



EVIDENCE-BASED BEST PRACTICES FOR THE TREATMENT OF BIPOLAR DISORDER FOR PRIMARY CARE IN SOUTH CAROLINA

Key Messages for Management of Bipolar Disorder (BPD)

- A**ccurate and timely diagnosis is critical to optimize clinical outcomes.
- R**eturn to full psychosocial functioning is the goal of treatment.
- M**edication is the mainstay of treatment for initial mood stabilization and maintenance.
- S**creen for substance abuse to increase the chance of clinical improvement.

BACKGROUND

A panel of 4 psychiatrists and 4 clinical pharmacists from different geographic regions of the state was created to consensually agree on evidence-based best practices for the treatment of bipolar disorder (BPD) 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.**^{1,2} 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 and other health care professionals to focus on treatment of BPD 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 BPD in primary care patients ≥ 18 years of age. 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).

Treatment options recommended throughout this document are based on available data derived from various sources. The following symbols, found in parentheses following statements, indicate the level of evidence for the statements as shown below:

- (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 and/or SCORxE panel
- (Level D) - Consensus among SCORxE mental health panel that differs from the TMAP panel

BIPOLAR DISORDER MANAGEMENT AT-A-GLANCE

➤ Initial Diagnosis

- Many patients with BPD are initially misdiagnosed with major depressive disorder (MDD); therefore, screening for a history of mania or hypomania in patients presenting with depressive symptoms is crucial. A higher index of suspicion for bipolar depression is warranted in patients presenting with the following features: atypical depressive symptoms, psychomotor retardation, psychotic symptoms and/or pathological guilt, early onset depression, multiple depressive episodes, shorter duration of depressive episodes, or family history of BPD.³
- Standardized assessment instruments, such as the Mood Disorder Questionnaire (MDQ) for manic and hypomanic symptoms and the Patient Health Questionnaire (PHQ-9) for depressive symptoms, should be used in conjunction to improve diagnostic accuracy.
- Clinicians should talk with family and friends to help confirm the diagnosis.

➤ Goal of Therapy

- The goal of treatment is complete symptom remission and prevention of symptom exacerbation.⁴
- Ongoing assessment of suicidality and use of suicide prevention strategies are essential.
- Brief symptom ratings (e.g., mood chart) should be reviewed at every visit to guide treatment decisions.⁵

➤ Treatment Strategies

- The algorithms in this summary are based on evidence. However, because there is scant evidence after the first two stages of treatment, consensus of clinical experts was used beyond Stage 2.
- Bipolar patients should receive continuous treatment with a mood stabilizer(s).
- Avoid antidepressant monotherapy; if necessary, use antidepressant with a concomitant mood stabilizer to minimize the risk of affective switches.
- In cases of mania, hypomania, or rapid cycling in patients on antidepressants, first consider discontinuing the antidepressant (quickly, unless contraindicated).
- Consider the use of evidence-based psychotherapy at any point during treatment.^{6,7,8}
- All patients who achieve symptom remission should continue treatment until a full response to treatment is sustained for at least four weeks before transitioning into maintenance treatment.
- If a patient completes two stages of the treatment algorithm without a positive outcome, re-evaluate for diagnostic accuracy, co-morbid medical/mental disorders, and substance abuse.

➤ Symptom Exacerbation

- Sleep disturbances may precipitate or be the first sign of a mood episode.⁹
- Identify relapse symptoms for an individual patient in order to tailor management strategies.
- Clinicians should talk with family and friends to help identify relapse symptoms.

➤ Substance Abuse

- If co-occurring substance abuse is present, concomitant treatment of both the BPD and the substance abuse disorder is critical in order to maximize patient outcomes.¹⁰

➤ Adherence

- Inadequate patient adherence is a major barrier to successful treatment. Emphasize treatment adherence, including lifestyle management training, intensive education, and cognitive behavioral therapy.
- It may help to have a family member share responsibility for medication adherence.
- Consider medication formulations (e.g., slow release) that are likely to be well tolerated by the patient and lead to enhanced adherence.
- If efficacy, safety and tolerability are similar, then consider selection of a less expensive medication regimen within a specific treatment stage.

BIPOLAR DISORDER

Prevalence of Bipolar Disorder

The World Health Organization has identified BPD, an illness characterized by periods of mood elevation, as the sixth leading cause of disability-adjusted life years among people between 15 and 44 years of age.¹¹ The first onset of BPD usually occurs in the second or third decade of life, although it may occur even earlier. Lifetime prevalence in community samples has varied from 0.4 to 1.6%.¹² The true prevalence is uncertain since patients usually present with symptoms of depression¹³ and are not specifically asked about symptoms suggestive of prior episodes of mania. Untreated BPD is associated with substantial morbidity and mortality, and treatment differs from that of major depressive disorder (MDD).¹⁴

Two types of BPD have been described: Bipolar I disorder manifests as episodes of sustained mania (or mixed episodes) with depressive episodes; Bipolar II disorder presents with one or more major depressive episodes, with at least one hypomanic episode.¹⁵ When an individual previously diagnosed with Bipolar II disorder develops a manic or mixed episode, the diagnosis is changed to Bipolar I disorder. Bipolar I disorder affects men and women equally, however Bipolar II disorder is more common in women.¹⁶

Diagnostic Criteria

Depressive Episode

The diagnostic criteria for bipolar depression are the same as those for MDD.¹² Certain features, however, appear more likely to be found in bipolar depression: some atypical depressive symptoms, specifically, increased appetite or weight gain, hypersomnia, and leaden paralysis; psychomotor retardation; psychotic symptoms and/or pathological guilt; lability of mood; earlier age of onset of first depressive episode (< 25 years of age); multiple prior depressive episodes (≥ 5 episodes); shorter duration of depressive episodes; and positive family history of BPD.³

Manic Episode

A diagnosis of mania can be made in patients experiencing abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary) when it is accompanied by at least three of the following symptoms (four if the mood is only irritable):

- (1) inflated self-esteem or grandiosity (e.g., exaggerated sense of one's importance, hyper-religiosity)
- (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
- (3) more talkative than usual or pressure to keep talking
- (4) flight of ideas or subjective experience that thoughts are racing
- (5) distractibility (e.g., attention too easily drawn to unimportant or irrelevant external stimuli)
- (6) increase in goal-directed activity (socially, sexually, or at work or school) or psychomotor agitation
- (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

Additionally, the mood disturbance is sufficiently severe: to cause marked impairment in occupational functioning or in usual social activities or relationships with others; to necessitate hospitalization to prevent harm to self or others; or to present with psychotic features.¹¹

Mixed Episode

A mixed episode can be diagnosed if patients experience symptoms meeting criteria for both a manic episode and for a major depressive episode (except for duration) nearly every day for at least 1 week.¹²

Hypomanic Episode

The diagnostic criteria for hypomania are the same as mania (listed above), except for a shorter duration (minimum of 4 days) and lesser severity. Hypomania is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic. The disturbance in mood and the change in functioning are observable by others, but are not severe enough to cause marked impairment in social or occupational functioning, to necessitate hospitalization, or to present with psychotic features.¹²

Initial Psychiatric and Medical Evaluation

The differential diagnosis for BPD includes several psychiatric conditions, a number of which may actually coexist with BPD, including: schizophrenia, schizoaffective disorder, post-traumatic stress disorder, substance abuse, and personality disorders. Other medical disorders to consider include thyroid disease, stroke, partial complex seizures, lupus, HIV, and tertiary syphilis. Drug-induced mania (e.g., cocaine, antidepressants, stimulants, corticosteroids) or drug-induced depression (e.g., beta-blockers, corticosteroids, interferon) should also be considered.

Given the extensive differential diagnosis when manic symptoms or a history of manic symptoms are evident, the patient needs a thorough medical and psychiatric history and detailed physical exam with special emphasis on signs of thyroid disease and neurological deficits. Standardized assessment instruments, such as the MDQ (Figure 1) for mania and hypomanic symptoms and the PHQ-9 (See SCORxE MDD topic) for depressive symptoms should be used in conjunction to improve diagnostic accuracy.

Patient evaluation should include:

- Physical examination with a particular focus upon the neurological and endocrine systems
- Observation for signs of abuse of alcohol or other substances
- Laboratory testing, including: thyroid stimulating hormone (TSH), complete blood count, blood chemistries, and urine toxicology for substances of abuse
- Other testing such as brain imaging or electroencephalogram (EEG) based on findings in the history, examination and laboratory studies

Assessment for Suicidality

Since bipolar depression and mixed states are associated with a significantly increased risk for suicide, assessment of suicidality is an essential component of evaluation (Level B). The risk of suicide attempt among patients with BPD is more than 6 times that of MDD patients. Between 25 - 50% of people with BPD attempt suicide, and 15% die by suicide, with the average age of their first attempt about age 26.¹⁷ Another study showed 18% of deaths in bipolar patients were the result of suicide.¹⁸ Only a fraction of BPD patients who commit suicide had received ongoing psychiatric treatment at the time of death. The current mood state is a critical determinant of suicide risk in BPD. Depressive and dysphoric-irritable mood states account for three-quarters of suicides in BPD. Suicide attempt is infrequent in mania and rare in hypomania.¹⁹

Other risk factors for suicide in BPD include (Level B):^{20,21}

- Personal or family history of suicidal behavior
- Younger age of onset
- Physical and/or sexual abuse during childhood
- Frequent and/or severe depressive episodes
- Alcohol or substance abuse
- Increased levels of pessimism, impulsivity or aggression

Effective assessment of suicidality involves the evaluation of several parameters, such as: severity, nature and frequency of suicidal ideation; details of suicide plans; access to lethal means (e.g., weapons, medications); current or recent stressors; past suicide attempts and plans; presence of risk factors and protective factors; and interpersonal and other social supports.¹⁸ Repeated assessments should be considered when suicide risk is suspected. Patients at high, acute suicidal risk should be transported to an emergency room as they often require immediate hospitalization, sometimes by legal commitment.¹⁹

Suicide prevention strategies should be considered as part of the ongoing treatment plan for BPD patients, based on the following three basic elements: (1) routine assessment of suicidality risk as described above; (2) education of patient and family regarding risk factors listed above; (3) and development of individual treatment plans, preferably in writing.²²

BIPOLAR DISORDER ALGORITHM

Use of Algorithm

The BPD algorithms (Figures 2 and 3) provide sequenced medication recommendations; it should be noted that evidence is often scant after the first two stages so consensus of clinical experts was used. Specific recommendations for Bipolar II Disorder are not included because of insufficient evidence; however, the current treatment approach is generally based on Bipolar I Disorder.

A thorough psychiatric evaluation, general medical history, comprehensive physical assessment and diagnostic tests should be performed, and a diagnosis of BPD made prior to engagement of a patient into the appropriate medication treatment algorithm. Patients may enter the algorithm at different stages depending on prior treatment history and response, relevant psychiatric factors (e.g., severity of symptoms, suicidality, co-morbidity) and general medical factors (e.g., concomitant medications or illnesses, age). Progression to different stages should be considered in cases of insufficient symptom improvement. Alternate medications (or combinations) within a stage may be considered in cases of non-response or intolerable side effects. Thorough and ongoing diagnostic re-evaluation and confirmation of BPD are recommended after two failed treatment stages, with special attention and screening for co-morbid medical and psychiatric disorders, including substance abuse.

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

Each stage of the BPD Algorithms represents a trial of a different medication or medication combinations. The algorithms' "strategies" are the medication options that clinicians and patients choose from within each stage. While medications are the algorithms' "strategies", specific recommendations concerning medication use (e.g., dose titration, measurement of treatment response, trial duration) are the algorithms' "tactics". In clinical practice, variations from these detailed recommendations may be necessary (e.g., severe mania may require more rapid titration and/or change in stage).

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 regimen (within the same stage or in the next stage of the algorithm).

At each CDP, brief symptom ratings are very valuable to assess the patient's level of response to the medication regimen (Table 1). The clinician can then make a therapeutic decision based on the results of the brief symptom ratings, 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., symptom remission).

MEDICATIONS AND DOSING

Phase of Treatment

The treatment of BPD is usually divided in two phases: acute (short-term) and maintenance (long-term). Acute treatment refers to the treatment of a current episode of mania or depression. See CDPs (Table 1) for more specific information on medication trials and time intervals for dosage adjustments and/or change in algorithm stage. Treatment should be continued until full response (ideally symptom remission) is sustained for at least 4 weeks (Level C). Maintenance treatment refers to the life-long treatment that is crucial to prevent future episodes of mania/hypomania/mixed episodes or depression (Level A).

Choice of Medication

The treatment of BPD centers around the use of medications called "mood stabilizers" and "antimanic agents". Ideally, a mood stabilizer should treat acute manic/hypomanic/mixed and depressive episodes, prevent further manic/hypomanic/mixed and depressive episodes, and not aggravate the illness (e.g., inducing mania or rapid cycling). Lithium, valproate, carbamazepine, and second generation antipsychotics (SGAs) are considered mood stabilizers. Antimanic agents are medications that effectively treat acute manic, hypomanic or mixed episodes. They include mood stabilizers, oxcarbazepine and first generation antipsychotics (FGAs). Lamotrigine, an agent with no antimanic properties, may be used for a patient with a current and/or recent episode of depression but no history of severe or recent mania (Level C).

Acute Mania

All patients with Bipolar I disorder should receive continuous treatment with an antimanic agent (see Figure 2 algorithm) (Level A). For severely ill, agitated or aggressive patients, consider the short-term use of adjunctive medications such as benzodiazepines or antipsychotics (Level A). If a patient is already taking an antipsychotic, consider using the same antipsychotic on an as needed basis before adding a different antipsychotic. The use of two different antipsychotics should generally be avoided. In cases of mania, hypomania, or rapid cycling in patients on antidepressants, first consider discontinuing the antidepressant (quickly, unless contraindicated) (Level C).

Acute Bipolar Depression

Bipolar depressive episodes are first managed with dose optimization of the mood stabilizer for patients already receiving a mood stabilizer (Level C), or initiation of a mood stabilizer (e.g., valproate [Level B], lithium [Level A], or quetiapine [Level A]) for those not receiving one (see Figure 3 algorithm). There is insufficient evidence supporting the use of lamotrigine as monotherapy (Level D), however it may be considered as add-on therapy (Level A). Given the limited efficacy of lamotrigine in preventing new manic episodes, the addition of an antimanic agent is recommended when lamotrigine is used in combination with an antidepressant (Level C). Antidepressant monotherapy is not recommended for the acute or maintenance treatment of BPD due to the risks of inducing a manic episode or accelerating the cycle (Level A). Antidepressants are usually reserved as third line strategy in the management of bipolar depressive episodes as combination therapy (Level C). When used in conjunction with mood stabilizers, the short- and long-term use of antidepressants in patients with BPD continues to be controversial due to limited and conflicting evidence of efficacy and the potential for mood destabilization (Level C).^{23,24,25}

Maintenance

Maintenance treatment typically begins with the same regimen used in acute treatment. The goal is to continue treatment at the minimum dose and number of medications necessary to optimize quality of life and prevent future episodes. Attempts to simplify maintenance regimens can begin 3 - 6 months after resolution of the acute episode, and changes should be made to one medication at a time (Level C). Although maintenance treatment research to date has focused on the use of monotherapy, the majority of patients in clinical practice require combination treatment to maintain long-term stability (Level C).

Treatment recommendations depend on the polarity of the most recent episode. For individuals with a history of frequent, recent, or severe mania, lithium or valproate are recommended (Level A). Alternative choices include carbamazepine (Level B) and SGAs. Of the SGAs, controlled evidence supports the use of aripiprazole (Level A); olanzapine (Level A); and the use of quetiapine as combination therapy (Level A). Maintenance treatment following a bipolar depressive episode may include lithium (Level A); lamotrigine for patients without frequent, recent, or severe mania (Level A); carbamazepine (Level B); valproate (Level B); or SGAs (Level B). Controlled evidence supports the use of quetiapine as combination therapy (Level A).

Mood Switching Associated with Antidepressant Use

Conflicting evidence suggests that the use of antidepressants in patients with BPD is associated with a risk of mood destabilization, such as “switching” to mania or hypomania, or inducing a rapid cycling course of illness (Level C). There appears to be an increased rate of “switching” to mania or hypomania with tricyclic antidepressants (TCAs) versus other classes of antidepressants (Level A). Limited data suggest that the risk of mania induction with venlafaxine may exceed that of other antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or bupropion (Level A). Risk factors associated with switching include: antidepressant monotherapy, multiple antidepressant trials, history of severe mania, and prior history of antidepressant-induced mood switching (Level B).

Medication Dosing

Medication doses should be maximized (either alone or in combination) as tolerated and for an adequate period of time to observe symptom improvement before changing treatment regimen (see Table 2 for appropriate dosage ranges). When adjusting medications, it is preferable to make adjustments to one medication at a time to allow for evaluation of response. If doses above the usual therapeutic range are used, it should be for a limited duration (e.g., 4 - 6 weeks), and response to this dose evaluated using brief symptom

ratings. If improvement has not occurred with the higher dosage within this time frame, consider moving to the next treatment stage or an alternative medication within the same stage, and use an overlap and taper strategy (Level C).

Medication Serum Concentrations

Serum concentrations are useful to check patient adherence and document what concentration correlates to an individual patient's response. After stabilization, serum concentrations should be ordered as necessary to ensure that dosing is within the therapeutic window for an individual patient. Toxic side effects should prompt immediate evaluation of serum concentrations.

Lithium therapy should include monitoring of serum concentrations for both safety and efficacy. Lithium has a well established therapeutic serum concentration range and a narrow therapeutic index (see Table 2). Serum lithium levels may be obtained after 5 days of constant dosing and should be drawn 12 hours post-dose. In general, lithium levels should range between 1.0 - 1.2 mEq/L for acute mania (Level A); range between 0.8 - 1.0 mEq/L (or lower e.g., 0.6 mEq/L) for maintenance (Level A); and be at least 0.8 mEq/L for acute depressive episodes (Level B).

Therapeutic serum concentrations for valproate and carbamazepine are extrapolated from the epilepsy literature, but are not as well established in the treatment of BPD (see Table 2). They may be used to help guide therapy and as supplemental clinical information. Serum valproate levels may be obtained after 3 days of constant dosing, and levels should be drawn 12 hours post-dose, except for the extended-release formulation (Depakote® ER). Ideally, Depakote® ER levels should be drawn 18 hours post-dose. Therapeutic serum levels should range between 50 - 150 mcg/mL. Best effects for acute mania are usually observed with valproate levels above 94 mcg/mL, but more side effects occur with levels above 125 mcg/mL (Level A). Serum carbamazepine levels may be obtained after 5 days of constant dosing, and levels should be drawn 12 hours post-dose. Therapeutic serum levels range between 4 - 12 mcg/mL (Level B). Since carbamazepine induces its own metabolism, regular serum level monitoring and dosage adjustments are required until maximal hepatic induction occurs (within 2 - 4 weeks).

Medication Changes or Discontinuation

Approaches vary depending on the degree of patient response. In cases of partial response with good tolerability, consider adding a second medication versus switching. Switching to an alternative medication (within the same stage), versus adding, should be considered in cases of intolerance or non-response using the overlap and taper approach if possible (Level C). In this approach, the new medication is started and titrated to a therapeutic dose, then, the medication to be discontinued is gradually tapered (e.g., at a rate of 25% every 1 - 2 weeks, over a minimum period of 2 - 4 weeks).

When stopping any psychotropic medication, a gradual tapering (2 - 4 weeks minimum) is recommended whenever possible to minimize exacerbation or relapse of mood (Level C). A gradual taper of lithium is especially important as sudden discontinuation of lithium maintenance treatment is associated with greater relapse of affective illness than a gradual taper (Level B).²⁶ Rapid discontinuation is indicated, on the other hand, when severe or potentially life-threatening side effects occur. Similarly, rapid discontinuation of antidepressant treatment is indicated should it be associated with the development of manic symptoms (Level C).

Evaluation of Side Effects

Side effect profiles (Tables 3 and 4) of the medications used in BPD vary. In general, side effects should be initially addressed by dose reduction or medication switching before considering medications to ameliorate symptoms due to side effects (Level C). Pharmacologic intervention may increase the risk of drug interactions and additional adverse effects, thus decreasing patient adherence. Specific monitoring parameters suggested for several agents are found in Tables 5 and 6.

EVALUATION OF PATIENT RESPONSE

Use of Measurement-Based Care

Measurement-based care (MBC) promotes the use of rating scales or questionnaires at every visit to measure symptoms, side effects and patient adherence as well as guide tactics to modify dosage and treatment duration. Currently, most clinicians tend to routinely use global measures rather than specific measures of affective symptoms during patient visits. Examples of symptom-based rating instruments include:

- MDQ (to assess the presence of manic symptoms)
- PHQ-9 (to assess the presence and severity of depressive symptoms)
- mood charts (which allow patients to track manic and depressive symptoms longitudinally)

Currently, there is no evaluation tool available to quickly and effectively grade manic symptoms as mild, moderate or severe. If a patient is currently manic or depressed, the MDQ and/or PHQ-9 may be used, in conjunction with a mood chart. If a patient is euthymic, a mood chart alone may be used.

Symptom Evaluation and Management Considerations

Remission, partial response, and non-response are best evaluated with the use of rating scales to obtain objective data. 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. Consider involving patients in their own care through psychoeducational programs and use of a daily mood chart. Patients may also benefit from evidence-based psychotherapy targeted for patients with BPD (Level A).

In patients who do not respond to an adequate trial of medication or who experience breakthrough symptoms, consider contributing factors such as non-adherence or substance abuse (Level C). Once these considerations have been ruled out, breakthrough symptoms should be addressed first by optimizing the medication dose (Level C). If the treatment regimen has been recently simplified (e.g., dosage or number of medications), then consider returning to the previously effective regimen. In cases of breakthrough mania, hypomania, or rapid cycling in patients on antidepressants, first consider discontinuing the antidepressant (quickly, unless contraindicated) (Level C). For severely ill, agitated or aggressive patients, consider the short-term use of adjunctive medications such as benzodiazepines or antipsychotics (Level A). Insomnia and excessive anxiety can also be managed with the short-term use of adjunctive medications such as benzodiazepines (Level A).

Visit Frequency

There is no evidence to support recommendations on monitoring frequency. The TMAP and SCORxE mental health panels suggest that patients be seen every 1 - 2 weeks while medications are being adjusted. As medications are stabilized and patients exhibit stable, positive response, visit intervals can be gradually lengthened to every 4 weeks. Additional patient contact (e.g., by telephone) may be necessary to provide optimal care for a symptomatic patient. Once patients are stable, visits can be scheduled every 8 - 12 weeks, as individually determined (Level C).

REFERRAL TO A PSYCHIATRIST

Patients with the following characteristics should be considered for referral to a psychiatrist:

- psychotic features
- severe mania
- active suicidal intent and/or plan
- uncertain diagnosis of BPD
- treatment failure after Stage 2 of the algorithm
- continued active substance use disorders
- severe personality disorders
- history of affective switch
- need for psychotherapy
- poor social support

Figure 1. Mood Disorder Questionnaire (MDQ)²⁷

Patient Name _____

Date of Visit _____

Please answer each question to the best of your ability.

Yes No

1. Has there ever been a period of time when you were not your usual self and ...		
.... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?		
.... you were so irritable that you shouted at people or started fights or arguments?		
.... you felt much more self-confident than usual?		
.... you got much less sleep than usual and found that you didn't really miss it?		
.... you were more talkative or spoke much faster than usual?		
.... thoughts raced through your head or you couldn't slow your mind down?		
.... you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
.... you had more energy than usual?		
.... you were much more active or did many more things than usual?		
.... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?		
.... you were much more interested in sex than usual?		
.... you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
.... spending money got you or your family in trouble?		
2. If you checked YES to <u>more than one</u> of the above, have several of these ever happened during the same period of time?		
3. How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights?		
<input type="checkbox"/> No problems <input type="checkbox"/> Minor problem <input type="checkbox"/> Moderate problem <input type="checkbox"/> Serious problem		
4. Have any of your blood relatives (i.e., children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?		
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?		

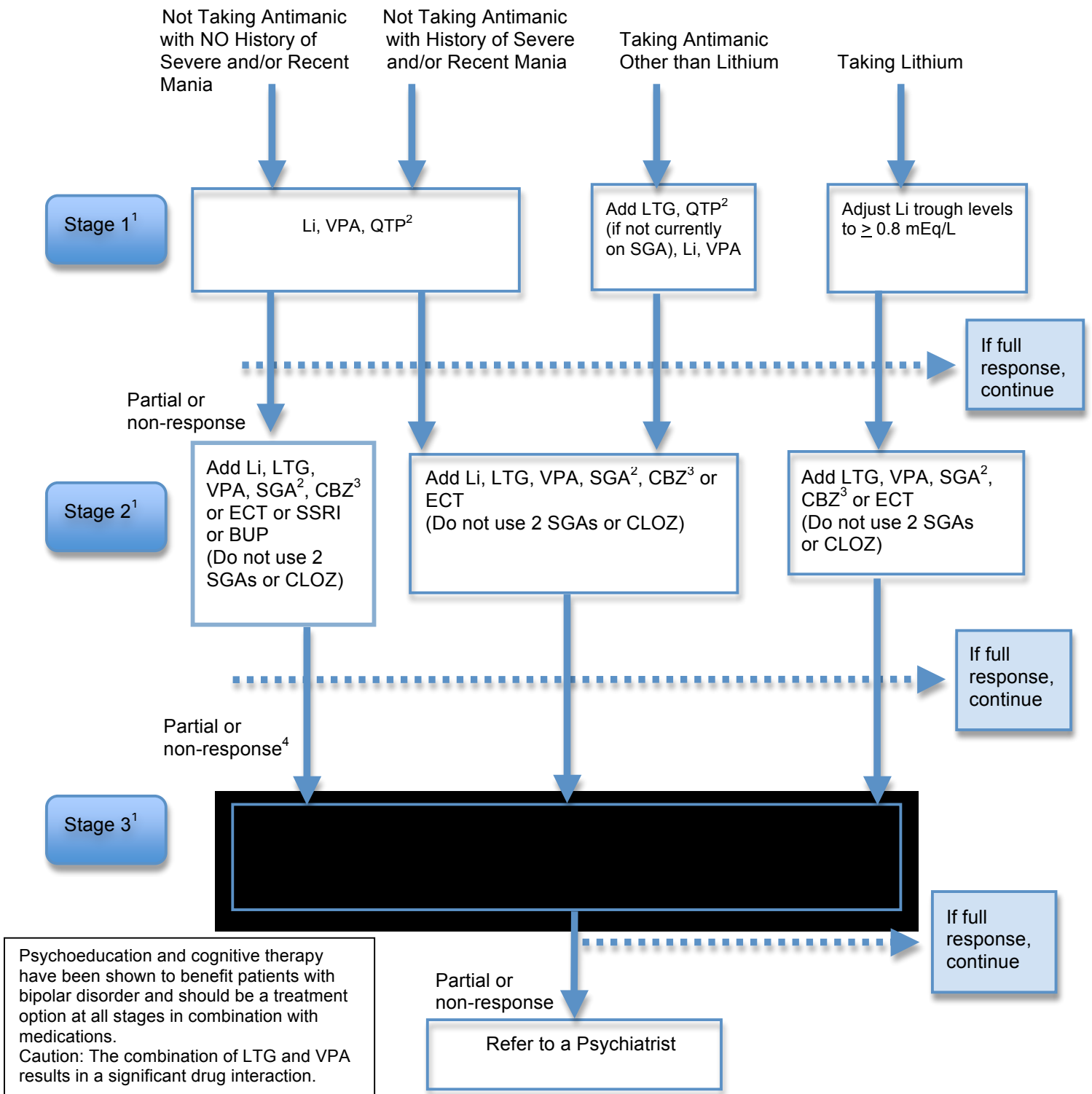
This instrument is designed for screening purposes only and not to be used as a diagnostic tool.

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Scoring the MDQ In order to screen positive for possible bipolar disorder, ALL 3 parts of the following criteria must be met:

1. YES to seven or more of the 13 items in question #1, **AND**
2. YES to question #2, **AND**
3. MODERATE or SERIOUS to question #3

Figure 3. Algorithm for the Treatment of Bipolar Disorder – Currently Depressed



1. Use targeted adjunctive treatment as necessary before moving to next stage.
2. Routine metabolic monitoring should occur for patients receiving SGAs.
3. CBZ has numerous significant drug interactions. Clinicians should closely monitor.
4. Consider referral to a psychiatrist if non-response after Stage 2.

Abbreviation Key

BUP = bupropion	OFC = olanzapine/fluoxetine combination
CBZ = carbamazepine	QTP = quetiapine
CLOZ = clozapine	SGA = 2 nd generation antipsychotic
ECT = electroconvulsive therapy	SSRI = selective serotonin reuptake inhibitor
Li = lithium	TCA = tricyclic antidepressant
LTG = lamotrigine	VPA = valproate

Adapted from Texas Implementation of Medication Algorithm (TIMA); Copyright © 2005, Texas Department of State Health Services.

Table 1. Critical Decision Points (CDPs)

In clinical practice, variations from these detailed recommendations may be necessary. When addressing goals of treatment for an individual, consider initial response and resolution of symptoms. More aggressive therapy may be needed in order to prevent further decompensation and hospitalization if patients' symptoms are severe.

CLINICAL STATUS	CDP ⁽ⁱ⁾	PLAN
Symptomatic	Week 0 (CDP #1) (initial presentation)	<ul style="list-style-type: none"> Assess patient; select appropriate algorithm and treatment stage; initiate medication regimen from selected stage at lower end of therapeutic dose range or serum concentration
No symptoms	Week 2 (CDP #2)	<ul style="list-style-type: none"> Continue current dose
Full Response	Week 4 (CDP #3)	
	Week 6 (CDP #4)	
	Week 8 (CDP #5)	
Mild to Moderate Symptoms	Week 2 (CDP #2)	<ul style="list-style-type: none"> Continue current dose Consider increasing dose if well tolerated
	Week 4 (CDP #3)	<ul style="list-style-type: none"> Increase dose if well tolerated Consider next stage or change medication(s) within stage
	Week 6 (CDP #4)	
	Week 8 (CDP #5)	
Severe Symptoms	Week 2 (CDP #2)	<ul style="list-style-type: none"> Increase dose if well tolerated
	Week 4 (CDP #3)	<ul style="list-style-type: none"> Increase dose if well tolerated Consider next stage or change medication(s) within stage
	Week 6 (CDP #4)	
	Week 8 (CDP #5)	<ul style="list-style-type: none"> Go to next stage or change medication(s) within stage

(i) Consider simplifying treatment regimen with fewer medications and/or lower dosages after patient maintains a full response for 4 - 6 months

Adapted from Texas Implementation of Medication Algorithm (TIMA) 2000. See clinician's manual under bipolar disorder. Available at: <http://www.dshs.state.tx.us/mhprograms/TIMA.shtm>.

Table 2. Medication Dosing Guidelines in the Management of Bipolar Disorder (BPD)

Oral Medication (i) [Brand Examples (ii)]	Starting Daily Dose	Target Daily Dose [Serum Level (iii)]	Maximum Daily Dose [Maximum Serum Level (iii)]	Recommended Administration
LITHIUM AND ANTICONVULSANTS				
Carbamazepine [Tegretol, Equetro]	200 - 600 mg/day	400 - 1600 mg/day [Serum level: 4-12 mcg/mL]	1600 mg/day (iv) [Serum level: 12 mcg/mL]	BID or TID
Divalproex Sodium (v) [Depakote]; Valproic Acid (v) [Depakene, Stavzor]	500 - 1000 mg/day	750 - 2000 mg/day [Serum level: 50-150 mcg/mL]	60 mg/kg/day (iv) [Serum level: 150 mcg/mL]	BID or HS
Lamotrigine (vi) [Lamictal]	25 mg/day	200 mg/day	400 mg/day	1 - 2 times daily
Lithium [Eskalith, Lithobid]	900 mg/day	900 - 2400 mg/day [Serum level: Acute mania: 1.0-1.2 mEq/L Depression: ≥ 0.8 mEq/L Maintenance: 0.8-1.0 or lower (0.6) mEq/L]	3600 mg/day (iv) [Serum level: Acute mania: 1.2-1.5 mEq/L Depression & maintenance: 1.0-1.2 mEq/L]	1 - 2 times daily
Oxcarbazepine [Trileptal]	600 mg/day	600 - 2100 mg/day	2400 mg/day	BID or TID
FIRST GENERATION ANTIPSYCHOTICS (FGAs)				
Chlorpromazine [Thorazine]	300 mg/day	400 - 1000 mg/day	2000 mg/day	TID
Fluphenazine [Prolixin]	2.5 mg/day	2.5 - 20 mg/day	40 mg/day	TID
Haloperidol [Haldol]	2 mg/day	2 - 20 mg/day	40 mg/day	1 - 3 times daily
Perphenazine [Trilafon]	6 - 8 mg/day	24 mg/day	64 mg/day	TID
SECOND GENERATION ANTIPSYCHOTICS (SGAs)				
Aripiprazole [Abilify]	15 mg/day	15 - 30 mg/day	30 mg/day	AM or HS
Olanzapine [Zyprexa]	5 - 10 mg/day	5 - 20 mg/day	20 mg/day	HS
Olanzapine/fluoxetine [Symbyax]	3/25 - 6/25 mg/day	6/25 - 12/50 mg/day	12/50 mg/day	HS
Paliperidone [Invega]	3 mg/day	6 - 12 mg/day	12 mg/day	HS or AM
Quetiapine [Seroquel]	100 mg/day	300 - 800 mg/day (depression) 550 - 800 mg/day (mania)	800 mg/day	BID or HS
Risperidone [Risperdal]	1 - 2 mg/day	4 - 6 mg/day	8 mg/day (vii)	HS or AM
Ziprasidone [Geodon]	80 mg/day	80 - 160 mg/day	160 mg/day	AM or BID with food (viii)

(i) All agents are FDA approved for the treatment of mania except: lamotrigine; oxcarbazepine; fluphenazine; haloperidol; perphenazine; olanzapine/fluoxetine combination; and paliperidone. FDA approved agents for the treatment of mixed episodes are: carbamazepine; valproate; aripiprazole; olanzapine; risperidone; and ziprasidone. FDA approved agents for the treatment of bipolar depression are: olanzapine/fluoxetine combination; and quetiapine. FDA approved agents for the maintenance treatment of BPD are: lamotrigine; lithium; aripiprazole; olanzapine; and quetiapine (as adjunctive therapy).

(ii) Not all brand name examples provided are FDA approved for the treatment of BPD. Many medications are available generically.

(iii) Therapeutic serum level monitoring should be drawn 12 hours after the last dose, except for Depakote ER which should be drawn 18 hours after the last dose or at trough prior to the next dose.

(iv) Maximum daily dosage should be based upon the serum level in the individual patient in the context of clinical response and tolerability.

(v) Commonly referred to as valproate.

(vi) Lower starting dose, slower titration schedule and lower maximum daily dose recommended for patients on concomitant valproate.

(vii) The risk of extrapyramidal side effects is significantly increased by using doses > 6 mg daily.

(viii) Presence of food can increase absorption two-fold.

Table 3. COMMON SIDE EFFECTS (SEs) OF LITHIUM AND ANTICONVULSANTS

Affected Organ System	Reaction	CBZ	Li	LTG	OXC	VPA
Blood Dyscrasias	Leukocytosis	1+	3+	0	1+	1+
	Leukopenia	3+	1+	1+	1+	1+
	Thrombocytopenia	2+	0	1+	0	4+ (i)
Central Nervous System	Asthenia	3+	4+ (ii)	2+	3+	3+
	Cognitive blunting	2+	3+	2+	2+	2+
	Drowsiness	3+	1+ (ii)	3+	3+	3+
	Headache	2+	2+	3+	4+	3+
Cardiovascular (iii)	ECG changes	2+	3+	1+	1+	2+
Dermatological	Rash	3+ (iv) (v)	3+	3+ (iv)	2+ (iv)	2+ (iv)
Endocrine	Hair loss/thinning	2+	3+	0	1+	3+
	Hypothyroidism	1+	4+	1+	?	1+
	Menstrual disturbances	4+	3+	2+	1+	4+
	PCOS	3+	0	0	?	4+
	Polyuria/polydipsia	2+	4+	0	1+	0
Gastrointestinal	Diarrhea	2+	3+ (ii)	2+	2+	3+
	Nausea/vomiting	3+	4+	3+	3+	3+
	Weight gain	2+	4+	1+	2+	4+
Hepatic	Enzyme elevation	3+	0	1+	1+	4+ (i)
Neurological	Ataxia	3+	1+ (ii)	3+	2+	2+
	Diplopia	3+	0	3+	3+	3+
	Dizziness	3+	0	4+	2+	3+
	Incoordination	3+	1+ (ii)	2+	2+	2+
	Tremor	4+	4+ (ii)	2+	3+	3+

Scale: ? = unknown, 0 = absent to 4+ = common. Key: CBZ = carbamazepine; Li = lithium; LTG = lamotrigine; OXC = oxcarbazepine; PCOS = Polycystic ovary syndrome; VPA = valproate

(i) Greater with higher doses; (ii) Higher incidence and severity with higher serum lithium levels; may be early sign of toxicity; (iii) ECG abnormalities usually without cardiac injury; including: ST segment depression, flattened T waves, increased U wave amplitude; (iv) Severe dermatological reactions reported; (v) Risk of dangerous and/or fatal skin reactions higher in patients with HLA-B*1502 allele.

References: **Clinical Handbook of Psychotropic Drugs**. Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Toronto, ON, Hogrefe & Huber, 2006; **Drug Information Handbook for Psychiatry**. Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007.

Table 4. COMMON SIDE EFFECTS OF ANTIPSYCHOTICS

Antipsychotic	Extra-Pyramidal Side Effects	Tardive Dyskinesia	Orthostatic Hypotension	Increased Prolactin	Sedation	Weight Gain	Anti Cholinergic Effects	Dyslipidemia	Glucose Dysregulation
FIRST GENERATION ANTIPSYCHOTICS (FGAs)									
Chlorpromazine	++	+++	++++	++	++++	++	+++	+++	+++
Fluphenazine*	++++	++++	+	+++	+	++	+	-	+/-
Haloperidol	++++	++++	+	+++	+	+	+	-	-
Perphenazine*	+++	+++	++	++	++	+	++	-	+/-
SECOND GENERATION ANTIPSYCHOTICS (SGAs)									
Aripiprazole	+/-	+/-	-	-	+	+/-	+	+/-	+
Olanzapine	+	+	+	+/-	+++	+++	++	++++	+++
Paliperidone	+ / ++	+	+	+++	+	++	+	+	+
Quetiapine	+/-	+/-	++	+/-	++++ (i)	++	+	+	+
Risperidone	+ / ++ (ii)	+	+	+++	+	++	+	+	+
Ziprasidone	+	+	+	+	+	+/-	+	+/-	-

Scale: (-) = none reported, (+/-) = absent or rare to (++++) = common

(i) During dose titration phase; (ii) ++ at doses > 6 mg/day

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

Table 5. MONITORING PARAMETERS FOR LITHIUM AND ANTICONVULSANTS

Medications	Monitoring Parameters	Frequency					Comments
		Baseline	Week 1	6 months	Annually	As clinically Indicated	
Carbamazepine	CBC, platelets	√	√ (i)			√	(i) After initiation and each dose increase
	Electrolytes	√				√	To monitor for hyponatremia
	HLA-B*1502	√					In genetically at risk patients (ancestry across broad areas of Asia). If positive, avoid using CBZ unless benefit clearly outweighs risk.
	LFTs	√				√	
	Pregnancy test					√	
	Serum level		√ (i)	√ (ii)		√	(i) After initiation and dose adjustment and until stable (ii) every 3 – 6 months
Lithium	BUN/creatinine	√				√	
	CBC	√			√	√	
	ECG	√			√	√	
	Electrolytes	√				√	
	Pregnancy test					√	
	Serum level		√ (i)			√	(i) After initiation and dose adjustment
	Thyroid	√		√ (i)		√ (i)	(i) TSH
	UA	√				√	
Lamotrigine	Pregnancy test					√	
Oxcarbazepine	Electrolytes	√				√	To monitor for hyponatremia
	Pregnancy test					√	
Valproate	CBC, platelets	√	√ (i)			√	(i) After initiation and each dose increase
	LFTs	√				√	
	Pregnancy test					√	
	Serum level		√ (i)			√	(i) After initiation and dose adjustment

Key: BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; HLA-B*1502 = human leukocyte antigen allele B*1502; LFTs = liver function tests; UA = urine analysis

Table 6. MONITORING PARAMETERS FOR PATIENTS ON SGAs

Monitoring Parameters	Frequency					
	Baseline	Week 4	Week 8	Week 12	Quarterly	Annually
Personal/Family History	√					√
Weight (BMI)	√	√	√	√	√	
Waist Circumference	√					√
Blood Pressure	√			√		√
Fasting Plasma Glucose	√	√*		√	√*	
Fasting Lipid Profile	√	√*		√		√*

* The SCORxE mental health panel suggests additional monitoring of fasting plasma glucose at 4 weeks and quarterly and fasting lipid profile at 4 weeks and annually. (Level D)

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For a complete list of references and detailed report see: <http://www.sccp.sc.edu/SCORxE>

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