

# **TIMA PROCEDURAL MANUAL**

## **BIPOLAR DISORDER ALGORITHMS**

**Trisha Suppes, M.D., Ph.D.**

**Ellen B. Dennehy, Ph.D.**

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Address Correspondence to:

Trisha Suppes, M.D., Ph.D.  
Associate Professor  
Director, Bipolar Disorder Module Texas Medication Algorithm Project  
Director, Bipolar Disorder Clinic and Research Program  
University of Texas Southwestern Medical School at Dallas  
5323 Harry Hines Boulevard  
Dallas, Texas 75390-9070

Phone: (214) 648-7480  
Fax: (214) 648-7499  
E-mail: [patricia.suppes@utsouthwestern.edu](mailto:patricia.suppes@utsouthwestern.edu)

# Table of Contents

## Bipolar Disorder Algorithms Manual

	<u>Page</u>
♦ Overview of TIMA	1
♦ Administrative Structure	4
♦ Bipolar Disorder Algorithms	5
Algorithm for Mania/Hypomania	5
Algorithm for the Treatment of Depression in Bipolar Disorder	6
♦ At-a-Glance Bipolar Disorder Medication Algorithms	7
♦ Description of Algorithm Stages	8
Algorithm for Mania/Hypomania	8
Algorithm for the Treatment of Depression in Bipolar Disorder	10
♦ Algorithm Implementation	15
General Principles Guiding Algorithm Development and Implementation	15
♦ Process Measures: Evaluation of Patient Response	18
Brief Bipolar Disorder Symptom Scale (BDSS)	18
Physician Ratings	19
♦ Critical Decision Points	20
♦ Overlap and Taper Guidelines	24
♦ Side Effect Management	25
♦ Continuation and Maintenance Guidelines	27
Algorithm for Treatment of Hypomania/Mania	27
Algorithm for the Treatment of Depression in Bipolar Disorder	28
♦ Modifications for Inpatient Use	30
♦ Documentation	31
Outpatient Data Collection	31
Inpatient Data Collection	31

# **Table of Contents**

## **Bipolar Disorder Algorithms Manual**

### **Page**

#### ◆ Appendix

##### Appendix A. Process Measures

Brief Bipolar Disorder Symptom Scale (BDSS)

BDSS Scoring Sheet

Critical Decision Points (CDPs) and Tactics for the Treatment  
of Bipolar Disorder

BDSS and CDP Worksheet

Scoring Criteria for Physician- and Patient-Rated Overall  
Symptom and Side Effect Ratings

##### Appendix B. Documentation

Forms for Outpatient Data Collection

Outpatient Intake Form

Outpatient Clinic Visit Clinical Record Form

Outpatient Interim Contact Form

Forms for Inpatient Data Collection

Inpatient Intake Form/Annual Update

Inpatient Clinical Record Form

Inpatient Contact Form

##### Appendix C. Communications

Important Telephone Numbers

##### Appendix D. Medication Descriptions

##### Appendix E. Drug Interactions

## Table of Tables

### Bipolar Disorder Algorithms Manual

	<u>Page</u>
Table 1: Summary of Recommended Doses of Medications Used for Acute Phase Treatment of Mania/Hypomania	12
Table 2: Doses of Medications Used for Acute Phase Treatment of Bipolar Depression	12
Table 3: Common Side Effects (SEs) for Medications in the Algorithm for Hypomania/Mania	13
Table 4: Common Side Effects (SEs) for Medications in the Algorithm for Treatment of Depression in Bipolar Disorder	14
Table 5: Summary of Critical Decision Points	23
Table 6: Side Effect Management	25

These guidelines reflect the state of knowledge, current at the time of publication, on effective and appropriate care, as well as clinical consensus judgments when knowledge is lacking. The inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revisions will be needed. These guidelines (algorithms) do not apply to all patients, and each must be adapted and tailored to each individual patient. Proper use, adaptation modifications or decisions to disregard these or other guidelines, in whole or in part, are entirely the responsibility of the clinician who uses the guidelines. The authors bear no responsibility for the use of these guidelines by third parties.

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## Overview of TIMA

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Algorithms facilitate clinical decision making by providing physicians with large amounts of current information on the newest psychotropic medications and research data, as well as specific treatment sequences with tactical recommendations. Patients receive the benefit of patient education, which should enhance adherence to the treatment program. Algorithms are designed with the objectives of long-term safety, tolerability, and full symptom remission — not just response. The employment of such treatment guidelines to aggressively treat the severely and persistently mentally ill (SPMI) population may bring about a decrease in the use of crisis/hospital services and the number of clinical visits — while presenting an accountability for scarce resources — thereby increasing the overall efficiency of patient care.

Beginning in 1995, The Texas Medication Algorithm Project (TMAP) was developed by the Texas Department of Mental Health and Mental Retardation (TDMHMR) in collaboration with Texas universities to assess the value of algorithms — along with clinical support and a patient/family educational package — in the pharmacological management of mentally ill patients. The result has been a set of algorithms for the treatment of the three major disorders most commonly encountered in the Texas public mental health system: schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). TDMHMR has defined a best practice treatment as a series of treatment steps that guides physicians in determining medication treatment plans, thereby generating the best outcome for each individual consumer. Practitioners, patients, families, and administrators all contributed to the formulation and implementation of TMAP, ensuring an optimum level of efficacy and practicality. Phase 1 of TMAP dealt with the development of these algorithms using expert consensus. In Phase 2, the feasibility of algorithm implementation in the TDMHMR system was evaluated. The goal of Phase 3 was to evaluate the clinical and economic impact of medication treatment algorithms for MDD, SCZ, and BD in comparison with treatment as usual (TAU).

Up until now, the effectiveness of these medication algorithms has only been put to use with a limited sample of patients. Implementation of the algorithms on a systemwide basis is the next step in offering a high quality of care to the SPMI patient population in the public mental health sector. Texas Implementation of Medication Algorithms (TIMA) is Phase 4 of TMAP: the "roll-out" of these bipolar disorder algorithms to TDMHMR clinics throughout the state. The rollout of TIMA has begun with the training of physicians and support personnel in algorithm implementation. Revisions may be required in the structure and function of clinical staff to increase patient education and adherence, to improve follow up, and to develop psychosocial supports to improve symptom recognition, symptom control, and functional restoration. Continuous education, consultation, and collaboration are necessary for both clinicians and administrators in making timely revisions in clinical procedures and budgetary allocations. From a clinical and administrative perspective, medication algorithms should demonstrate validity with far-reaching and long-term applications.

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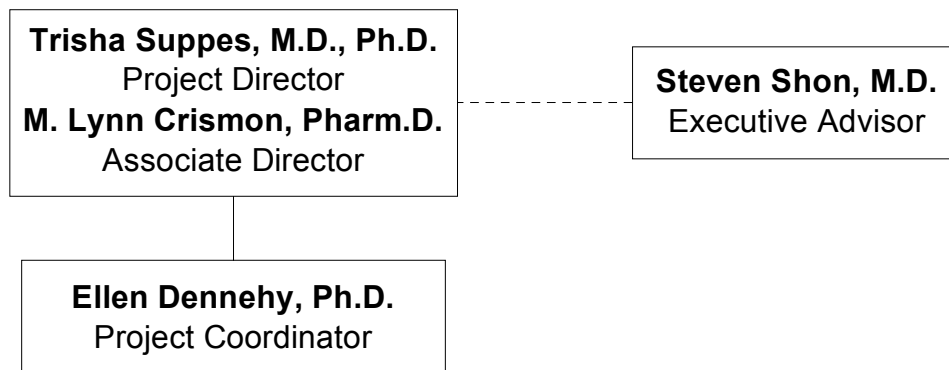
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## ***Administrative Structure***

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### **Project Management Team**

Steven Shon, M.D.

Trisha Suppes, M.D., Ph.D.

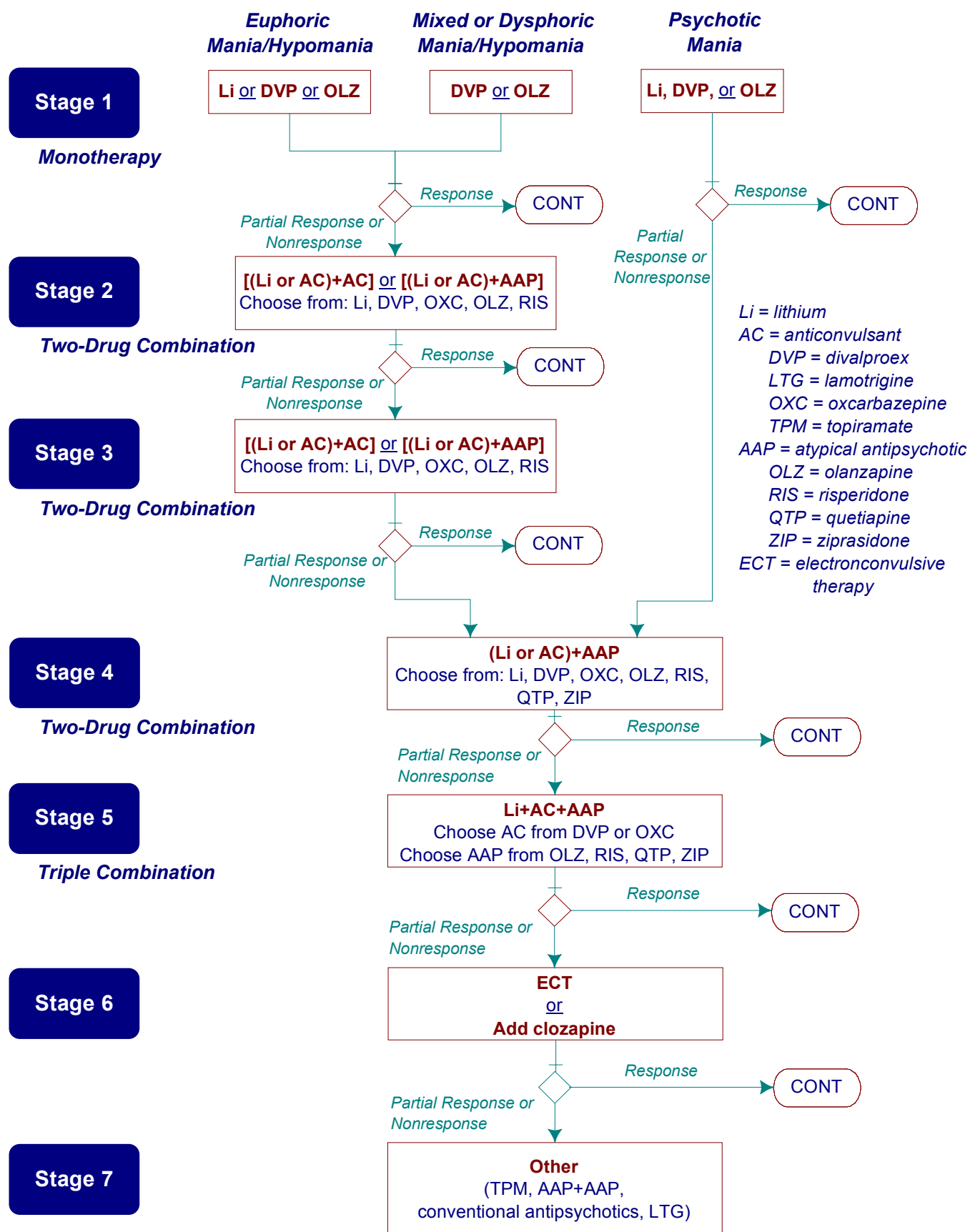
M. Lynn Crismon, Pharm.D.

Ellen B. Dennehy, Ph.D.

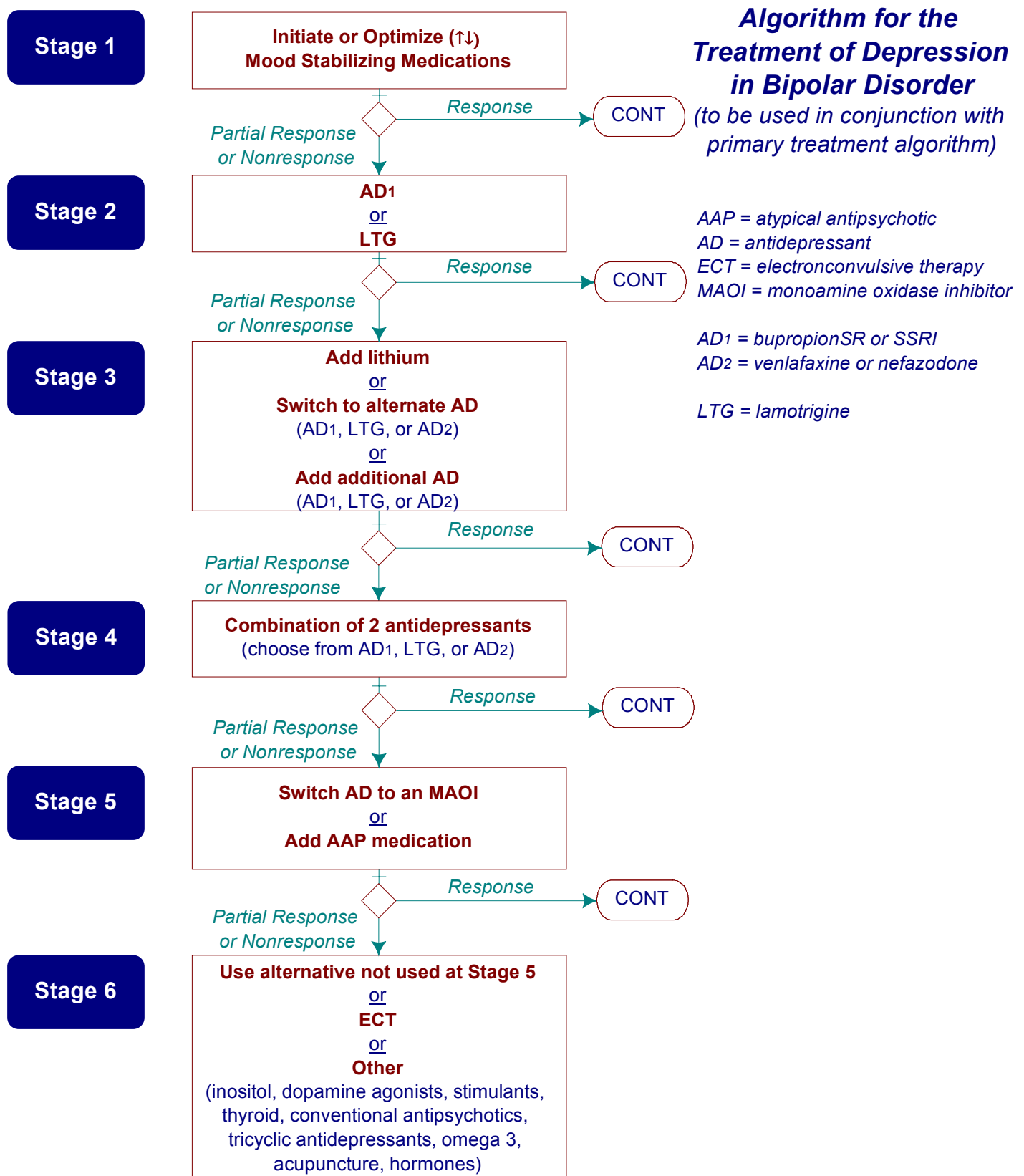
Marcia Toprac, Ph.D.

## Bipolar Disorder Algorithms

### Algorithm for Mania/Hypomania



## Bipolar Disorder Algorithms



## At-a-Glance

### Bipolar Disorder Medication Algorithms

**Visit Frequency:** While medications are being actively adjusted, patients should be seen every 2 weeks. As medications are stabilized and patients exhibit stable, positive response, visit intervals can be gradually lengthened to every 4 weeks. When patients enter continuation phase, visit frequency should be every 8-12 weeks, as individually determined. Support personnel may contact patients by phone if the physician is unable to see them.

**Assessment Frequency:** The Brief BD Symptom Scale (BDSS) should be completed at each clinic visit. If the patient is contacted by phone, an Interim Contact Form (ICF) must be completed.

**Criteria for Medication Change:** Medication changes are made after evaluation of tolerability, efficacy across multiple symptom domains, and safety. Clinicians consult Critical Decision Points and Tactics for the Treatment of Bipolar Disorder after review of symptom patterns and severity on the BDSS score sheet. The goals of treatment are full symptomatic remission, return of psychosocial functioning, and prevention of relapses and recurrences. Any symptoms, even those in the mild to moderate range, warrant consideration of tactics that may further optimize response.

**Evaluations:** At each visit, a physician will assess core symptom severity, overall functional impairment, and side effect severity. Algorithm Coordinator (AC) or the physician can complete the BDSS and patient global self-rating of symptom severity and side effects.

**Medication Doses:** See Tables 1 and 2. ***Doses outside of the ranges should have a chart note indicating “change from algorithm recommended” and documentation of rationale for change.***

**Blood Levels:** Serum levels should be obtained about 5 days (5 half-lives) after reaching the minimum target dose (see Table 1) for Li or DVP. Levels should be ordered as necessary to ensure that dosing is within therapeutic window for individual patient. Intolerable side effects require immediate evaluation of serum levels.

**Treatment of Depressive Symptoms:** All patients will be maintained on the primary algorithm for treatment of hypomania/mania. If depressive symptoms warrant medication intervention, the clinician should utilize the strategies for treatment of bipolar depression in a similar, systematic, step-wise fashion as the primary algorithm, as an adjunct to the primary treatment stage.

## Description of Algorithm Stages<sup>\*</sup>

### Algorithm for Mania/Hypomania

This is the primary treatment algorithm. All patients diagnosed with Bipolar I disorder should be treated with medication or medication combinations recommended within this guideline. Consistent with other published guidelines for treatment of bipolar disorder, the majority of treatment options consist of medication combinations. If possible, when adjusting medications, it is preferable to make adjustments to one agent at a time, to allow for evaluation of response.

When utilizing mood-stabilizing medications, it is recommended that the dose be pushed (either alone or in combination) as much as possible before moving to the second or third mood stabilizer. Switching to alternative mood stabilizers, versus adding, is recommended in cases of intolerance. If a patient has no or low-partial response to a medication, and **is tolerating** the medication, a new medication should be added using the overlap and taper tactics provided. It is recommended that the clinician try to taper the first medication at a later date if the patient's mood stabilizes.

When treating patients with hypomania or mania, a first consideration involves decreasing and/or discontinuing antidepressant medications. This taper should be done relatively quickly, except in cases where it is contraindicated. For those patients with rapid cycling, antidepressants should be tapered and discontinued. Some patients may still need an antidepressant plus mood stabilizers in order to minimize depressive symptoms and suicidality.

**Serum Levels:** If lithium or divalproex sodium are utilized, serum levels are part of the consideration of response and tolerability. In practice, serum levels may not be available at each visit. It is recommended that by 2 weeks after initiating lithium or divalproex sodium the patient be receiving the minimum target dose. If possible, we recommend a serum level 5 days after reaching the target dose and before the first appointment to assess response (e.g., 2-3 weeks after starting the trial). While awaiting serum levels (e.g., 4 weeks), it is generally safe to gradually increase DVP and, more cautiously, Li if no side effects develop.

Target serum levels are provided in Table 1, Summary of Recommended Doses of Medication Used in Algorithm for Hypomania/Mania. For Li and DVP, evidence supports differences in clinical response for some patients between therapeutic and high therapeutic levels. Clinically, it is reasonably safe and well tolerated to exceed the recommended therapeutic range for DVP (> 125 ug/ml), but few psychiatric patients appear to need these higher levels. The upper limits of Li (1.2 mEq/L) are usually associated with side effects, and levels over these limits are potentially toxic, with the exception of patients in a full-blown manic episode who may tolerate and benefit from levels of Li between 1.0 –1.2 mEq/L.

Similarly, it is necessary to obtain more frequent levels of DVP when used in combination with an auto-inducer such as carbamazepine. Once you have obtained a couple of levels for DVP or Li, it is generally possible to estimate the likely increase of serum levels with dose changes and collect serum levels somewhat less often. However, the development of side effects should always signal considering obtaining a serum level.

<sup>\*</sup> We are currently in the process of preparing a manuscript which details rationale and data regarding stage contents and placement. The paper will be distributed when it is accepted for publication.

**Stage 1.** All the options for Stage 1 include monotherapy with either lithium, divalproex, or olanzapine. For patients presenting with euphoric mania/hypomania or psychotic mania, choice is from any of the three agents. For dysphoric or mixed mania, the recommendation is to choose between divalproex and olanzapine. Divalproex is recommended instead of valproic acid due to significantly better tolerability.

Generally, in the case of partial response with good tolerance, the recommendation will be to add a medication (move to combination therapy, i.e., Stage 2) versus switching. If the patient is intolerant in Stage 1, the recommendation will be to try an alternative mood stabilizer within Stage 1.

**Stage 2.** Stage 2 treatment includes combination treatment with two of the following: lithium, divalproex, oxcarbazepine, olanzapine and risperidone. Oxcarbazepine and risperidone are added as options here. Oxcarbazepine is recommended over carbamazepine due to apparent similar efficacy with fewer drug interactions, adverse events, increased tolerability, and less physician supervision required. Therefore, the combination is (Li or AC) + AC, or (Li or AC) + AAP.

**Stage 3.** In Stage 3, physicians are asked to attempt another combination of medications, drawing from the same group described in Stage 2. Preferably, they would keep one agent from the previous combination, and change to a different second agent. Again, the combination can be either (Li or AC) + AC, or (Li or AC) + AAP.

**Stage 4.** This stage also includes combination therapy, but at this point, the physician is prompted directly to use an atypical antipsychotic agent in combination with lithium, divalproex, or oxcarbazepine. Therefore, it is a combination of Li or AC and an atypical antipsychotic medication [(Li or AC) + AAP]. For patients with psychotic mania, the recommendation is to progress immediately to this combination if Stage 1 monotherapy with either lithium, divalproex, or olanzapine is ineffective or only partially effective. Quetiapine and ziprasidone are added as additional choices here.

**Stage 5.** Stage 5 includes “triple therapy,” with lithium, an anticonvulsant (choose from divalproex or oxcarbazepine), and an atypical antipsychotic medication (choose from olanzapine, risperidone, quetiapine, ziprasidone); therefore, Li + AC + AAP.

**Stage 6.** ECT has demonstrated efficacy for treatment of acute mania. Safety, tolerability, and patient acceptance issues warrant its placement further down in the algorithm at Stage 6. Alternatively, clozapine could be added to other medications as a treatment option here. The placement of clozapine after other atypical antipsychotic medications is consistent with clinical recommendations to attempt treatment with other atypical antipsychotic medications before initiating clozapine treatment. If the patient is taking clozapine, weekly blood draws (WBCs) are necessary (*for more information, see the medication descriptions in Appendix D*).

**Stage 7.** This stage includes other options to be used as adjuncts to partially effective medication combinations. It includes topiramate, a combination of medications that includes two atypical antipsychotic medications, conventional antipsychotics, and lamotrigine. Consultation with the module director, Dr. Suppes, is available if a clinician is considering treatment from Stage 7 for a patient who achieved no or partial response to all other algorithm options. See Appendix C, Communications, for contact information.

## ***Algorithm for the Treatment of Depression in Bipolar Disorder***

This algorithm should be utilized in conjunction with the primary treatment algorithm for mania/hypomania. If a patient reports symptoms of depression significant enough to warrant intervention, the clinician is directed to utilize this algorithm as a concomitant treatment strategy, in addition to any stage of treatment within the Mania/Hypomania algorithm. As with any algorithm, if insufficient response in depressive symptoms is achieved, the clinician should continue through the algorithm until satisfactory symptom reduction is achieved.

It is important to carefully consider the addition of an antidepressant to a bipolar patient's medication regimen. If the patient presents with a "pure" BP-MDE, without mood lability or hypomania, the decision is relatively clear as the degree of suffering will justify initiating an antidepressant. However, many patients will have significant depressive symptoms, but also periods of dysphoric hypomania, mood lability, irritability, and other complicated states. Patients may need both a mood stabilizer and an antidepressant. The balancing of optimizing mood stabilizers, possibly adding Li, or adding an antidepressant must be done on a case-by-case basis.

The algorithm to treat Bipolar Depression assumes antidepressants will only be used in conjunction with a mood stabilizing medication, because of the risk of inducing manic symptoms. It may be necessary to adjust the mood stabilizer during treatment (i.e., increase dose with development of irritability or mood lability). In some cases, it may be clinically indicated to switch or combine mood stabilizers (i.e., an effective antidepressant is found and continued need for the medication is provided, but the drug is associated with mild mood lability). It is expected that the physician will continue to utilize recommendations of the hypomania/mania algorithm even when prescribing antidepressant treatment.

Selection of a specific antidepressant medication should be made based on individual factors such as the expected side-effect profile, potential toxicity, concomitant medical problems and medications. The initial algorithm stages focus on antidepressant monotherapy with medications associated with favorable risk-benefit ratios and for which there is evidence of efficacy in bipolar patients.

**Stage 1.** The first stage includes initiating and/or optimizing mood-stabilizing medications. The recommendation is that all patients diagnosed with Bipolar I disorder be prescribed anti-manic medications, using the algorithm for treatment of mania/hypomania. The committee made explicit the recommendation that optimizing mood-stabilizing medications might mean either an increase or decrease in dosing, though no data is available to clearly direct tactics on this issue.

**Stage 2.** Patients entering Stage 2 of the algorithm should have a major depressive episode of sufficient severity to merit medication treatment. Stage 2 includes the addition of an SSRI, bupropion SR, or lamotrigine to existing medications. The SSRI options are open, and include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram. Bupropion SR is an additional option, and the committee recommended the sustained release version of bupropion, due to improved tolerability. While there is a risk of rash with lamotrigine, there is positive Level A data in support of its efficacy for treatment of bipolar depression.

**Stage 3.** At this point, the algorithm begins to rely more heavily on clinical consensus and expert opinion, as there is only limited data on treatment of bipolar depression following failure

in Stage 2. The algorithm development philosophy was that when there are several options available, with little or no empirically derived reason to rank them, to offer the choices so that the clinician and patient can choose what is best for that individual. Therefore, Stage 3 offers the clinician and patient several options, including addition of lithium, switching to an alternative antidepressant medication (adding venlafaxine and nefazodone as additional options), or adding from Stage 2 options a second antidepressant or lamotrigine.

If Stage 2 treatment was unsuccessful primarily because of intolerable side effects, consider selecting an antidepressant from a different class with a contrasting side effect profile (e.g., if the patient experienced sexual dysfunction on an SSRI, consider bupropion SR or nefazodone).

**Stage 4.** Stage 4 includes the combination of two antidepressant medications. This includes selection from the SSRI group, bupropion SR, and lamotrigine. In choosing an antidepressant combination, it is recommended to use medications from different classes (i.e., not 2 SSRIs). The goal of combination antidepressant regimens is to combine medications to enhance clinical response. In general, because of the potential for drug interactions, antidepressant combination treatment should be used carefully, and patients monitored closely.

**Stage 5.** Stage 5 includes changing the antidepressant medication to an MAOI, or adding an atypical antipsychotic medication. Because of potential health risks and the need to follow special dietary restrictions and avoid certain medications, MAOIs are located in Stage 5, after medications and medication combinations with less Level A and B data. Diet restriction guidelines should be provided to all patients receiving MAOI medications.

**Stage 6.** Recommendations at this stage include using the alternative not used in Stage 5, ECT, or Other. The “Other” category is exploratory, and includes a number of options to be considered in addition to partially effective medication combinations. It includes inositol, dopamine agonists, stimulant medications, thyroid, conventional antipsychotics, tricyclic antidepressants, omega 3, acupuncture and hormones. Consultation with the module director, Dr. Suppes, is available if a clinician is considering treatment from Stage 7 for a patient who achieved no or partial response to all other algorithm options. See Appendix C, Communications, for contact information.



**Table 1: Summary of Recommended Doses of Medications Used for Acute Phase Treatment of Mania/Hypomania\***

<i>Type/Class</i>	<i>Medication</i>	<i>Usual Target Dose</i>	<i>Usual Maximum Recommended Dose (level)</i>	<i>Recommended Administration Schedule</i>
	Lithium	(0.8-1.0 mEq/L)	(1.2 mEq/L)	BID or QHS
Anticonvulsants	Oxcarbazepine	600-2100 mg/day	2400 mg/day	BID or TID
	Divalproex Sodium	(80 ug/mL)	(125 mg/mL)	BID or QHS
Atypical Antipsychotics	Clozapine	100-300 mg/day	900 mg/day	QHS
	Olanzapine	10-15 mg/day	20 mg/day	BID or QHS
	Risperidone	2 mg/day	6 mg/day	BID or QHS
	Quetiapine	200-600 mg/day	800 mg/day	BID or QHS
	Ziprasidone	40-160 mg/day	160 mg/day	BID

***\*Doses used for maintenance treatment may be lower.***

**Table 2: Doses of Medications Used for Acute Phase Treatment of Bipolar Depression**

<i>Type/Class</i>	<i>Medication</i>	<i>Usual Target Dose</i>	<i>Usual Maximum Recommended Dose (level)</i>	<i>Recommended Administration Schedule</i>
SSRIs	Citalopram	20-40	60	QD
	Fluoxetine	20	80	QD
	Fluvoxamine	150-250	250	QD
	Paroxetine	20	60	QD
	Sertraline	50	200	QD
Anticonvulsant	Lamotrigine	200**	600	QD
Others	Bupropion SR	300	400	BID
				<i>*200 mg maximum in each dose</i>
	Nefazodone	300-600	600	QD
	Venlafaxine	150	375	BID or TID
	Venlafaxine XR	75 mg/day	225 mg/day	QD

***\*Doses used for maintenance treatment may be lower.***

***\*\*Please refer to the Medications Description section (Appendix D) for instructions regarding initiation of this medication, due to risk of serious side effects associated with rapid titration.***

**Table 3: Common Side Effects (SEs) for Medications in the Algorithm for Hypomania/Mania**

<i>Medication</i>	<i>Common Side Effects*</i>
<b>Lithium</b>	Tremor, drowsiness, nausea/vomiting, polyuria, muscle weakness, thirst, dry mouth, cognitive impairment
<b>Anticonvulsants</b>	
Oxcarbazepine	Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.
Divalproex sodium	Nausea/vomiting, increased appetite with weight gain, sedation
<b>Atypical Antipsychotics</b>	
Clozapine	Sedation, anticholinergic effects, hypotension, weight gain, hypersalivation, constipation, nausea, and vomiting
Olanzapine	Weight gain, sedation, anticholinergic effects, mild EPS, hypotension, potential TD
Risperidone	EPS, weight gain, mild sedation, anticholinergic effects, changes in blood pressure, sexual dysfunction, potential TD
Quetiapine	Sedation, blood pressure, weight gain
Ziprasidone	Rash, nausea and vomiting, constipation, somnolence, EPS, dizziness

\* For more information about potential side effects, please consult the Physician's Desk Reference (PDR) or package inserts.

**Table 4: Common Side Effects (SEs) for Medications in the Algorithm for Treatment of Depression in Bipolar Disorder**

<i>Medication</i>	<i>Common Side Effects*</i>
<b>SSRIs</b> Citalopram Fluoxetine Paroxetine Sertraline Fluvoxamine	Dizziness, dry mouth, insomnia, agitation, nausea, sexual dysfunction, headache
<b>Bupropion SR</b>	Headache, agitation, weight loss, insomnia, nausea
<b>Lamotrigine</b>	Headache, nausea, dizziness, ataxia, somnolence, rhinitis, rash
<b>Nefazodone</b>	Dizziness, headache, nausea, somnolence, insomnia
<b>Venlafaxine XR</b>	Dizziness, somnolence, insomnia, decreased appetite, anxiety, headache, nausea, sexual dysfunction
<b>MAOIs</b> Phenelzine Tranylcypromine	Restlessness, dizziness, blurred vision, diarrhea, insomnia, weakness, arrhythmias, headache, sexual dysfunction

\* For more information about potential side effects, please consult the Physician's Desk Reference (PDR) or package inserts.

## Algorithm Implementation

The purpose of treatment algorithms is to integrate available research information and clinical experience into the development of user-friendly, step-by-step "preferred practices," medication guidelines, or medication algorithms. **Algorithms do not decrease the need for clinicians having adequate education and clinical training, nor are they intended to restrict treatment options.** Rather, they are designed to facilitate a systematic approach to recommended treatment interventions.

It is assumed that a comprehensive psychiatric evaluation, a complete general medical history, and relevant diagnostic tests are completed prior to entry into any treatment algorithm. Some patients may not be appropriate for entry into the algorithms. In addition, patients may enter the algorithms at different stages depending upon their specific clinical features and previous treatment histories.

**Treatment algorithms are not a substitute for clinical assessment or clinical judgment. They are tools to assist clinicians in making clinical decisions to optimize therapeutic outcomes. The purpose of this document is to amplify the steps in implementing a medication algorithm in order to maximize effectiveness. We describe issues related to the strategic choices for pharmacological interventions based on the TMAP Bipolar Disorder Algorithm(s). Additionally, preferred tactical steps and critical decision points are described to enable users to best apply the strategy selected for implementation.**

These algorithms focus on the pharmacotherapy and patient/family education for bipolar disorder. This does not imply that other nonpharmacological treatments including psychotherapy and rehabilitation are not indicated for the treatment of bipolar disorder (BD). *Instead, this algorithm is restricted to a single focus: a multi-step medication approach in the treatment of patients with BD in the public sector.* Other modalities used in the treatment of mental disorders are sufficiently complex that it is felt that patient care in TDMHMR can be best enhanced, initially, by utilizing algorithms that focus on one major aspect of treatment — in this case the use of pharmacological interventions. Additionally, patient and family education packages (ED packages) are also included in the overall package, since it is felt that proper implementation of the medication algorithm is enhanced through active participation of patients and families. Subsequent iterations may include psychological and rehabilitative services in the treatment package(s).

### General Principles Guiding Algorithm Development and Implementation

- The algorithm development process was guided by the need to balance data, tolerability, and safety. These core principles apply to clinical decisions for individuals as well.
- The goals of treatment are (1) symptomatic remission; (2) full return of psychosocial functioning; and (3) prevention of relapses and recurrences.
- The treatment options recommended at the various points in the algorithms are based upon available data from: (a) controlled clinical trials [level A evidence]; (b) open trials and retrospective data analyses [level B evidence]; and (c) case reports and expert clinical consensus [level C evidence]. The later stages in the algorithm involve more complicated regimens, while the earlier stages involve simpler treatments in terms of safety, tolerability,

ease of use, side-effect profiles, etc. The treatment algorithms will be adapted as more controlled scientific studies (level A) or the weight of open trials (level B) argues for adjustment.

### **Choice of Treatment**

- Eligibility and point of entry into an algorithm for an individual patient should be determined by the clinician based upon a review of relevant general medical and psychiatric factors (e.g., symptom severity, suicidality, comorbidity, etc.), general medical factors (e.g., concomitant medications or illnesses, age, etc.), and prior treatment history.
- If a patient responded well to a specific pharmacotherapy during a previous mood episode, and it was well tolerated, that same treatment is recommended again. Similarly, a given algorithm option should be skipped if there is a clear history of intolerance and/or strong patient preference. Physicians are requested to move, as much as possible, linearly down the algorithm. Patient history and preference may dictate initiating treatments from an advanced stage. It is also acceptable to move up the algorithm at a later time.

### **Patient/Clinician Relationship**

- An adequate discussion between the clinician and the patient regarding available treatment options and specific medications (including expected results, dosing strategies, side-effect profiles, drug interactions, potential toxicity, and safety in overdose) should occur. When medical considerations make several medications equivalent, patient preference defines the particular option selected.
- When possible, physicians should develop a treatment plan with the patient that involves critical others in that person's life. Family participation is encouraged not only at initial assessment, but also throughout the patient's treatment, and may be especially helpful in monitoring the patient's progress and response to medication treatments.
- It is recommended that patients participate in their treatment planning by keeping a daily mood chart, or completing the symptom and side effect monitoring forms included as part of the TIMA bipolar disorder education package.

### **Visit Frequency**

- At the beginning of entry into an algorithm, relatively frequent (e.g., every 2 weeks) patient follow-up appointments for further evaluation and assessment should be scheduled in order to optimize treatment outcomes by: (a) encouraging patient adherence with treatment, (b) making medication dose changes in a timely manner, and (c) rapidly identifying and correcting potential problems or adverse events associated with treatment.

**Clinical Management**

- All patients with bipolar disorder who achieve a satisfactory clinical response (and preferably symptom remission) should receive continuation phase treatment.
- Adequate documentation should be completed for each algorithm stage and treatment choice (i.e., decision points). If algorithm stages are skipped or if treatment is different from the algorithms, the rationale should be adequately documented.
- At baseline and throughout treatment, the patient should be evaluated for possible psychosocial interventions, including psychotherapy.
- Use of the algorithms for treatment of patients with a history of mania assumes that you have made a thorough evaluation and diagnosis and that selection of these treatments is appropriate for a given patient. If a patient completes trials of two stages of the algorithm without observable positive outcomes, it may be helpful to revisit the diagnosis and perform another evaluation.
- When there is a choice between brand, generic, or different (i.e., slow release) forms of a recommended medication, always initiate treatment with the form that is most likely to be tolerated.

## Process Measures: Evaluation of Patient Response

### Brief Bipolar Disorder Symptom Scale (BDSS)

Patients with a diagnosis of Bipolar I disorder will be evaluated using the Brief Bipolar Disorder Symptoms Scale, or BDSS. This scale is derived from items included on the 24-item Brief Psychiatric Rating Scale\*. The 10-item version utilized for TIMA includes items assessing hostility, elevated mood, grandiosity, excitement, motor hyperactivity, depressed mood, anxiety, emotional withdrawal, blunted affect, and unusual thought content.

Physicians can use the scoring sheet to graph patient scores on each of these 10 symptom domains. While the presence of one or more of these symptoms might be suggestive of different things, they are loosely grouped within the categories of mania/hypomanic symptoms, depressive symptoms, and psychotic symptoms. Of course, physician judgment will be necessary to evaluate the source of particular symptoms. For example, blunted affect may be a result of increased depression, increased psychosis, or other sources. Elevated Mood may be related to increased hypomania/mania or a manifestation of increased delusional/psychotic symptoms. The grouping is intended to help facilitate decision-making within the algorithms, but is not exclusive.

A copy of this scale and the scoring sheet can be found in Appendix A.

### Texas Implementation of Medication Algorithms Brief Bipolar Disorder Symptom Scale

Visit Date: \_\_\_\_\_

Overall Side Effect Severity (from CRF): \_\_\_\_\_

**Instructions:** Indicate the score for each item by [circling, outlining, checking] the appropriate cell to the right of the item. Evaluate the pattern and severity of symptom(s) to guide clinical decision making.

Presence of **Mild to Moderate Symptoms** may indicate need for medication adjustment.

Any score >4 is within the range of **Severe Symptoms**, and indicates a need to make treatment changes.

		NA Not assessed	1 Not present	2 Very mild	3 Mild	4 Moderate	5 Moderately Severe	6 Severe	7 Extremely severe
Symptom Group	Symptoms	NA	1	2	3	4	5	6	7
Manic/Hypomanic	Hostility								
	Elevated Mood								
	Grandiosity								
	Excitement								
	Motor Hyperactivity								
Major Depressive	Depressed Mood								
	Anxiety								
	Emotional Withdrawal								
	Blunted Affect								
Psychotic	Unusual Thought Content								

Scale Total: \_\_\_\_\_

\* Overall JE, Gorham DR. Introduction - the Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacol Bull* 1988;24:97-99.

## Physician Ratings

Each of the symptom clusters is rated on a 10-point scale (from “no symptoms” to “extremely severe”). The rating is based on your impression of the patient at this visit, as well as information you have about the patient’s clinical status during the week prior to the visit.

- **Core Symptoms:**

Based upon all available information, clinician impression of the presence and severity of each of the symptoms in this patient.

- **Other Symptoms:**

Clinician rating of other symptoms associated with the patient’s disorder, but not core symptoms of the patient’s illness. Rate your impression for each of the specific “other symptoms” listed (irritability, mood lability, insomnia, agitation, anxiety, level of interest, appetite, energy level). Under “other,” specify and rate any other symptom that you feel is significant.

- **Overall Side Effect Severity:**

Overall rating of side effects from all medications being taken by the patient.

- **Overall Functioning:**

Overall impression of this patient’s ability to function on a daily basis. “10” is the highest possible functioning, and “1” is the lowest possible functioning.

### Scoring Criteria for Physician and Patient Overall Symptom and Side Effect Ratings

0	=	No Symptoms
1	=	Borderline
2	=	Mild
3	=	Mild – Moderate
4	=	Moderate
5	=	Moderate – Marked
6	=	Marked
7	=	Marked – Severe
8	=	Severe
9	=	Severe – Extreme
10	=	Extreme

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Ventura J, Green MF, Shaner A, Liberman RP. Training and quality assurance with the Brief Psychiatric Rating Scale: “The drift busters.” *Int J Methods Psychiatric Res* 1993;221-244.



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## ***Critical Decision Points***

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Critical Decision Points (CDPs) are designed to prompt an assessment of symptoms and a determination of a need for a change in strategy or tactics. At each CDP, the physician should assess the patient for improvement and make a decision to either continue or change treatment based on improvement in symptoms or lack thereof. Note: Patients begin at CDP # 1 at the beginning of each stage.

Critical Decision Points involve a consideration of efficacy among all symptom domains, tolerability, and safety. Clinicians must use their own judgment in evaluating the symptoms of the bipolar patient. Evaluate the pattern and severity of symptoms by reviewing the BDSS score sheet. For example, if most symptoms are contained within the light gray column, follow treatment recommendations within that column. Depending on the pattern and severity of symptom scores, the clinician may follow recommendations within the column that includes the most severe symptoms, or the column that contains the majority of clinical symptoms. The symptoms are loosely grouped by clinical presentation to allow for quicker assessment of potential treatment decisions. For example, if symptoms that are suggestive of hypomania/mania are elevated, the clinician would make adjustments to medications prescribed in the algorithm for hypomania/mania. If symptoms of psychosis are prominent, and an antipsychotic medication is included in the treatment regimen, the clinician may make the adjustment to that medication versus another anti-manic agent. The Critical Decision Points and Tactics for treatment of the bipolar patient allow for physician judgment and choice in determining where to make adjustments to medications, responsive to the individual patient's presentation.

Patients should return to the clinic or be contacted by clinic personnel every two weeks (office visit or by phone) until symptom patterns are primarily contained within the mild range on the BDSS. Patients will then be evaluated monthly, until the clinician determines the patient may enter continuation phase treatment. It is recommended that clinicians see the patient every 8-12 weeks while they are in continuation phase. Support personnel may contact patients by phone if the physician is unable to see them.

All recommendations assume that side effects are tolerable. Please refer to the Side Effects Management section for suggestions on how to manage typical side effects. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all Critical Decision Points.

The Critical Decision Points and Tactics for the Treatment of Bipolar Disorder assume that you are working on one clinical presentation at a time, i.e., hypomania/mania or depressive symptoms. If symptom patterns change, requiring a shift in algorithm focus, return to CDP#1 to evaluate and direct the change in treatment.

## Critical Decision Points (CDPs) and Tactics for the Treatment of Bipolar Disorder\*

*Instructions: To identify the recommendations for the appropriate CDP, trace to the right to the degree of symptom severity indicated by the BDSS Chart.*

		Mild to Moderate				Severe			
Critical Decision Point		NA	1	2	3	4	5	6	7
Week 0: CDP #1	Symptomatic.			Start medications.			Start medications.		
Week 2: CDP #2	Order serum levels (if applicable) to adjust dose.	Continue current dose.		Continue current dose. Consider increasing dose.			Increase dose.		
Week 4: CDP #3	Order serum levels (if applicable) to adjust dose.	Continue current dose.		Increase dose or consider next stage.			Increase dose or consider next stage.		
Week 6: CDP #4	All serum levels should be within therapeutic range.	Continue current dose.		Increase dose or consider next stage.			Increase dose or consider next stage.		
Week 8: CDP #5		Continue current dose.		Consider next stage.			Go to next stage.		

*\*Side Effects: Treatment recommendations assume that side effects are tolerable. Refer to the Side Effects Management section of the physician manual. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all Critical Decision Points.*

### CDP # 1, Week 0

All patients are treated with the algorithm for hypomania/mania. Treatment with this algorithm assumes that the clinician has made a thorough assessment of history and symptoms and determined that the patient has a diagnosis of Bipolar I disorder.

Additionally, patients with depressive symptoms may require concomitant treatment with the algorithm for treatment of bipolar depression. The first stage of that algorithm recommends optimizing treatment with mood stabilizing medications. Therefore, the recommendation is to initiate treatment within the algorithm for hypomania/mania, stabilize those medications, and then assess symptoms of depression to determine if additional pharmacotherapy is needed.

At CDP#1, the clinician has determined that the patient requires medication treatment for symptoms associated with Bipolar I disorder. After review of patient symptoms, history, etc., a determination is made regarding where to initiate new treatment (in algorithm for mania/hypomania or depression, and at which stage). Each course through the CDP sequence is unique to one stage of treatment, in either algorithm. The recommendation is to minimize adjustments to multiple medications simultaneously as much as possible, to better allow for evaluation of the current stage of treatment.

### CDP #2, Week 2

The first critical decision point occurs two weeks after the initiation of a new treatment stage. If medications that require serum levels have been prescribed, ideally the physician will have lab results to guide treatment decisions. Clinicians or support staff may administer the BDSS, and report scores on the BDSS Score Sheet. The rating of side effect severity from the Clinical Record Form may be entered on the score sheet as well.

***Bipolar Disorder is a complex, multi-dimensional illness, with prominent components of hypomania/mania, depression, and psychosis. Critical Decision Points involve a consideration of efficacy among all symptom domains, tolerability, and safety. Clinicians must use their own judgment in evaluating the symptoms of the bipolar patient. Evaluate the pattern and severity of symptoms by reviewing the BDSS score sheet. If most symptoms are contained within the light gray column, follow treatment recommendations within that column. Similarly, follow the recommendations that are most appropriate given the severity of symptom scores on the BDSS.***

***Additionally, symptoms are loosely grouped into categories to further guide the clinician. For example, if symptom scores within the depressive spectrum are elevated, the clinician may want to consult the Algorithm for Treatment of Depression in Bipolar Disorder, initiate a new treatment for depressive symptoms, and begin again at CDP#1. If scores within the manic spectrum are elevated, the clinician should make adjustments according to the recommendations of the primary treatment algorithm. Decisions whether to adjust an anticonvulsant or an atypical antipsychotic medication being used in combination treatment may be made clear after a review of the symptom pattern.***

At CDP#2, if the patient continues to experience symptoms within the mild to moderate range, the clinician may choose between continuing the current dosing or increasing the dose of medication(s). For symptoms within the severe range, the recommendation is to increase the dose of medication(s). If medications that require serum levels are adjusted (Li or DVP), order lab work so that dosage can be evaluated at CDP#3.

#### **CDP #3, Week 4**

If symptoms are not present, continue with current dosing. For symptoms within the mild to severe range, the clinician may choose between increasing the current dosing or moving to the next stage of treatment. If medications that require serum levels are adjusted (Li or DVP), order lab work so that dosage can be evaluated at CDP#4.

#### **CDP#4, Week 6**

Medications should be within the range of therapeutic dosing by this CDP. If symptoms are not present, continue with current dosing. The patient has been treated for 6 weeks with the current stage of treatment. Continued symptoms that are mild to severe warrant a further increase in dose, or consideration of the next stage of treatment.

#### **CDP#5, Week 8**

If symptoms are not present, continue with current dosing. If the patient is experiencing continued symptoms that are mild to moderate, the recommendation is to consider the next stage of treatment. However, it is possible that for some patients, this is a positive outcome, and continuing with the present treatment is a reasonable clinical decision. If severe symptoms are present, the clinician is directed to move to the next stage of treatment.

At any point within the CDPs, if medications are stabilized and patient outcomes remain positive and stable, visit intervals can be extended to every four weeks. All patients with Bipolar I disorder who achieve a satisfactory clinical response (preferably symptom remission) should receive continuation phase treatment. Please refer to the section on continuation and maintenance phase treatment for further recommendations.

**Table 5: Summary of Critical Decision Points**

<i><b>Critical Decision Point</b></i>	<i><b>Clinical Status</b></i>	<i><b>Plan</b></i>
Week 0 (CDP # 1)	Symptomatic	♦ Initiate medication; adjust dose to lower end of therapeutic dose range or serum level.
Week 2 (CDP # 2)	Full Response (No Symptoms)	♦ Continue current dose.
	Mild to Moderate Symptoms	♦ Continue current dose. ♦ Consider increasing dose.
	Severe Symptoms	♦ Increase dose.
Week 4 (CDP # 3)	Full Response (No Symptoms)	♦ Continue current dose.
	Mild to Moderate Symptoms	♦ Increase dose. ♦ Consider the next stage.
	Severe Symptoms	♦ Increase dose. ♦ Consider the next stage.
Week 6 (CDP # 4)	Full Response (No Symptoms)	♦ Go to continuation phase if full response is sustained for at least 4 weeks. Otherwise, continue current dose.
	Mild to Moderate Symptoms	♦ Increase dose. ♦ Consider the next stage.
	Severe Symptoms	♦ Increase dose. ♦ Consider the next stage.
Week 8 (CDP # 5)	Full Response (No Symptoms)	♦ Go to continuation phase if full response is sustained for at least 4 weeks. Otherwise, continue current dose.
	Mild to Moderate Symptoms	♦ Consider the next stage.
	Severe Symptoms	♦ Go to the next stage.

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## **OVERLAP AND TAPER GUIDELINES**

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Considerable evidence in patients with bipolar disorder suggest that a sudden discontinuation of lithium maintenance treatment is associated with a greater relapse of affective illness than a gradual taper (Suppes et al., 1996). Some evidence in patients with schizophrenia suggests that the abrupt discontinuation of maintenance antipsychotic treatment is also associated with a greater risk of relapse than is a gradual taper (Viguera et al., 1997). Thus, a gradual tapering of psychotropic medications in persons with bipolar disorder is strongly recommended when possible to minimize exacerbation or relapse of mood symptoms. Exceptions to this rule would be when severe or potentially life-threatening side effects occur or if manic symptoms should develop during antidepressant therapy.

In general, if a medication is to be discontinued, the new medication should be started and brought to a therapeutic level. Then the medication to be discontinued is gradually tapered over a period of at least one month. For example, if a patient was nonresponsive and had side effects during an adequate trial of lithium monotherapy at 1,200 mg per day and the decision was made to discontinue lithium and begin therapy with divalproex sodium, the guidelines would recommend beginning divalproex sodium at 500-750 mg per day, checking blood levels and bringing the patient to a therapeutic level of divalproex sodium ( $\geq 50$  ug/ml). At this point, the lithium could then be tapered at 300 mg per 1 to 2 weeks monitoring for evidence of increased symptoms of mania during this time.

If during the increasing dose period of the second medication, presumptive side effects from the first medication increase, it would be reasonable to begin tapering the first med prior to reaching full therapeutic dose of the second new medication. On the other side, if, during the taper of a medication, the patient shows a good response to a particular combination, it would be reasonable to continue with both medications. At a later time, the taper could be resumed to further evaluate the need for both medications.

## Side Effect Management

Table 6: Side Effect Management

Side Effects	Recommendations*
GI Upset	<ul style="list-style-type: none"> <li>- Administer medication with food and large quantities of liquid.</li> <li>- Consider lowering dose, if possible.</li> <li>- Use sustained release preparations of medications when available.</li> <li>- Some data suggest that this side effect can be successfully treated with H2 blockers (e.g., cimetidine, ranitidine).</li> </ul>
Tremor	<p><b><u>Enhanced physiologic tremor</u></b> – A fine tremor of approximately 8-10 Hz; made worse with outstretched hands.</p> <ul style="list-style-type: none"> <li>- Check blood levels of medication.</li> <li>- Decrease dose, divide dose, or change to slow release preparation of the medication.</li> <li>- Propranolol can be given at 20-30 mg tid.</li> </ul> <p><b><u>Parkinsonian tremor</u></b> – Coarse tremor at rest of approximately 4-6 Hz.</p> <ul style="list-style-type: none"> <li>- Decrease dose, divide dosing, use QHS dosing, or switch to alternate medication.</li> <li>- Pharmacological treatments include benztropine 1-2 mg bid, amantadine 100 mg bid or tid, and diphenhydramine 25-50 mg bid or tid.</li> </ul>
Sedation	<ul style="list-style-type: none"> <li>- Change dosing to QHS.</li> <li>- Substitute a less sedating alternative medication.</li> </ul>
Extrapyramidal Symptoms (EPS)	<ul style="list-style-type: none"> <li>- Usually seen with typical antipsychotics.</li> <li>- Treat tremor as suggested above.</li> <li>- Reduce dose of antipsychotic medication.</li> <li>- Akathisia may respond to propranolol 20-30 mg tid, benztropine, amantadine, or diphenhydramine. If these are not effective, alternatives include clonidine 0.1 mg tid, and lorazepam 1 mg bid or tid.</li> <li>- Dystonic reactions can often prevented by benztropine 1 mg bid or tid for the first few days of antipsychotic therapy. Acute dystonic reactions are generally managed with benztropine 1-2 mg im or lorazepam 1 mg im.</li> </ul>

<b>Side Effects</b>	<b>Recommendations*</b>
Tardive Dyskinesia	<ul style="list-style-type: none"> <li>- Prescribe antipsychotics in the lowest dose necessary for the shortest time possible.</li> <li>- Consider alternatives for mood stabilization and control of agitation.</li> <li>- Use atypical antipsychotic medications.</li> <li>- Some evidence that vitamin E given in high doses (&gt;1,000 units per day) may decrease some symptoms of tardive dyskinesia for some patients.</li> </ul>
Insomnia	<ul style="list-style-type: none"> <li>- Use QAM dosing, or divided dosing as early in the day as possible.</li> <li>- Use QHS dosing for any potentially sedating medications.</li> <li>- Use zolpidem at 5-10 mg QHS, zaleplon 5-20 mg (10 mg recommended dose) QHS, or benzodiazepine such as temazepam 15-30 mg at night. Antipsychotics should always be considered second or third line agents for insomnia due to their risk of extrapyramidal side effects and tardive dyskinesia. Avoid use of trazodone for sleep as it is an antidepressant and thus has the potential for increasing symptoms of mania in bipolar patients.</li> </ul>
Sexual Dysfunction	<ul style="list-style-type: none"> <li>- Add yohimbine at 4-7.5 mg, 3 times a day, cyproheptadine at 4-8 mg given shortly before sexual intercourse, or bupropion given at dosages of 75-300 mg per day. Bupropion has the advantage of potentially also augmenting the antidepressant efficacy of the SSRI. However, a disadvantage of bupropion is possible induction or worsening of manic symptomatology with the use of two antidepressants.</li> </ul>

\*In general, treatment emergent side effects should be addressed first by dose reduction or medication switching.

\*Benzodiazepines are best avoided in patients with prior history of substance abuse/dependence or who are at risk for substance abuse. Nonaddicting agents are preferred.

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## ***Continuation and Maintenance Guidelines***

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### ***Algorithm for Treatment of Hypomania/Mania***

#### **Continuation Guidelines**

##### **If patient received pharmacotherapy during acute phase:**

At baseline and throughout treatment, other psychosocial or nonmedication treatment modalities such as concomitant psychotherapy should be considered. After full response, the medication(s) should be continued for 3 months at the dose effective during the acute phase. Patients should be evaluated at least every 3 months during continuation treatment (if possible, every 1-2 months).

Importantly, once stabilized during the latter portion of continuation phase, it is recommended that efforts be made to simplify the medication regimen. When discontinuing one of the ongoing medications, the dosage should be tapered no more rapidly than 25% per week and not before 3 months of full remission have occurred. Tapering and discontinuation usually can be completed over a 1-2 month period. Patients should be educated concerning the signs and symptoms of recurrence of depressive symptoms.

At this time, little is scientifically known about the relative need for combined mood stabilizers long term. Thus, treatment decisions should be empiric. Once the patient is stabilized, consideration of tapering a medication either associated with side effects or limited partial response, while continuing other medications, is reasonable.

If mood instability recurs, prompt treatment with the medication previously effective should be initiated (i.e., initiate algorithm stage and tactic that previously resulted in remission of symptoms).

##### **If patient received ECT during acute phase:**

Continuation phase treatment with mood stabilizers is recommended after the initial treatment phase of ECT is completed. Selecting a mood stabilizer(s) that the patient has not previously received or one that the patient has responded to during a previous episode is generally recommended. However, if necessary, a previously partially effective mood stabilizer may be used alone or in combination with other mood stabilizers. Dosing, duration of treatment, monitoring, and medication tapering are as above.

If a patient relapses during continuation phase treatment, continuation ECT should be considered.

#### **Maintenance Guidelines**

Guidelines are limited due to relatively few scientific studies on the long-term management of bipolar patients. Treatment should be empirically based. In practice, usually all patients will need mood stabilizers to prevent return of symptoms. The lowest possible dose is recommended, while maintaining the mood stabilizing treatment at therapeutic levels. General practice at this time is lifetime mood stabilizers following 2 manic episodes, or 1 episode if there is a severe episode and/or significant family history of bipolar or major depressive



disorder. For a first episode of bipolar mania with no family history of bipolar or major depression, medication tapering and discontinuation may be considered after the continuation period is completed (usually 6 months in remission), depending on the severity of the first episode, surrounding factors, and prodromal history.

Active discussions regarding the initiation and duration of maintenance treatment are an important element in the clinician-patient collaboration for this as well as other phases of pharmacological management of bipolar disorder. The patient's personal preference as well as the risk factors for recurrence should be considered in the decision process.

## ***Algorithm for the Treatment of Depression in Bipolar Disorder***

### **Continuation Guidelines**

#### **If patient received pharmacotherapy during acute phase:**

At baseline and throughout treatment, other psychosocial or nonmedication treatment modalities such as concomitant psychotherapy should be considered. After full response, the antidepressant medication(s) should be continued for 1-3 months at the dose effective during the acute phase. Patients should be evaluated at least every 3 months during continuation treatment (if possible, every 1-2 months).

For initial episodes of bipolar major depression and in all bipolars without a proven continued need for antidepressants, medication tapering and discontinuation should be considered after the continuation period is completed. If previous depressive episodes occurred with antidepressant discontinuation, maintenance treatment should be considered.

When discontinuing the antidepressant, the dosage should be tapered no more rapidly than 25% per week and not before 1-3 months of full remission have occurred. Tapering and discontinuation usually can be completed over a 1-2 month period. In major depressive disorder (unipolar), a new depressive episode is most likely to occur within the first 8 months of medication discontinuation; therefore, patients should be evaluated every 2 to 4 months during that period. Patients should be educated concerning the signs and symptoms of recurrence of depressive symptoms.

If depression recurs, prompt treatment with the medication previously effective should be initiated (i.e., initiate algorithm stage and tactic that previously resulted in remission of depressive symptoms). At this time, little is scientifically known about the relative need for combined antidepressants long term. Thus, treatment decisions should be empiric, and once the patient is stabilized, consideration of tapering one of the antidepressants is reasonable.

#### **If patient received ECT during acute phase:**

Continuation phase treatment with mood stabilizers is recommended after the initial treatment phase of ECT is completed. Selecting a mood stabilizer(s) that the patient has not previously received or one that the patient has responded to during a previous episode is generally recommended. However, if necessary, a previously partially effective mood stabilizer may be used alone or in combination with other mood stabilizers. Generally, mood stabilizers would be

used prior to initiating an antidepressant. Dosing, duration of treatment, monitoring, and medication tapering are as above.

If a patient relapses during continuation phase treatment with an antidepressant, continuation ECT should be considered.

### **Maintenance Guidelines**

Guidelines are limited due to few scientific studies on the long-term management of antidepressants in bipolar patients. Treatment should be empirically based. In practice, some patients will need antidepressants to prevent return of symptoms. The lowest possible dose is recommended, while maintaining the mood stabilizing treatment at therapeutic levels.

Active discussions regarding the initiation and duration of maintenance treatment are an important element in the clinician-patient collaboration for this as well as other phases of pharmacological management of bipolar disorder. The patient's personal preference as well as the risk factors for recurrence should be considered in the decision process.

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## ***Modifications for Inpatient Use***

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Patients who have been hospitalized for symptoms of bipolar disorder require fast acting interventions to achieve stabilization and discharge. It is likely that a clinician may make the following modifications to these algorithms to achieve these goals.

**Adjustment to Critical Decision Points** – The critical decision points are set at 2-week intervals, assuming outpatient treatment. Of course, opportunities to evaluate the patient and make clinical decisions and medication adjustments will happen on an expedited schedule when the patient is inpatient. The recommendation is to observe the patient at least every 48 hours to evaluate symptoms, assess side effects to medications, and judge response.

**Accelerated movement to advanced treatment stage** – The clinician may use an advanced stage of treatment to achieve quick symptom relief and stabilization. If this is indicated as the best course of treatment, it is recommended to document the rationale for this decision. The clinician might suggest medications to taper and discontinue at a later point in discharge documentation, once the patient is stable, in order to minimize medication combinations and simplify medication regimens.

**Use of alternate medications** – If clinicians prescribe lithium and/or divalproex, it is unlikely that they will have the opportunity to monitor effects through blood levels over the course of a brief hospitalization. In this case, again, documentation of the prescribing intent would be helpful to ensure consistency when the patient continues in outpatient care. For example, at the time of discharge, please include instructions for follow-up procedures, including target dose, expected blood levels, and intended taper of short-term medications.

Additionally, clinicians may utilize faster acting forms of medications contained in these algorithms. Oral loading of divalproex sodium can be utilized for quick stabilization of manic patients (20 mg/kg is the standard formula). Additionally injectable and deconoate forms of atypical antipsychotic medications may be available before the next substantial revision of this algorithm and manual.

## Documentation

The Bipolar Disorder Module will utilize the same forms developed for use in the Texas Implementation of Medications Algorithms project, and modified for use by various centers. The critical information needed for implementation of the BD algorithms is:

1. Past and current psychoactive medications and response.
2. Primary current diagnosis. (Please note that these algorithms were developed for patients diagnosed with Bipolar I Disorder.)
3. Core symptoms.
4. Other symptoms.
5. Side effects (to evaluate tolerability).
6. Response to treatment: overall functioning, BDSS scores, patient self-report of symptom severity and side effects.

### Outpatient Data Collection

**Outpatient Intake Form:** Complete as usual.

**Outpatient Clinic Visit Clinical Record Form:** Complete as usual. Please note that all patients will have a stage entered for the principal treatment algorithm, Algorithm for treatment of Hypomania/Mania. Additional staging information for the treatment of depression in bipolar disorder will be entered ONLY if the patient is being treated for depressive symptoms. **As there is one line available to document stage of treatment, please utilize the format of “Stage Mania Algorithm/Stage Depression Algorithm”. For example,**

*Patient is on Stage 3 of the algorithm for Mania/Hypomania, and not being treated within the algorithm for treatment of Depressive symptoms:*

**Stage: 3/NA**

*Patient is on Stage 2 of the algorithm for Mania/Hypomania, and on Stage 2 of the algorithm for treatment of Depressive symptoms:*

**Stage: 2/2**

**Outpatient Interim Contact Form:** In the event that the patient does not come into the clinic or there is not time for a complete visit, the ICF is documented by support personnel or the physician.

### Inpatient Data Collection

**Inpatient Intake Form:** Complete as usual.

**Inpatient Clinic Visit Clinical Record Form:** Complete as usual. Please note that all patients will have a stage entered for the principal treatment algorithm, Algorithm for treatment of Hypomania/Mania. Additional staging information for the treatment of depression in bipolar disorder will be entered ONLY if the patient is being treated for depressive symptoms.

**As there is one line available to document stage of treatment, please utilize the format of “Stage Mania Algorithm/Stage Depression Algorithm”. Use NA (Not Applicable) if the patient is not being treated with the algorithm for treatment of depression in bipolar disorder. For example,**

*Patient is on Stage 3 of the algorithm for Mania/Hypomania, and not being treated within the algorithm for treatment of Depression:*

**Stage: 3/NA**

*Patient is on Stage 2 of the algorithm for Mania/Hypomania, and on Stage 2 of the algorithm for treatment of Depression:*

**Stage: 2/2**

**Inpatient Contact Form:** Complete as usual.

Copies of all TIMA forms can be found in Appendix B.

## ***Appendix: Table of Contents***

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### Appendix A. Process Measures

- Brief Bipolar Disorder Symptom Scale (BDSS)

- BDSS Scoring Sheet

- Critical Decision Points (CDPs) and Tactics for the Treatment of Bipolar Disorder

- BDSS and CDP Worksheet

- Scoring Criteria for Physician- and Patient-Rated Overall Symptom and Side Effect Ratings

### Appendix B. Documentation

- Forms for Outpatient Data Collection

  - Outpatient Intake Form

  - Outpatient Clinic Visit Clinical Record Form

  - Outpatient Interim Contact Form

- Forms for Inpatient Data Collection

  - Inpatient Intake Form/Annual Update

  - Inpatient Clinical Record Form

  - Inpatient Contact Form

### Appendix C. Communications

- Important Telephone Numbers

### Appendix D. Medication Descriptions

### Appendix E. Drug Interactions

## **Appendix A. Process Measures**

*Brief Bipolar Disorder Symptom Scale (BDSS)*

*BDSS Scoring Sheet*

*Critical Decision Points (CDPs) and Tactics for the Treatment of Bipolar Disorder*

*BDSS and CDP Worksheet*

*Scoring Criteria for Physician- and Patient-Rated Overall Symptom and Side Effect Ratings*

## BRIEF BIPOLAR DISORDER SYMPTOM SCALE

1. **HOSTILITY:** Animosity, contempt, belligerence, threats, arguments, tantrums, property destruction, fights and any other expression of hostile attitudes or actions. Do not infer hostility from neurotic defenses, anxiety or somatic complaints. Do not include incidents of appropriate anger or obvious self-defense.

*How have you been getting along with people (family, co-workers, etc.)?*

*Have you been irritable or grumpy lately? (How do you show it? Do you keep it to yourself?)*

*Were you ever so irritable that you would shout at people or start fights or arguments? (Have you found yourself yelling at people you didn't know?)*

*Have you hit anyone recently?*

### NA Not assessed

#### 1 Not Present

#### 2 Very Mild

Irritable or grumpy, but not overtly expressed.

#### 3 Mild

Argumentative or sarcastic.

#### 4 Moderate

Overtly angry on several occasions OR yelled at others excessively.

#### 5 Moderately Severe

Has threatened, slammed about or thrown things.

#### 6 Severe

Has assaulted others but with no harm likely, e.g., slapped or pushed, OR destroyed property, e.g., knocked over furniture, broken windows.

#### 7 Extremely Severe

Has attacked others with definite possibility of harming them or with actual harm, e.g., assault with hammer or weapon.

2. **ELEVATED MOOD:** A pervasive, sustained and exaggerated feeling of well-being, cheerfulness, euphoria (implying a pathological mood), optimism that is out of proportion to the circumstances. Do not infer elation from increased activity or from grandiose statements alone.

*Have you felt so good or high that other people thought that you were not your normal self?*

*Have you been feeling cheerful and "on top of the world" without any reason?*

[If patient reports elevated mood/euphoria, ask the following]:

*Did it seem like more than just feeling good? How long did that last?*



**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Seems to be very happy, cheerful without much reason.

**3 Mild**

Some unaccountable feelings of well-being that persist.

**4 Moderate**

Reports excessive or unrealistic feelings of well-being, cheerfulness, confidence or optimism inappropriate to circumstances, some of the time. May frequently joke, smile, be giddy or overly enthusiastic OR few instances of marked elevated mood with euphoria.

**5 Moderately Severe**

Reports excessive or unrealistic feelings of well-being, confidence or optimism inappropriate to circumstances much of the time. May describe "feeling on top of the world," "like everything is falling into place," or "better than ever before," OR several instances of marked elevated mood with euphoria.

**6 Severe**

Reports many instances of marked elevated mood with euphoria OR mood definitely elevated almost constantly throughout interview and inappropriate to content.

**7 Extremely Severe**

Patient reports being elated or appears almost intoxicated, laughing, joking, giggling, constantly euphoric, feeling invulnerable, all inappropriate to immediate circumstances.

3. **GRANDIOSITY:** Exaggerated self-opinion, self-enhancing conviction of special abilities or powers or identity as someone rich or famous. Rate only patient's statements about himself, not his demeanor. Note: If the subject rates a "6" or "7" due to grandiose delusions, you must rate Unusual Thought Content at least a "4" or above.

*Is there anything special about you? Do you have any special abilities or powers? Have you thought that you might be somebody rich or famous?*

[If the patient reports any grandiose ideas/delusions, ask the following]:

*How often have you been thinking about [use patient's description]? Have you told anyone about what you have been thinking? Have you acted on any of these ideas?*

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Feels great and denies obvious problems, but not unrealistic.

**3 Mild**

Exaggerated self-opinion beyond abilities and training.

**4 Moderate**

Inappropriate boastfulness, claims to be brilliant, insightful, or gifted beyond realistic proportions, but rarely self-discloses or acts on these inflated self-concepts. Does not claim that grandiose accomplishments have actually occurred.

**5 Moderately Severe**

Same as 4 but often self-discloses and acts on these grandiose ideas. May have doubts about the reality of the grandiose ideas. Not delusional.

**6 Severe**

Delusional--claims to have special powers like ESP, to have millions of dollars, invented new machines, worked at jobs when it is known that he was never employed in these capacities, be Jesus Christ, or the President. Patient may not be very preoccupied.

**7 Extremely Severe**

Delusional--Same as 6 but subject seems very preoccupied and tends to disclose or act on grandiose delusions.

- 4. DEPRESSION:** Include sadness, unhappiness, anhedonia, and preoccupation with depressing topics (can't attend to TV, conversations due to depression), hopelessness, loss of self-esteem (dissatisfied or disgusted with self or feelings of worthlessness). Do not include vegetative symptoms, e.g., motor retardation, early waking, or the amotivation that accompanies the deficit syndrome.

*How has your mood been recently? Have you felt depressed (sad, down, unhappy as if you didn't care)?*

*Are you able to switch your attention to more pleasant topics when you want to?*

*Do you find that you have lost interest in or get less pleasure from things you used to enjoy, like family, friends, hobbies, watching TV, eating?*

[If subject reports feelings of depression, ask the following]:

*How long do these feelings last? Has it interfered with your ability to perform your usual activities/work?*

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Occasionally feels sad, unhappy or depressed.

**3 Mild**

Frequently feels sad or unhappy but can readily turn attention to other things.

**4 Moderate**

Frequent periods of feeling very sad, unhappy, moderately depressed, but able to function with extra effort.

**5 Moderately Severe**

Frequent, but not daily, periods of deep depression OR some areas of functioning are disrupted by depression.

**6 Severe**

Deeply depressed daily but not persisting throughout the day OR many areas of functioning are disrupted by depression.

**7 Extremely Severe**

Deeply depressed daily OR most areas of functioning are disrupted by depression.

5. **ANXIETY:** Reported apprehension, tension, fear, panic or worry. Rate only the patient's statements, not observed anxiety that is rated under **TENSION**.

*Have you been worried a lot during [mention time frame]? Have you been nervous or apprehensive? (What do you worry about?)*

*Are you concerned about anything? How about finances or the future?*

*When you are feeling nervous, do your palms sweat or does your heart beat fast (or shortness of breath, trembling, choking)?*

[If patient reports anxiety or autonomic accompaniment, ask the following];

*How much of the time have you been [use patient's description]?*

*Has it interfered with your ability to perform your usual activities/work?*

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Reports some discomfort due to worry OR infrequent worries that occur more than usual for most normal individuals.

**3 Mild**

Worried frequently but can readily turn attention to other things.

**4 Moderate**

Worried most of the time and cannot turn attention to other things easily but no impairment in functioning OR occasional anxiety with autonomic accompaniment but no impairment in functioning.

**5 Moderately Severe**

Frequent, but not daily, periods of anxiety with autonomic accompaniment, OR some areas of functioning are disrupted by anxiety or worry.

**6 Severe**

Anxiety with autonomic accompaniment daily but not persisting throughout the day OR many areas of functioning are disrupted by anxiety or constant worry.

**7 Extremely Severe**

Anxiety with autonomic accompaniment persisting throughout the day OR most areas of functioning are disrupted by anxiety or constant worry.

- 6. UNUSUAL THOUGHT CONTENT:** Unusual, odd, strange or bizarre thought content. Rate the degree of unusualness, not the degree of disorganization of speech. Delusions are patently absurd, clearly false or bizarre ideas that are expressed with full conviction. Consider the patient to have full conviction if he/she has acted as though the delusional belief were true. Ideas of reference/persecution can be differentiated from delusions in that ideas are expressed with much doubt and contain more elements of reality. Include thought insertion, withdrawal and broadcast. Include grandiose, somatic and persecutory delusions even if rated elsewhere. Note: If Somatic Concern, Guilt, Suspiciousness, or Grandiosity are rated "6" or "7" due to delusions, then Unusual Thought Content must be rated a "4" or above.

*Have you been receiving any special messages from people or from the way things are arranged around you? Have you seen any references to yourself on TV or in the newspapers?*

*Can anyone read your mind?*

*Do you have a special relationship with God?*

*Is anything like electricity, X-rays, or radio waves affecting you?*

*Are thoughts put into your head that are not your own?*

*Have you felt that you were under the control of another person or force?*

[If patient reports any odd ideas/delusions, ask the following]:

*How often do you think about [use patient's description]?*

*Have you told anyone about these experiences? How do you explain the things that have been happening [specify]?*

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Ideas of reference (people may stare or may laugh at him), ideas of persecution (people may mistreat him). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in one's own abilities. Not strongly held. Some doubt.

**3 Mild**

Same as 2, but degree of reality distortion is more severe as indicated by highly unusual ideas or greater conviction. Content may be typical of delusions (even bizarre), but without full conviction. The delusion does not seem to have fully formed, but is considered as one possible explanation for an unusual experience.

**4 Moderate**

Delusion present but no preoccupation or functional impairment. May be an encapsulated delusion or a firmly endorsed absurd belief about past delusional circumstances.

**5 Moderately Severe**

Full delusion(s) present with some preoccupation OR some areas of functioning disrupted by delusional thinking.

**6 Severe**

Full delusion(s) present with much preoccupation OR many areas of functioning are disrupted by delusional thinking.

**7 Extremely Severe**

Full delusions present with almost total preoccupation OR most areas of functioning are disrupted by delusional thinking.

**Rate the following items on the basis of observed behavior and speech.**

- 7. EXCITEMENT:** Heightened emotional tone, or increased emotional reactivity to interviewer or topics being discussed, as evidenced by increased intensity of facial expressions, voice tone, expressive gestures or increase in speech quantity and speed.

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Subtle and fleeting or questionable increase in emotional intensity. For example, at times, seems keyed-up or overly alert.

**3 Mild**

Subtle but persistent increase in emotional intensity. For example, lively use of gestures and variation in voice tone.

**4 Moderate**

Definite but occasional increase in emotional intensity. For example, reacts to interviewer or topics that are discussed with noticeable emotional intensity. Some pressured speech.

**5 Moderately Severe**

Definite and persistent increase in emotional intensity. For example, reacts to many stimuli, whether relevant or not, with considerable emotional intensity. Frequent pressured speech.

**6 Severe**

Marked increase in emotional intensity. For example reacts to most stimuli with inappropriate emotional intensity. Has difficulty settling down or staying on task. Often restless, impulsive, or speech is often pressured.

**7 Extremely Severe**

Marked and persistent increase in emotional intensity. Reacts to all stimuli with inappropriate intensity, impulsiveness. Cannot settle down or stay on task. Very restless and impulsive most of the time. Constant pressured speech.

8. **MOTOR HYPERACTIVITY:** Increase in energy level evidenced in more frequent movement and/or rapid speech. Do not rate if restlessness is due to akathisia.

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Some restlessness, difficulty sitting still, lively facial expressions, or somewhat talkative.

**3 Mild**

Occasionally very restless, definite increase in motor activity, lively gestures, 1-3 brief instances of pressured speech.

**4 Moderate**

Very restless, fidgety, excessive facial expressions or nonproductive and repetitious motor movements. Much pressured speech, up to one third of the interview.

**5 Moderately Severe**

Frequently restless, fidgety. Many instances of excessive non-productive and repetitious motor movements. On the move most of the time. Frequent pressured speech, difficult to interrupt. Rises on 1-2 occasions to pace.

**6 Severe**

Excessive motor activity, restlessness, fidgety, loud tapping, noisy, etc., throughout most of the interview. Speech can only be interrupted with much effort. Rises on 3-4 occasions to pace.

**7 Extremely Severe**

Constant excessive motor activity throughout entire interview, e.g., constant pacing, constant pressured speech with no pauses, interviewee can only be interrupted briefly and only small amounts of relevant information can be obtained.

9. **EMOTIONAL WITHDRAWAL:** Deficiency in patient's ability to relate emotionally during interview situation. Use your own feeling as to the presence of an "invisible barrier" between patient and interviewer. Include withdrawal apparently due to psychotic processes.

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Lack of emotional involvement shown by occasional failure to make reciprocal comments, occasionally appearing preoccupied, or smiling in a stilted manner, but spontaneously engages the interviewer most of the time.

**3 Mild**

Lack of emotional involvement shown by noticeable failure to make reciprocal comments, appearing preoccupied, or lacking in warmth, but responds to interviewer when approached.

**4 Moderate**

Emotional contact not present much of the interview because subject does not elaborate responses, fails to make eye contact, doesn't seem to care if interviewer is listening, or may be preoccupied with psychotic material.

**5 Moderately Severe**

Same as "4" but emotional contact not present most of the interview.

**6 Severe**

Actively avoids emotional participation. Frequently unresponsive or responds with yes/no answers (not solely due to persecutory delusions). Responds with only minimal affect.

**7 Extremely Severe**

Consistently avoids emotional participation. Unresponsive or responds with yes/no answers (not solely due to persecutory delusions). May leave during interview or just not respond at all.

- 10. BLUNTED AFFECT:** Restricted range in emotional expressiveness of face, voice, and gestures. Marked indifference or flatness even when discussing distressing topics. In the case of euphoric or dysphoric patients, rate Blunted Affect if a flat quality is also clearly present.

Use the following probes at end of interview to assess emotional responsivity:

*Have you heard any good jokes lately? Would you like to hear a joke?*

**NA Not assessed**

**1 Not Present**

**2 Very Mild**

Emotional range is slightly subdued or reserved but displays appropriate facial expressions and tone of voice that are within normal limits.

**3 Mild**

Emotional range overall is diminished, subdued, or reserved, without many spontaneous and appropriate emotional responses. Voice tone is slightly monotonous.

**4 Moderate**

Emotional range is noticeably diminished, patient doesn't show emotion, smile, or react to distressing topics except infrequently. Voice tone is monotonous or there is noticeable decrease in spontaneous movements. Displays of emotion or gestures are usually followed by a return to flattened affect.

**5 Moderately Severe**

Emotional range very diminished, patient doesn't show emotion, smile or react to distressing topics except minimally, few gestures, facial expression does not change very often. Voice tone is monotonous much of the time.

**6 Severe**

Very little emotional range or expression. Mechanical in speech and gestures most of the time. Unchanging facial expression. Voice tone is monotonous most of the time.

**7 Extremely Severe**

Virtually no emotional range or expressiveness, stiff movements. Voice tone is monotonous all of the time.

Sources of information (check all applicable):

\_\_\_\_\_ Patient  
\_\_\_\_\_ Parents/Relatives  
\_\_\_\_\_ Mental Health Professionals  
\_\_\_\_\_ Chart

Confidence in assessment:

\_\_\_\_\_ 1 = Not at all - 5 = Very confident

Explain here if validity of assessment is questionable:

\_\_\_\_\_ Symptoms possibly drug-induced  
\_\_\_\_\_ Underreported due to lack of rapport  
\_\_\_\_\_ Underreported due to negative symptoms  
\_\_\_\_\_ Patient uncooperative  
\_\_\_\_\_ Difficult to assess due to formal thought disorder  
\_\_\_\_\_ Other \_\_\_\_\_



# Texas Implementation of Medication Algorithms

## Brief Bipolar Disorder Symptom Scale

Visit Date: \_\_\_\_\_

Overall Side Effect Severity (from CRF): \_\_\_\_\_

**Instructions:** Indicate the score for each item in the appropriate cell to the right of the item. Evaluate the pattern and severity of symptom(s) to guide clinical decision making.

NA  
Not assessed    1    Not present    2    Very mild    3    Mild    4    Moderate    5    Moderately Severe    6    Severe    7    Extremely severe

*Presence of Mild to Moderate Symptoms may indicate need for medication adjustment.*

*Any score >4 is within the range of Severe Symptoms, and indicates a need to make treatment changes.*

Symptom Group	Symptoms	NA	1	2	3	4	5	6	7
Manic/Hypomanic	Hostility								
	Elevated Mood								
	Grandiosity								
	Excitement								
Major Depressive	Motor Hyperactivity								
	Depressed Mood								
	Anxiety								
	Emotional Withdrawal								
Psychotic	Blunted Affect								
	Unusual Thought Content								

Scale Total: \_\_\_\_\_

# Critical Decision Points (CDPs) and Tactics for the Treatment of Bipolar Disorder\*

**Instructions:** To identify the recommendations for the appropriate CDP, trace to the right to the degree of symptom severity indicated by the BDSS Chart.

Critical Decision Point		Mild to Moderate				Severe		
		NA	1	2	3	4	5	6 7
Week 0: CDP #1	Symptomatic.			Start medications.			Start medications.	
Week 2: CDP #2	Order serum levels (if applicable) to adjust dose.	Continue current dose.	Continue current dose.	Continue current dose. Consider increasing dose.			Increase dose.	
Week 4: CDP #3	Order serum levels (if applicable) to adjust dose.	Continue current dose.	Continue current dose.	Increase dose or consider next stage.			Increase dose or consider next stage.	
Week 6: CDP #4	All serum levels should be within therapeutic range.	Continue current dose.	Continue current dose.	Increase dose or consider next stage.			Increase dose or consider next stage.	
Week 8: CDP #5		Continue current dose.	Continue current dose.	Consider next stage.			Go to next stage.	

**\*Side Effects:** Treatment recommendations assume that side effects are tolerable. Refer to the Side Effects Management section of the physician manual. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all Critical Decision Points.

# BDSS/CDP Worksheet

Visit Date: \_\_\_\_\_

*Instructions:* Indicate the score for each item in the appropriate cell to the right of the item. Evaluate the pattern and severity of symptom(s) to guide clinical decision making.

Overall Side Effect Severity (from \_\_\_\_\_)

*Presence of Mild to Moderate Symptoms may indicate need for medication adjustment.*

*Any score >4 is within the range of Severe Symptoms, and indicates a need to make treatment changes.*

Symptom	Symptoms	Not assessed	Not present	Very mild	Mild	Moderate	Moderately Severe	Severe	Extremely severe
Manic/Hypomani	Hostility	NA	1	2	3	4	5	6	7
	Elevated								
	Grandiosity								
	Excitement								
	Motor y								
Major	Depressed								
	Anxiety								
	Emotional								
	Blunted								
Psychotic	Unusual Thought								

Scale Total: \_\_\_\_\_

Critical Decision Points and Tactics *			Mild to		Severe		
Week 0: CDP	Symptomatic		Start	Start			
Week 2: CDP	Order serum levels applicable) to adjust	Continue current dose.	Continue current dose. increasing	Increase			
Week 4: CDP	Order serum levels (if applicable) to adjust	Continue current dose.	Increase dose or consider stage.	Increase dose or consider next stage.			
Week 6: CDP	All serum levels should within therapeutic	Continue current dose.	Increase dose or stage.	Increase dose or consider stage.			
Week 8: CDP		Continue current dose.	Consider next	Go to next stage.			

\* Side Effects: Treatment recommendations assume that side effects are tolerable. Refer to the Side Effects Management section of the physician manual. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all Critical Decision Points.

# **Scoring Criteria for Physician and Patient Overall Symptom and Side Effect Ratings**

<b>0</b>	<b>=</b>	<b>No Symptoms</b>
<b>1</b>	<b>=</b>	<b>Borderline</b>
<b>2</b>	<b>=</b>	<b>Mild</b>
<b>3</b>	<b>=</b>	<b>Mild – Moderate</b>
<b>4</b>	<b>=</b>	<b>Moderate</b>
<b>5</b>	<b>=</b>	<b>Moderate – Marked</b>
<b>6</b>	<b>=</b>	<b>Marked</b>
<b>7</b>	<b>=</b>	<b>Marked – Severe</b>
<b>8</b>	<b>=</b>	<b>Severe</b>
<b>9</b>	<b>=</b>	<b>Severe – Extreme</b>
<b>10</b>	<b>=</b>	<b>Extreme</b>

## ***Appendix B. Documentation***

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### **Forms for Outpatient Data Collection**

***Outpatient Intake Form***

***Outpatient Clinic Visit Clinical Record Form***

***Outpatient Interim Contact Form***

### **Forms for Inpatient Data Collection**

***Inpatient Intake Form/Annual Update***

***Inpatient Clinical Record Form***

***Inpatient Contact Form***

# TIMA Texas Implementation of Medication Algorithms

## Outpatient Intake Form

Date of Visit: \_\_\_\_/\_\_\_\_/\_\_\_\_ mm dd yy MHRM Physician Code: \_\_\_\_\_

**SAMPLE**

**DO NOT USE**

Age: \_\_\_\_ Gender: ☐ Female ☐ Male Ethnic or Racial Group (please check only one response): ☐ White ☐ Hispanic ☐ African-American ☐ Asian or Pacific Islander ☐ American Indian or Alaskan Native ☐ Other

Principal Diagnosis (DSM-IV Axis I code): \_\_\_\_\_

Age at Onset: \_\_\_\_ # of Episodes: \_\_\_\_ Onset of Current Episode: \_\_\_\_\_

Other current diagnoses not including principal diagnosis:

Axis I: \_\_\_\_\_ Axis II: \_\_\_\_\_

Alcohol/Substance Abuse: ☐ No ☐ Yes If yes, ☐ Current ☐ Past

Axis III (Current General medical conditions, check all that apply):

- ☐ Hypertension ☐ Hypothyroidism ☐ Head Injury ☐ HIV  
☐ CHF ☐ Diabetes ☐ Seizure Disorder ☐ Cancer  
☐ Heart Disease ☐ Endocrine (Other) ☐ Stroke ☐ Chronic Lung Disorder  
☐ Cardiac (Other) ☐ Asthma ☐ Neurological (Other)  
☐ Allergies (If yes, explain below) ☐ Other Significant Systemic Illness (specify): \_\_\_\_\_

Additional Information:

Any family members with a history of any of the following (please check all that apply):

	Depression	Schizophrenia	Bipolar	Substance Abuse	Suicide	Other	Effective Treatments
Parent							
Sibling							
Children							
Aunt/Uncle							
Grandparent							

Number of Psychiatric Hospitalizations (best estimate): Past Year: \_\_\_\_ Past 5 Years: \_\_\_\_ Lifetime: \_\_\_\_

Past and Current Psychoactive Medications (Patient Self-Report/Records):

Medication <i>Please provide medications for the past two years, record the highest dose given</i>	Taken for this episode?	Dose	Freq.	Start/Stop (Mo/Yr)	Response	Well Tolerated
1.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
3.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
5.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
6.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
7.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
8.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No

Signature/ title

Date

# TIMA Texas Implementation of Medication Algorithms

## OutPatient Clinic Visit

### Clinical Record Form

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Service Activity Code: \_\_\_\_\_

Physician Code: \_\_\_\_\_ Start Time: \_\_\_\_\_ Stop Time: \_\_\_\_\_

Current Diagnoses: \_\_\_\_\_. \_\_\_\_\_. \_\_\_\_\_. \_\_\_\_\_. \_\_\_\_\_. \_\_\_\_\_

Current Algo: (check ) ☐ MDD-NP ☐ MDD-P BD [☐ MANIA ☐ DEP] ☐ SCZ ☐ None

Stage: \_\_\_\_\_ Weeks in this stage: \_\_\_\_\_

Vital Signs: BP \_\_\_\_/\_\_\_\_ Pulse \_\_\_\_ Temp \_\_\_\_ Weight \_\_\_\_ Height \_\_\_\_ (if needed)

#### Most Recent Drug Levels:

Medication Name	Date Drawn	Serum Level	WNL

Has patient taken medications as prescribed? ☐ Yes/Mostly ☐ No/Inadequate

Any other medications taken during the past week? ☐ No ☐ Yes (If yes, specify below) \_\_\_\_\_

#### Patient Global Self Report (0-10) 0 = No symptoms 5 = moderate 10 = extreme

Symptom Severity: \_\_\_\_ Side Effects: \_\_\_\_

#### Clinical Rating Scales

POS SX: \_\_\_\_ NEG SX: \_\_\_\_ QIDS-SR: \_\_\_\_ QIDS-C: \_\_\_\_ BDSS: \_\_\_\_ OTHER: \_\_\_\_\_

Use for all physician's ratings below: (0-10) 0 = No symptoms 5 = moderate 10 = extreme

Core Symptoms: \_\_\_\_ Mania \_\_\_\_ Depression \_\_\_\_ Positive Sx or Psychosis \_\_\_\_ Negative Sx

Other Symptoms: \_\_\_\_ Irritability \_\_\_\_ Mood Lability \_\_\_\_ Agitation \_\_\_\_ Anxiety

\_\_\_\_ Level of Interest \_\_\_\_ Appetite \_\_\_\_ Energy Level \_\_\_\_ Insomnia

\_\_\_\_ Other (specify): \_\_\_\_\_ Overall Side Effect Severity: \_\_\_\_ (0-10)

Is patient presently suicidal? ☐ Yes ☐ No homicidal? ☐ Yes ☐ No Overall Functioning: \_\_\_\_ (0-10)

If yes, comment in progress note.

0=Low 10=High

Are serum levels needed? ☐ Yes ☐ No (if yes, specify in progress note)

Medication Response: ☐ Full ☐ Partial ☐ Minimal ☐ None ☐ Symptoms Worsening

(Since beginning of stage.)

If medication being changed at this visit, indicate reason for change (Include Dose Changes):

☐ Critical Decision Point Indicates Change Necessary ☐ Insufficient Improvement ☐ Patient Preference

☐ Side Effects Intolerable ☐ Symptoms Worsening ☐ Diagnosis Change ☐ Other: \_\_\_\_\_

# TIMA Texas Implementation of Medication Algorithms

[illegible]

<sup>1</sup>S=Meds Targeted at core syndrome. OS=Meds targeted at other symptoms. SE=Meds for side effects of S or OS

**Progress Note:** (☐ Check here if note was dictated. Date of dictation \_\_\_\_/\_\_\_\_/\_\_\_\_)

This image shows a single sheet of white paper with horizontal blue or grey ruling lines. The lines are evenly spaced and run across the width of the page. There are approximately 20 lines visible. The paper has a slight shadow on the right side, suggesting it's resting on a surface.

Return to clinic: \_\_\_\_\_ weeks

Next appointment date: \_\_\_\_/\_\_\_\_/\_\_\_\_

**Signature/Title:** \_\_\_\_\_



### Outpatient Interim Contact Form

Case #: \_\_\_\_\_ Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Primary Diagnosis: ☐ MDD-NP ☐ BPD-M ☐ BPD-D ☐ SCZ  
(check one) ☐ MDD-P ☐ BPD-MX ☐ SCZ-A (BP) ☐ SCZ-A ☐ Other (specify): \_\_\_\_\_

Type of Contact: ☐ Telephone ☐ Office Visit

All Prescription Medications In Last Week	
Medication Name – Please provide information on dosing, frequency and any other pertinent information.	Was the medication taken as prescribed?
1.	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.	<input type="checkbox"/> Yes <input type="checkbox"/> No
3.	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.	<input type="checkbox"/> Yes <input type="checkbox"/> No
5.	<input type="checkbox"/> Yes <input type="checkbox"/> No

Adherence to medication treatment? ☐ Yes ☐ No If no, document in progress note.

Significant Side Effects Reported? ☐ Yes ☐ No If yes, describe: \_\_\_\_\_

Overall Patient Global (self report): 0=none 5=moderate 10=extreme  
Symptom Severity: (0-10) \_\_\_\_\_ Side Effects: (0-10) \_\_\_\_\_

Is patient currently suicidal? ☐ Yes ☐ No homicidal? ☐ Yes ☐ No

#### Progress Note

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Stage: \_\_\_\_\_ Weeks in Stage: \_\_\_\_\_ Change to Treatment Recommended? ☐ YES ☐ NO

IF yes, schedule physician visit. Appointment Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Signature/Title: \_\_\_\_\_

**TIMA** Texas Implementation of Medication Algorithms  
**Inpatient Intake Form/Annual Update**

☐ Initial Visit ☐ 90-day review Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

**MHMR Physician Code:** \_\_\_\_\_ **Length of Contact:** \_\_\_\_\_

**SAMPLE**

**DO NOT USE**

**Age:** \_\_\_\_ **Gender:** ☐ Female ☐ Male **Ethnic or Racial Group** (please check only one response): ☐ White ☐ Hispanic ☐ African-American ☐ Asian or Pacific Islander ☐ American Indian or Alaskan Native ☐ Other

**Principal Diagnosis** (DSM-IV Axis I code): \_\_\_\_ . \_\_\_\_

**Age at Onset:** \_\_\_\_ **# of Episodes:** \_\_\_\_ **Onset of Current Episode:** \_\_\_\_\_

**Other current diagnoses not including principal diagnosis:**

**Axis I:** \_\_\_\_ . \_\_\_\_ **Axis II:** \_\_\_\_\_

**Alcohol/Substance Problem** (within last 6 months): ☐ Yes ☐ No (If yes, specify substance): \_\_\_\_\_

**Axis III** (Current General medical conditions, check all that apply):

- ☐ Hypertension ☐ Hypothyroidism ☐ Head Injury ☐ HIV  
☐ CHF ☐ Diabetes ☐ Seizure Disorder ☐ Cancer  
☐ Heart Disease ☐ Endocrine (Other) ☐ Stroke ☐ Chronic Lung Disorder  
☐ Cardiac (Other) ☐ Asthma ☐ Neurological (Other)  
☐ Allergies (If yes, explain below) ☐ Other Significant Systemic Illness (specify): \_\_\_\_\_

**Additional Information:**

**Any family members with a history of any of the following** (please check all that apply):

	Depression	Schizophrenia	Bipolar	Substance Abuse	Suicide	Other	Effective Treatments
Parent							
Sibling							
Children							
Aunt/Uncle							
Grandparent							

**Number of Psychiatric Hospitalizations** (best estimate): Past Year: \_\_\_\_ Past 5 Years: \_\_\_\_ Lifetime: \_\_\_\_

**Past and Current Psychoactive Medications** (Patient Self-Report/Records): Please provide medications for the past two years, record the highest dose given.

Medication	Taken for this episode?	Dose	Freq.	Start/Stop (Mo/Yr)	Response	Well Tolerated
1.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
3.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
5.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
6.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
7.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No
8.	<input type="checkbox"/> Yes <input type="checkbox"/> No				<input type="checkbox"/> Full <input type="checkbox"/> Partial <input type="checkbox"/> Minimal <input type="checkbox"/> None	<input type="checkbox"/> Yes <input type="checkbox"/> No

Signature/ title

Date

# Clinical Inpatient Record Form

**SAMPLE**

**DO NOT USE**

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time: \_\_\_\_\_

TIMA Stage: \_\_\_\_\_ Weeks in this stage: \_\_\_\_\_ Physician Code: \_\_\_\_\_

Type of Review : ☐ Daily ☐ Weekly ☐ Monthly ☐ Quarterly ☐ Other

Patient seen and chart reviewed? ☐ Yes ☐ No Level of Service ☐ Low ☐ Medium ☐ High

Primary Current Dx : ☐ MDD-NP ☐ BPD-M ☐ BPD-D ☐ SCZ ☐ Other (specify): \_\_\_\_\_  
(check one) ☐ MDD-P ☐ BPD-MX ☐ SCZ-A (BP) ☐ SCZ-A \_\_\_\_\_

**Use for all physician's ratings below: (0-10) 0 = No symptoms 5 = moderate 10 = extreme**

Core Symptoms: \_\_\_\_ Mania \_\_\_\_ Depression \_\_\_\_ Positive Sx of Psychosis \_\_\_\_ Negative Sx of Psychosis

Other Symptoms: \_\_\_\_ Irritability \_\_\_\_ Mood Lability \_\_\_\_ Insomnia \_\_\_\_ Agitation \_\_\_\_ Anxiety  
\_\_\_\_ Appetite \_\_\_\_ Level of Interest \_\_\_\_ Energy Level Other: \_\_\_\_\_

## Psychotropic Medication Information

<u>Medication Name</u> Document any new or discontinued medications, or dosage changes of established medications.	<u>Dosing Information</u> Please provide information on titration, dose, dose frequency, duration the medication is to be taken, start and stop date (if applicable) and any other pertinent information describing this medication.	<u>Indication</u> (Check all that apply.) <sup>1</sup>
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE
<input type="checkbox"/> New <input type="checkbox"/> Change <input type="checkbox"/> D/C		<input type="checkbox"/> S <input type="checkbox"/> OS <input type="checkbox"/> SE

S=Meds Targeted at core syndrome. OS=Meds targeted at other symptoms. SE=Meds for side effects of S or OS<sup>1</sup>

**Change from medication algorithm recommended?** ☐ YES ☐ NO (If yes, check all that apply)

☐ Patient previously failed next step. ☐ Next step not acceptable to patient. ☐ Next step not available at this site.

☐ Next step not medically safe for this patient. ☐ No options left. ☐ Other \_\_\_\_\_

Reason for Antidepressant Choice: ☐ SE Profile ☐ Pattern of Associated Sx ☐ Past Response ☐ Other: \_\_\_\_\_

Reason for Antipsychotic Choice: ☐ SE Profile ☐ Pattern of Associated Sx ☐ Past Response ☐ Other: \_\_\_\_\_

Reason for Mood Stabilizer Choice: ☐ SE Profile ☐ Pattern of Associated Sx ☐ Past Response ☐ Other: \_\_\_\_\_

Reason for Augmentation Choice: ☐ SE Profile ☐ Pattern of Associated Sx ☐ Past Response ☐ Other: \_\_\_\_\_

**Patient Global Self Report (0-10) 0 = No symptoms 5 = moderate 10 = extreme**

Symptom Severity: \_\_\_\_\_ Side Effects: \_\_\_\_\_

## Clinical Rating Scales

MMSE\_\_\_\_ AIMS\_\_\_\_ POS SX:\_\_\_\_ NEG SX:\_\_\_\_ IDS-SR:\_\_\_\_ Altman:\_\_\_\_ OTHER\_\_\_\_\_

# TIMA Texas Implementation of Medication Algorithms

Are serum levels needed? ☐ Yes ☐ No

Labs WNL? ☐ Yes ☐ No If no, describe below.

<u>Medication Name</u>	<u>Date Drawn</u>	<u>Serum Level</u>

Pertinent Lab Data :

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Patient Education Completed? ☐ Yes ☐ No

## Progress Note

(☐ Check here if note was dictated. Date of dictation \_\_\_\_/\_\_\_\_/\_\_\_\_)

**Subjective** (Sleep, appetite, side effects, medication efficacy, other patient reports.)

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**SAMPLE**  
**DO NOT USE**

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**Objective** (Orientation, appearance, rapport, speech patterns, suicidal or homicidal ideations, psychosis thought content & process, mood, affect, insight, judgment, cognition, other observations)

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**Assessments** (Diagnosis, clinical progress, formulations, problems, prognosis, other appraisals.)

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**Plan** (Current direction for biopsychosocial treatment, discharge planning, placements, other needs.)

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**Inpatient Psychiatric Hospital Services continues to be medically necessary for :**

☐ Treatment which can reasonably be expected to improve the patient's condition and/or ☐ Diagnostic Study

**Physician Signature :** \_\_\_\_\_

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## ***Appendix C. Communications***

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### **Important Phone Numbers**

Trisha Suppes, M.D., Ph.D.

UT Southwestern Medical Center  
Department of Psychiatry  
5323 Harry Hines Blvd.  
Dallas, Texas, 75390-9070

Office number (214) 648-7480

Fax number (214) 648-7499

E-mail address: [patricia.supes@utsouthwestern.edu](mailto:patricia.supes@utsouthwestern.edu)

M. Lynn Crismon, Pharm. D.

Clinical Pharmacy Division  
UT College of Pharmacy  
200 W. University Ave. (PHR 5.110)  
Austin, TX 78712-9101

Office number (512) 232-2630

Fax Number (512) 471-3756

Pager number (512) 397-7102

TDMHMR number (512) 206-5068

TDMHMR fax (512) 206-4744

E-mail address: [crismonl@mail.utexas.edu](mailto:crismonl@mail.utexas.edu)

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## Appendix D. Medication Descriptions

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### **Medications Included in Algorithm for Mania/Hypomania**

(Please refer to the PDR, package inserts, or other sources for more complete information.)

#### **Lithium**

Startup and Dosing: The initial dosing strategy for acute phase treatment of mania is 900 mg/day and obtaining a lithium level after 5-7 days. The approximate target dose range and schedule is 900-2400 mg/day given b.i.d. or, if appropriate, given qd (up to 1200 mg in a single bedtime dose as tolerated). If available, the slow release formulations are often better tolerated and provide a more even serum level once daily dosing is stabilized.

Side Effects: Patients should be monitored closely for emergence of side effects during initiation of treatment. Common side effects include: thirst, polyuria, cognitive changes, tremor, weight gain, sedation, weakness, diarrhea, nausea (watch for dehydration leading to toxicity), abdominal pain, ECG changes, acne, psoriasis, hypothyroidism, and acute renal dysfunction. Lithium use during pregnancy has been associated with birth defects including Epstein's anomaly. A recent analysis of these data suggested that the risk of this malformation may be less than previously thought, but nonetheless the use of lithium in pregnant women should be avoided.

Baseline Labs: A general health screen should be completed prior to initiation of lithium therapy. This should include a chemistry panel, creatinine and creatinine clearance, complete blood count, thyroid function tests, a urine HCG if appropriate, and an ECG if the patient is greater than fifty years of age and/or has a history of cardiac disease.

After initiation of lithium therapy, patients should have a follow-up serum creatinine drawn, then another after reaching a therapeutic blood level. Follow-up ECGs should be performed as clinically indicated.

Monitoring and Blood Levels: During long-term lithium use, serum levels can be obtained every 3 months. Serum creatinine, BUN, and TSH should be drawn every 6 months or if signs of renal or thyroid toxicity appear. Serum lithium levels of 0.8 - 1.2 mEq/L generally provide a therapeutic response to episodes of acute mania. For maintenance phase treatment levels above, 0.6 mEq/L are recommended.

Drug Interactions: Central nervous system depressants, including alcohol, antidepressants, antipsychotics, and antihypertensive agents, may interact with lithium to produce sedation or confusional states. The following drug interactions may raise lithium levels: thiazide diuretics, nonsteroidal anti-inflammatory agents, and angiotensin-converting enzyme inhibitors. In addition, the following drug interactions may lower lithium levels: acetazolamide, theophylline, aminophylline, caffeine, and osmotic diuretics.

#### **Divalproex Sodium (enteric-coated valproic acid)**

Startup and Dosing: This medication is generally started at 250 mg/day x 2 days; 500 mg/day x 2 days; 750 mg/day until the next visit at which time a serum blood level should be drawn. The approximate target dose range is 750-2000 mg/day. For the treatment of acute mania, one can also load 20 mg/kg over 1-1½ days. However, this loading technique is generally reserved for hospitalized patients. In many cases, it is possible to give the entire dose in the evening - especially when the enteric coated form is used. This will help minimize daytime sedation.

**Side Effects:** Common side effects associated with divalproex include tremor, vomiting, heartburn, ataxia, sedation, diarrhea, nausea, weight gain, hair loss, and mild elevation of liver function tests. The sedation and tremor generally subside with chronic use and/or decreased dosage. Administration with food and the use of enteric coated preparations or H<sub>2</sub> antagonists, such as ranitidine, may help diminish gastrointestinal effects. Divalproex may also cause mild impairment of cognitive function. The most severe side effects include hepatitis, hepatic failure, pancreatitis, and drug rashes including erythema multiform. Should significant liver function abnormalities or symptoms of hepatitis occur, the drug should be discontinued and the patient carefully monitored.

**Baseline Labs:** A general health screen should be completed prior to initiation of divalproex including a chemistry panel, liver function tests, a CBC with platelets, and a human chorionic gonadatropin (HCG) test if appropriate. Divalproex should not be given to patients with known liver disease.

**Monitoring and Blood Levels:** Optimal blood levels appear to be in the range of 50-125 micrograms per milliliter, and blood levels may be obtained weekly until the patient is stable. Since blood levels are trough measurements, levels should be drawn 12 hours post-dose or immediately prior to taking the next dose. Many clinicians also obtain LFTs and a CBC at the same time blood levels are assessed (Hyman et al., pg. 126), and these should be repeated after beginning divalproex therapy. In asymptomatic patients receiving stable dosages, blood levels, LFTs, and a CBC may be obtained every 6 months.

**Drug Interactions:** Divalproex may have pharmacodynamic interactions with other psychotropic drugs, including carbamazepine, lithium, and antipsychotic drugs. In addition, divalproex produces pharmacokinetic interactions with many drugs. It will increase the levels of lamotrigine and may increase levels of tricyclic antidepressants and possibly selective serotonin reuptake inhibitors (SSRIs), phenytoin, phenobarbital, and other drugs. Divalproex may also change the effective levels of other protein bound drugs by competing for protein binding sites. Furthermore, divalproex combinations may be decreased by drugs, such as carbamazepine, that induce hepatic microsomal enzymes. Its concentrations can be increased by drugs, such as SSRIs, that inhibit hepatic microsomal enzymes. Thus blood levels of divalproex should be carefully monitored when used in combination with other medications.

### **Carbamazepine**

**Startup and Dosing:** For acute mania, dosages of 400-1200 mg/day are frequently used. Patients must be carefully observed after a therapeutic dose is established, because after several weeks carbamazepine may induce its own metabolism, requiring a dosage increase. The initial dosing strategy for acute phase treatment of mania is 200-400 mg/day, increasing by 200 mg/day q 2-4 days. Due to decreased toxic metabolite and drug interactions, oxcarbazepine is recommended if available.

**Side Effects:** Common side effects include dizziness, ataxia, rash, nystagmus, headache, sedation, dysarthria, diplopia, nausea and gastrointestinal upset, reversible mild leukopenia, and reversible mild increases in liver function tests. Less common dosage-related side effects include tremor, memory disturbance, confusional states, cardiac conduction delay, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Some idiosyncratic toxicities include lenticular opacities, hepatitis, and blood dyscrasias.

**Baseline Labs:** Prior to initiation of carbamazepine, the physician should order and evaluate the results of a general health screen including a chemistry panel, CBC, liver function tests, and human chorionic gonadatropin (HCG) test, if appropriate.

Monitoring and Blood Levels: Blood levels may be obtained weekly until the patient is stable. Collection of electrolytes, CBC, and platelets is recommended weekly or biweekly during initial titration. The therapeutic blood levels of carbamazepine in the treatment of mania is not known; however, blood levels of about 4-12 micrograms per milliliter appear to be effective in epilepsy. This has been debated, however, resulting in many clinicians refraining from using blood levels to titrate efficacy in bipolar disorder.

During maintenance therapy serum level should be obtained every 3-6 months, and a CBC and LFTs every 6 months.

Drug Interactions: Carbamazepine can induce the metabolism of many psychotropics including lamotrigine, divalproex, benzodiazepines, antipsychotics, and tricyclic antidepressants, and frequently prescribed non-psychotropics including doxycycline, phenytoin, corticosteroids, theophyllin, and coumadin. Carbamazepine can decrease the efficacy of oral contraceptives. Erythromycin, diltiazem, verapamil, cimetidine and divalproex and other medications have been reported to increase levels of carbamazepine or its epoxide metabolite potentially resulting in increased side effects. Phenobarbital, phenytoin, theophylline and tricyclic antidepressants are among the medications reported to potentially decrease carbamazepine levels. Because of concern about agranulocytosis the FDA currently does not recommend the concurrent use of clozapine and carbamazepine. The use of carbamazepine with monoamine oxidase inhibitors may increase risk of hypertensive crises and should be used with great caution.

### **Oxcarbazepine**

Startup and Dosing: Recommended daily dose is between 600-2100 mg/day, to a maximum 2400 mg/day, in a BID or TID dosing schedule. No autoinduction has been observed with oxcarbazepine. For patients with renal impairment, initial dosing should begin at one-half the usual starting dose, increased, if necessary, at a slow rate.

Side Effects: Clinically significant hyponatremia (sodium <125 mmol/L) can develop during oxcarbazepine use. Patients who have had hypersensitivity reactions to carbamazepine may have a similar reaction to oxcarbazepine. Common side effects include dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Baseline Labs: Prior to initiation of oxcarbazepine, the physician should order and evaluate the results of a general health screen including a chemistry panel, CBC, liver function tests, and human chorionic gonadotropin (HCG) test, if appropriate.

Monitoring and Blood Levels: Measurement of serum sodium levels should be considered for patients on oxcarbazepine. Routine blood serum levels are not necessary.

Drug Interactions: Oxcarbazepine may reduce the efficacy of hormonal contraceptives. Oxcarbazepine may lower the plasma concentrations of dihydropyridine calcium antagonists (e.g., felodipine and verapamil). It can inhibit CYP2C19 and induce CYP3A4/5. Protein binding is low (40%).

### **Risperidone**

Start-up and Dosing: In patients with schizophrenia, bid dosing beginning with 1 mg bid and increasing to a target dose of 2-4 mg bid over a period of several weeks is often used. The effective dosage in bipolar disorder is not known; however, clinical experience would suggest beginning at a low dose, 1-2 mg per day or less, and increasing as needed to control target



symptoms including psychosis. The maximum recommended dose is 16 mg daily. Half the usual dose should be used in persons with renal impairment.

Side Effects: Side effects include orthostatic hypotension, and extrapyramidal side effects at higher doses including possible tardive dyskinesia and somnolence.

Baseline Labs: Baseline liver function tests and renal function should be assessed, since risperidone is hepatically metabolized and has active metabolites that are renally eliminated.

Monitoring and Blood Levels: None.

Drug Interactions: This medication is metabolized by the P4502D6 system. Therefore, concurrent use of medication that inhibits this system, which includes selective serotonin reuptake inhibitors, may increase plasma levels of risperidone and thus, increase side effects.

### **Olanzapine**

Start-up and Dosing: The effective dose of this medication in bipolar disorder is 5-20 mg. A commonly prescribed dose for schizophrenia is 5-15 mg per day. The patient should generally be started at 2.5-5 mg daily and increased to control target symptoms including psychosis to a maximum dose of 20 mg daily.

Side Effects: The side effects of this medication include somnolence, weight gain, elevations in triglycerides and serum glucose, and extrapyramidal side effects including a possible risk of tardive dyskinesia.

Baseline Labs: Weight, blood glucose, and lipid panel.

Monitoring and Blood Levels: Weight, blood glucose, and lipid panel.

Drug Interactions: Elevated levels of olanzapine can result when the medication is used in conjunction with fluvoxamine. In addition, olanzapine interacts with carbamazepine that can cause up to a 50% increase in the clearance of olanzapine from the system.

### **Clozapine**

Start-up and Dosing: The effective dose of this medication in bipolar disorder is not known. A commonly prescribed starting dose is 25-50 mg per day. This is then increased in 25 mg increments no more frequently than every 2-3 days to control target symptoms including psychosis. Daily dosages of 100-400 mg per day are typical.

Side Effects: The most common side effects include somnolence, sedation, weight gain, hypersalivation, tachycardia, dizziness, constipation, weight gain, and nausea and vomiting. A less common but potential life threatening side effect is agranulocytosis, which has been reported in about 1-2% of patients receiving clozapine (Kaplan & Sadock, p. 934). An additional side effect is seizures which is a dose-dependent side effect reported in about 3-4% of patients receiving clozapine at daily dosages greater than 600 mg.

Baseline Labs: A general health screen that includes a complete blood count, LFTs, and an EKG is recommended.

Monitoring and Blood Levels: White blood count is to be obtained weekly during the first six months of clozapine therapy. If no change in white blood count is measured over the first six months, then white blood count monitoring can be reduced to every two weeks. The current guidelines recommend discontinuing the medication if the white blood count drops to less than 2000 mm<sup>3</sup> or if the granulocyte count drops to less than 1000 mm<sup>3</sup> (Kaplan & Sadock, p. 935).

The monitoring of blood levels is not currently a standard of practice with clozapine; however, some data suggest a trough level of at least 350 ug/ml may be effective.

Drug Interactions and Laboratory Interferences: Clozapine should not be given with other drugs that are associated with the risk of agranulocytosis. This includes carbamazepine, propylthiouracil, sulfonamides, and captopril. No laboratory interferences are known with clozapine. Since a large percentage of clozapine is metabolized via Cyt P450 1A2 and 3A3/3A4, fluvoxamine and nefazodone may inhibit its metabolism, raising the levels of clozapine.

### **Quetiapine**

Start-up and Dosing: The effective dose of this medication in bipolar disorder is not known. Commonly prescribed dosages for schizophrenia begin at 25 mg bid and increase by 25-50 mg per day to a target dose of 300 mg. In general, dosages of 300-700 mg appear to be effective in schizophrenia. Bipolar patients may respond to lower dosing.

Side Effects: Side effects include orthostatic hypotension, sedation, and limited weight gain. In some animal studies, this medication has been demonstrated to increase the risk of cataracts. Currently, the manufacturer recommends a baseline and follow-up eye exams.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: This medication is metabolized by the P4503A4 system; therefore, medications that inhibit this enzyme system, including fluvoxamine and nefazodone, may increase blood levels of quetiapine. Medications that enhance this metabolic system such as carbamazepine and phenytoin may decrease blood levels of this medication.

### **Ziprasidone**

Start-up and Dosing: The effective dose of this medication in bipolar disorder is not known. A commonly prescribed dose for schizophrenia begins at 20 mg bid taken with food and increasing to a target dose of 20-80 mg bid per day with a total maximum dose of 160 mg per day.

Side Effects: The side effects of this medication include somnolence, extrapyramidal effects, nausea, insomnia, akathisia, dyspepsia, dizziness, and constipation.

Baseline Labs: None needed unless a patient is at risk for significant electrolyte disturbances, hypokalemia in particular. Such patients should have baseline serum potassium and magnesium measurements. An ECG is also recommended.

Monitoring and Blood Levels: None.

Drug Interactions: This medication should not be used with drugs that prolong the QT interval, including quinidine, dofetilid, sotalol, thioridazine, moxifloxacin, and sparfloxacin. In addition, this drug has the potential to antagonize levo-dopa and other dopamine agonists and can enhance the effects of serotonin agonists. In addition, carbamazepine has been shown to decrease levels of ziprasidone.

### **Topiramate**

Start-up and Dosing: The effective dose of this medication in bipolar disorder is not known. Commonly prescribed dosages for epilepsy are 200-400 mg daily, with a maximum recommended dose of 1600 mg per day.

Side Effects: Side effects include somnolence, dizziness, ataxia, nistagmus, parasthesias, fatigue, anxiety, decreased appetite, weight loss, and tremor. An additional risk is kidney stones that were reported in 1.5% of patients receiving this medication. The concurrent use of carbonic anhydrase inhibitors such as acetazolamide or zonisamide appear to increase the risk of kidney stones. Patients are advised to drink adequate amounts of fluid to possibly decrease the risk of kidney stones.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: This medication can potentially decrease divalproex levels. Also, divalproex and carbamazepine appear to decrease topiramate levels; therefore, careful monitoring of divalproex and carbamazepine levels are useful when topiramate is prescribed.

**Medications Included in Algorithm for the Treatment of Depression in Bipolar Disorder**

(Please refer to the PDR, package inserts, or other sources for more complete information.)

**Lamotrigine**

Start-up and Dosing: The effective dose of this medication in bipolar depression is targeted at 200 mg. However, doses of 200-500 mg daily may be effective in the control of seizures. In general, this medication is started at 25 mg daily for the first two weeks and increased in 25 mg increments every two weeks thereafter. *If the bipolar patient is concurrently taking divalproex*, the medication should be started at 25 mg every other day and increased by 25 mg every two weeks. *If the bipolar patient is concurrently taking carbamazepine*, the dosage should be 50 mg per day for the first two weeks and then increased in 25-50 mg increments every two weeks thereafter. If divalproex is also being used, the dose should be 12.5 mg per day for two weeks, then increased to 25 mg for two weeks.

Side Effects: Common side effects include headache, nausea, dizziness, ataxia, somnolence, and rhinitis. These side effects can often be treated by slowing the rate of upper titration or decreasing the dose. An additional side effect is a rash that has been reported to occur in 3-4% of patients receiving lamotrigine and which in some cases can become severe and life threatening (<1%). If a drug rash develops, the current guidelines recommend immediately discontinuing the medication and having the rash evaluated by a dermatologist or internist. Rapid titration and the current use of divalproex appear to be risk factors for rash.

Baseline Labs: None.

Monitoring and Blood Levels: Blood levels are not currently recommended and no routine labs are currently recommended.

Drug Interactions: Divalproex inhibits the metabolism of lamotrigine; therefore, care should be used when these medications are combined and lamotrigine should be increased slowly. Carbamazepine induces the metabolism of lamotrigine; therefore, higher dosages of lamotrigine are required when used concurrently with carbamazepine.

**Fluoxetine**

Start-up and Dosing: This medication is generally started at 20 mg in the morning and this is often the target dose. If dose increases are needed, they should not be done for at least 4 weeks, then the dose can be increased by 10-20 mg to a maximum dose of 80 mg q/day.

Common Side Effects: Common side effects include headache, nervousness, insomnia, somnolence, nausea, diarrhea, dry mouth, and weight loss (Kaplan & Sadock, p. 978).

Baseline Labs: None.

Monitoring and Blood Levels: Blood levels are not currently obtained on a regular basis with this medication.

Drug Interactions: This medication inhibits the P450 enzyme system and will result in increased concentrations of medications metabolized by this system, such as tricyclic antidepressants, antipsychotics, and carbamazepine. In addition, this medication should not be taken in combination with MAOIs or in a patient who has recently discontinued taking an MAOI.

**Paroxetine**

Start-up and Dosing: This medication is generally started at 20 mg usually taken in the morning. The target dose is often 20 mg per day; however, the dose can be increased up to 50 mg per day.

Side Effects: The side effects of this medication include nausea and vomiting, headaches, dry mouth, and sedation (Kaplan & Sadock, p. 979).

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: This medication has a number of drug interactions with medications inhibited by the P450 enzyme system, including tricyclic antidepressants, propranolol, and coumadin, causing increased plasma levels of these medications. Careful monitoring for side effects is advised when these medications are given together.

**Sertraline**

Start-up and Dosing: This medication is generally started at 50 mg in the morning and this is often the target dose. The medication can be increased in 50 mg increments to a maximum dose of 200 mg per day.

Side Effects: The side effects of this medication include nausea, vomiting, dry mouth, diarrhea, insomnia, and somnolence (Kaplan & Sadock, p. 939).

Baseline Labs: None.

Monitoring and Blood Levels: None

Drug Interactions: This medication inhibits the P450 enzyme system resulting in elevated plasma levels of drugs metabolized by that system such as the TCAs.

**Bupropion SR**

Start-up and Dosing: This medication is generally started at 150 mg in the morning. The target dose is generally 150 mg bid. The medication can be increased up to 200 mg bid.

Side Effects: Common side effects include constipation, headache, dizziness, and insomnia. Another potential side effect of this medication is seizures. This appears to be a dose-dependent side effect increasing to about 5% at dosages greater than 450 mg per day (Kaplan & Sadock, p. 919). The use of bupropion in persons with seizure disorders or eating disorders is not advised.

Baseline Labs: None

Monitoring and Blood Levels: None.

Drug Interactions: Bupropion should not be given along with monoamine oxidase inhibitors because of the possible increased risk of hypertensive crisis (Kaplan & Sadock, p. 919).

**Nefazodone**

Start-up and Dosing: This medication is generally started at 50 mg bid with the target dose of 300-600 mg per day. The maximum dose of this medication is 600 mg per day.

Side Effects: Common side effects with this medication include headache, dry mouth, nausea, constipation, and somnolence.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: Nefazodone inhibits the cytochrome P450 3A4 system and therefore can decrease the metabolism of other medications metabolized through this system including terfenadine, astemizole, or cisapride. These medications should not be given along with nefazodone. Nefazodone can increase plasma concentrations of drugs that are highly protein bound including monoamine oxidase inhibitors, haloperidol, lorazepam, triazolam, alprazolam, digoxin, and propranolol.

**Venlafaxine**

Start-up and Dosing: This medication is generally started at 37.5 mg bid. The target dose is generally 150-225 mg given daily in divided doses. The maximum daily dose for this medication is 375 mg per day.

Side Effects: Common side effects include decreased appetite, nausea, vomiting, anxiety, dizziness, insomnia, somnolence, sweating, and abnormalities of visual accommodation.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: Venlafaxine is contraindicated with the MAOIs. Do not begin treatment with venlafaxine until at least two weeks after discontinuation of an MAOI. MAOI treatment should not begin until at least seven days after discontinuation of venlafaxine.

**Fluvoxamine**

Start-up and Dosing: This medication is generally started at 50 mg per day. The target dose is 100-200 mg per day. The maximum daily dose is 300 mg per day.

Side Effects: Side effects include nausea, somnolence, insomnia, nervousness, and dizziness.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: Fluvoxamine inhibits certain P450 enzymes 1A2 and therefore increases the plasma levels of medications metabolized through these enzymes. These include terfenadine, astemizole, and cisapride. In addition, alprazolam and diazepam may also have their plasma levels increased with fluvoxamine. It is not recommended that fluvoxamine be used in combination with these medications.

**Citalopram**

Start-up and Dosing: This medication is generally started at 20 mg, usually taken in the morning. It can be increased in 10 mg increments to a target dose of 20-40 mg. Maximum daily dose is 60 mg; for adults older than 65, maximum daily dose is 40 mg.

Side Effects: Side effects include dizziness, headache, sleep disturbance, dry mouth, and/or nausea.

Baseline Labs: None.

Monitoring and Blood Levels: None.

Drug Interactions: This medication should not be used in combination with an MAOI. Citalopram is 80% protein-bound, and has a low potential for interactions with drugs metabolized by the CYP2D6 system or other CYP isoenzymes. It is less cardiotoxic than tricyclic and tetracyclic antidepressants.

**Monoamine Oxidase Inhibitors**

Phenelzine

Tranylcypromine

Start-up and Dosing: Two monoamine oxidase inhibitors are currently available in the United States, phenelzine and tranylcypromine. Phenelzine is generally started at 15 mg tid with a target dose of 60-90 mg per day. Tranylcypromine is generally started at 30 mg per day in divided doses with a target dose of 30-40 mg per day in divided doses.

Side Effects: Common side effects include orthostatic hypotension, weight gain, edema, sexual dysfunction and insomnia (Kaplan & Sadock, p. 974). A potentially life-threatening side effect is hypertensive crisis. This can be brought on by combining monoamine oxidase inhibitors with certain medications including meperidine, over-the-counter cold, hay fever, and sinus medications, and stimulants including amphetamines, cocaine, methylphenidate, dopamine, epinephrine, norepinephrine, isoproterenol (Kaplan & Sadock, p. 975). Hypertensive crisis can also be brought on by ingesting foods with a high tyramine content, including certain alcohol beverages (e.g., Chianti wine), fava beans, aged cheeses, and beef or chicken liver. All patients should be given information about tyramine rich foods and medications to be avoided before beginning monoamine oxidase inhibitors.

Baseline Labs: None.

Monitoring and Blood Levels: Blood levels are not routinely obtained for these medications.

Drug Interactions: See Side Effect section. These medications should not be administered along with serotonin selective reuptake inhibitors or stimulants.

## Appendix E. Drug Interactions

<b>Medication</b>	<b>Interacting Medicine</b>	<b>Effect</b>
<b>Lithium</b>	Benzodiazepines	Increased risk for CNS depressant effects (mild)
	Haloperidol	Altered mental status, extrapyramidal symptoms (rare)
	Clozapine	Few cases of seizure and diabetic ketoacidosis
	Divalproex sodium	Slightly increased concentrations of divalproex sodium
	MAOIs	Few reports of myoclonic jerks in patients
	Carbamazepine	Increased neurotoxicity of lithium
<b>Anticonvulsants</b>		
<b>Carbamazepine</b>	Divalproex sodium	Toxic levels of carbamazepine.; decreased levels of valproate
	Lamotrigine	Decreased levels
	Haloperidol & other antipsychotics	Decreased levels of haloperidol and other antipsychotics
	TCAs	Decreased levels of TCAs
	Benzodiazepines	Decreased levels of benzodiazepines
	Antiepileptics	Increased toxicity of carbamazepine
	Lithium	Increased neurotoxicity of lithium
	Clozapine	Increased risk for agranulocytosis
	Olanzapine	May get a 50% increase in the clearance of olanzapine
	Fluoxetine	Increased levels of carbamazepine
	Quetiapine	Decreased levels of quetiapine
<b>Divalproex Sodium</b>	Ziprasidone	Decreased levels of ziprasidone
	Topiramate	Decreased topiramate levels
	Phenobarbital	Increased levels of phenobarbital
	Phenytoin	Increased levels of phenytoin
	TCAs	Increased levels of TCAs
	Carbamazepine	Decreased levels of divalproex sodium
	Fluoxetine	Increased levels of divalproex sodium
	Topiramate	Decreased levels of divalproex sodium, Decreased levels of topiramate
	Lithium	Slightly increased levels of divalproex sodium
	Lamotrigine	Increased levels of lamotrigine



<b>Medication</b>	<b>Interacting Medicine</b>	<b>Effect</b>
<b><u>Atypical Antipsychotics</u></b>		
Clozapine	Carbamazepine	Potential increased risk for agranulocytosis
	Fluvoxamine	Increased levels of clozapine
	Nefazodone	Increased levels of clozapine
Olanzapine	Fluvoxamine	Increased levels of olanzapine
	Carbamazepine	May get a 50% increase in the clearance of olanzapine
	Fluvoxamine	Increased levels of quetiapine
Quetiapine	Nefazodone	Increased levels of quetiapine
	Carbamazepine	Decreased levels of quetiapine
	Phenytoin	Decreased levels of quetiapine
Risperidone	SSRIs	Enhanced side effects of risperidone
Ziprasidone	Carbamazepine	Decreased levels of ziprasidone
<b><u>SSRIs</u></b>		
Citalopram	MAOIs	Risk of serotonin syndrome – possibly death
Fluoxetine	TCAs	Increased levels of TCAs
	Haloperidol	Increased levels of haloperidol
	Benzodiazepines	Increased levels of benzodiazepines
	Carbamazepine	Increased levels of carbamazepine
	Divalproex Sodium	Increased levels of divalproex sodium
	Clozapine	Increased levels of clozapine
Fluvoxamine	Carbamazepine	Increased levels of carbamazepine
	TCAs	Increased levels of TCAs
	Imipramine	Increased levels of imipramine
	Clozapine	Increased levels of clozapine
	Olanzapine	Increased levels of olanzapine
	Quetiapine	Increased levels of quetiapine
Paroxetine	TCAs	Increased levels of TCAs
Sertraline	TCAs	Increased levels of TCAs

<b>Medication</b>	<b>Interacting Medicine</b>	<b>Effect</b>
<b>Bupropion SR</b>	MAOIs	Increased risk of hypertensive crisis
<b>Lamotrigine</b>	Divalproex Sodium	Increased levels of lamotrigine
	Carbamazepine	Decreased levels of lamotrigine
<b>Nefazodone</b>	Alprazolam, Triazolam, Lorazepam	Highly increased levels of these benzodiazepines
	MAOIs	Increased levels of MAOIs
	Haloperidol	Increased levels of haloperidol
	Clozapine	Increased levels of clozapine
	Quetiapine	Increased levels of quetiapine
<b>Venlafaxine XR</b>	MAOIs	Increased risk for neuroleptic malignant-like syndrome, hypertensive crisis, or a serotonin-like syndrome
<b>Topiramate</b>	Divalproex Sodium	Decreased levels of divalproex sodium; decreased levels of topiramate
	Carbamazepine	Decreased levels of topiramate
<b>Ziprasidone</b>	Carbamazepine	Decreased levels of ziprasidone

\*More detailed information about drug interactions can be obtained from the PDR or individual package inserts.