December 2007

Figure 3. CRITICAL DECISION POINTS (CDPs) FOR ACUTE PHASE TREATMENT OF NON-PSYCHOTIC MAJOR DEPRESSIVE DISORDER



Definitions

Partial Response: > 20% decrease from baseline PHQ-9 score or any clinically meaningful response short of remission.

Non-response: ≤ 20% decrease from baseline PHQ-9 score.

* At CDPs 3,4,5,6 consider switching antidepressants if side effects are intolerable.

Table 1: DOSING GUIDELINES FOR ANTIDEPRESSANT AGENTS

Type/Class	Medication	Initial Starting Daily Dose	Initial Target Daily Dose* (Serum Level)	Maximum Daily Dose (Serum Level)	Recommended Administration
SSRI	Citalopram	10-20 mg	20 mg	60 mg	AM
	Escitalopram	5-10 mg	10 mg	20 mg	AM
	Fluoxetine	10-20 mg	20 mg	40–80 mg	AM
	Paroxetine (i)	10-20 mg	20-30 mg	40–60 mg (ii)	AM or HS
	Sertraline	25-50 mg	50-100 mg	150–200 mg	AM
SNRI	Duloxetine	20-30 mg	40-60 mg	120 mg (iii)	Daily or BID
	Venlafaxine	37.5-75 mg	150-225 mg	375 mg	BID
	Venlafaxine XR	37.5-75 mg	75-225 mg	225 mg	Daily
Other (iv)	Bupropion	75 mg	225-300 mg	450 mg	TID ≤ 150mg/dose
	Bupropion SR	100-150 mg	200-300 mg	400 mg	BID ≤ 200mg/dose
	Bupropion XL	150 mg	300 mg	450 mg	Daily
	Mirtazapine	7.5-15 mg	30 mg	60 mg (v)	HS
TCA	Amitriptyline	25-50 mg	150–200 mg	300 mg	HS
	Clomipramine	25 mg	100–150 mg	250 mg	HS
	Desipramine	25-50 mg	150 mg (> 125 ng/ml)	300 mg	HS
	Imipramine	25-50 mg	150 mg (> 200 ng/ml) (vi)	300 mg (200-400 ng/ml) (vi)	HS
	Nortriptyline	25-50 mg	75–100 mg (50–150 ng/ml)	150 mg (50-150 ng/ml)	HS

Key: SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

* Antidepressant dosage can be increased every 2 to 3 weeks as tolerated if remission has not occurred.

(i) Paroxetine and paroxetine CR have similar side effect profiles, comparable half-lives, and reach steady state plasma concentrations at similar time intervals.^{17,18}

(ii) Manufacturer recommended maximum dose for MDD is 50 mg/day.

(iii) Manufacturer recommended maximum dose for MDD is 60 mg/day.

(iv) Trazodone is not included as a treatment option for MDD because therapeutic doses are hard to achieve due to excessive sedation (therapeutic dose 300-600 mg/day). Trazodone may be considered during the acute treatment phase as adjunctive therapy when sedation is desired.^{19,20}

(v) Manufacturer recommended maximum dose is 45 mg/day.

(vi) Serum level includes parent drug and active metabolite (imipramine and desipramine, respectively).

Table 2: DOSING GUIDELINES FOR AUGMENTATION AGENTS

Medication	Starting Daily Dose*	Target Daily Dose**	Maximum Daily Dose	Recommended Administration Schedule
Buspirone	15 mg	30 to 60 mg	60 mg	BID
T ₃ (Liothyronine)	25 mcg	25-50 mcg	50 mcg	Daily
Aripiprazole ¹	2 to 5 mg	5 to 10 mg	15 mg	AM or HS
Olanzapine	5 mg	5 to 20 mg	20 mg	HS
Quetiapine	50 mg	150 to 400 mg	800 mg	HS
Risperidone	0.25 mg	0.25 to 2 mg	6 mg	HS
Ziprasidone	20 to 40 mg	20 to 160 mg	160 mg	BID or HS with food

*When using second generation antipsychotics, dosing should start low and increase only as tolerated. Clinicians should also follow side effects and obtain metabolic assessments. **All medication dosages may be increased at weekly intervals as tolerated.

¹Aripiprazole is the only FDA approved medication for augmentation therapy in MDD.

Table 3: COMMON SIDE EFFECTS (SEs) OF ANTIDEPRESSANT MEDICATIONS

Class	Antidepressant	Anticholinergic	Conduction Abnormalities	Drowsiness	Gastrointestinal Distress	Headache	Insomnia	Orthostatic Hypotension	Sexual Disturbances	Weight Gain	Comments
SSRI	Citalopram	0	0	0	3+	2+	2+	0	4+	1+	Activation, agitation and restlessness reported with all SSRIs
	Escitalopram	0	0	0	3+	0	2+	0	2+	1+	
	Fluoxetine	0	0	0	3+	2+	2+	0	4+	1+	
	Paroxetine	1+	0	1+	3+	2+	2+	0	4+	2+	
	Sertraline	0	0	0	3+	2+	2+	0	4+	1+	
SNRI	Duloxetine	1+	1+	1+	3+	2+	2+	0	4+	0	Higher rate of hypertension with doses > 225 mg/day
	Venlafaxine	1+	1+	1+	3+	2+	2+	0	4+	0	
Other	Bupropion	0	0/1+	0	1+	2+	2+	0	0	0	Increased risk of seizures with doses > 450 mg/day
	Mirtazapine	1+	1+	3+	0	1+	1+	1+	2+	3+	Less sedation with doses > 15 mg/day
TCA	Amitriptyline	4+	3+	4+	1+	1+	1+	3+	1+	4+	
	Clomipramine	4+	3+	4+	1+	1+	2+	2+	4+	4+	
	Desipramine	1+	2+	2+	0	0	1+	2+	1+	1+	
	Imipramine	3+	3+	3+	1+	2+	2+	4+	4+	4+	
	Nortriptyline	2+	2+	2+	0	0	0	1+	0	1+	

Scale: 0 = absent or rare to 4+ = common

Key: SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
References: **Drug Information Handbook for Psychiatry**. Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

Clinical Handbook of Psychotropic Drugs. Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Toronto, ON, Hogrefe & Huber, 2006.

Table 4: COMMON SIDE EFFECTS (SEs) OF AUGMENTATION AGENTS

Medication	Side Effects
Bupirone	Dizziness (12%); headache (6%); nervousness (5%); lightheadedness (3%); excitement (2%); fatigue, paresthesia, numbness, and gastrointestinal upset (<10%).
T ₃ (Liothyronine)	Arrhythmia (6%); tachycardia (3%); cardiopulmonary arrest (2%); hypotension (2%); myocardial infarction (2%); allergic skin reactions, angina, congestive heart failure (CHF), fever, hypertension, phlebitis, and twitching (<1%). <i>Chronic overdose: hyperthyroidism, weight loss, nervousness, sweating, tachycardia, insomnia, heat intolerance, menstrual irregularities, palpitations, psychosis, and fever.</i> <i>Acute overdose: fever, hypoglycemia, CHF, and unrecognized adrenal insufficiency.</i>

References: **Drug Information Handbook for Psychiatry**. Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

Clinical Handbook of Psychotropic Drugs. Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Toronto, ON, Hogrefe & Huber, 2006.

Table 5: COMMON SIDE EFFECTS (SEs) OF ANTIPSYCHOTIC AUGMENTATION AGENTS

Second Generation Antipsychotics	Extrapyramidal Side Effects	Tardive Dyskinesia	Orthostatic Hypotension	Increased Prolactin	Sedation	Weight Gain	Anticholinergic Effects	Dyslipidemia	Glucose Dysregulation
Aripiprazole	0	0	N	N	1+	0	1+	0	1+
Olanzapine	1+	1+	1+	0	3+	3+	2+	4+	3+
Quetiapine	0	0	2+	0	4+ (*)	2+	1+	1+	1+
Risperidone	1-2+(**)	1+	1+	3+	1+	2+	1+	1+	1+
Ziprasidone	1+	1+	1+	1+	1+	0	1+	0	N

Scale: N = none reported, 0 = Absent or rare to 4+ = common

* During dose titration phase

** 2+ at doses > 6 mg/day

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For further information, including complete list of references, see: <http://www.sccp.sc.edu/SCORxE>