Appendix K:

Michigan Implementation of Medication Algorithms (MIMA)
Guidelines for Treating Bipolar Disorder
MIMA Physician Procedural Manual

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MIMA Physician Procedural Manual

2004

This manual is adapted from Trisha Suppes and Ellen B. Dennehy, *Texas Implementation of Medication Algorithms (TIMA) Procedural Manual, Bipolar Disorder Algorithms,* (Dallas, Texas: Bipolar Disorder Module Texas Medication Algorithm Project, August 27, 2002), available on the TIMA website: *http://www.mhmr.state.tx.us/centraloffice/medicaldirector/timasczman.pdf.*

Notice

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 MIMA

The Michigan Implementation of Medication Algorithms (MIMA) presented here are part of a broader action plan aimed at encouraging greater use of evidence-based practice (EBP) in mental health care in Michigan. As the name suggests, these medication algorithms for major depression, bipolar disorder, and schizophrenia were adapted from the Texas Implementation of Medication Algorithms (TIMA) project, implemented in that state over the past five years.

Funding for the Michigan EBP project was provided by the Ethel and James Flinn Foundation of Detroit, in partnership with Public Sector Consultants Inc. of Lansing. The project goal, simply stated, was to develop an action plan that would bridge the gap between what is known and what is done in psychiatry, between scientific evidence and actual practice.

Both the MIMA and the action plan of which the algorithms are a part were developed by the project Steering Committee, a diverse group of Michigan mental health experts with demonstrated expertise in EBP. Subcommittees of the Steering Committee reviewed various publicly available algorithms and guidelines and ultimately endorsed those used in Texas on the grounds that they were scientifically sound, had been field-tested and evaluated, were regularly updated, and were part of a broader disease management program.

The disease management component warrants special emphasis. The MIMA should not be viewed in isolation but as part of a program that includes clinical and technical support for physicians and patients, patient/family education, uniform documentation of patient outcomes, and a quality management program. The various components of this multifaceted program will be pilot-tested and evaluated in several Michigan locales over the next few years, with the results informing follow-up EBP programs in the future.

The Michigan EBP project, like other similar projects across the country, was devised in response to accumulating evidence that there is a significant gap between the state of knowledge and the treatment of patients in clinical practice. In many fields of medicine, psychiatry included, practice lags years behind research findings. Research also demonstrates that there are wide variations in practice even within a single state. It is therefore reasonable to conclude that the practices of at least some clinicians vary substantially from what is known to be effective.

Part of the problem is "information overload." It is impossible for any psychiatrist to keep up with all the developments in his or her field. Another aspect of the problem is the uncritical acceptance of information from sources such as friends and colleagues, flawed studies, or pharmaceutical companies.

EBP has been criticized as a cost-cutting approach that undermines the "art" of medicine. The express intent of the MIMA, however, is actually the reverse. The MIMA in no way trivialize the clinician's role, but rather formalize what has long been the ideal of practice: the use of science to inform the art of medicine. Clinical expertise continues to play an important role in the MIMA by allowing the clinician to rapidly integrate

research evidence and/or the practice judgments of the broader medical community in making decisions about patient care. Rather than being "cookbook medicine," the MIMA empower clinicians to make their own decisions about patient care, guided by the best available evidence to support those decisions.

Introduction to Algorithm Implementation

Algorithms go beyond guidelines in providing an explicit framework for clinical decision making. Algorithms do not dictate decisions, but rather provide an approach to clinical decision making that should yield similar answers in similar situations. The MIMA are not just general recommendations for medication treatment, they are also a systematic guide to the treatment of individual patients, which includes a number of critical factors: initial medication and dosage, dosage changes, methods and frequency of assessment, and minimum and maximum treatment periods.

Further, algorithms can be divided into *strategies* and *tactics*. Strategies are the various acceptable treatment regimen options for the care of an individual condition. Tactics address how optimally to implement a chosen regimen, and include such considerations as dose, monitoring, and how best to help an inadequately responding patient. Tactics also address the degree of symptom and functional improvement. As was the case with the TIMA, the MIMA presume that the aim of treatment is remission or the maximum possible improvement in cases where remission is not possible.

The MIMA approach is informed by the experience of Texas, which demonstrated that the successful implementation of algorithms is a human and social, as well as a technical, consideration. Assuring implementation of a treatment algorithm within a health care organization is a complex endeavor, requiring, in addition to research evidence, integrated changes in health care system design, patient and family education, and evaluation. Recommendations for just such a comprehensive, multifaceted approach are detailed in the Michigan EBP action plan.

Implementation of treatment algorithms is an evolutionary process, and change within systems does not occur without significant planning, goodwill, and effort. Yet the payoff in improved patient care is potentially enormous. Through an explicit process of algorithm implementation, evaluation, and revision, incremental improvements in many areas can result in major improvements in the overall quality of care.

At-a-Glance
Bipolar Disorder Medication Algorithms

Visit Frequency

While medications are being actively adjusted, patients should be seen every two weeks. As medications are stabilized and patients exhibit stable, positive response, visit intervals can be gradually lengthened to every four 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) may be completed at each visit.

Criteria for Medication Change

Medication changes are made after evaluation of tolerability, efficacy across multiple symptom domains, and safety. Clinicians consult Critical Decision Points (CDPs) and Tactics for the Treatment of Bipolar Disorder (see Exhibit 3, page 15) after review of symptom patterns and severity on the BDSS worksheet. 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. Physician can complete the BDSS and patient global self-rating of symptom severity and side effects.

Medication Doses

Recommended doses are provided in the Medications and Dosing section. **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 five days (five half-lives) after reaching the minimum target dose (see Exhibit 5, page 19) for lithium (Li) or divalproex sodium (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 (see Exhibits 1 and 2, pages 6–7).

EXHIBIT 1
Algorithm for the Treatment of Mania\Hypomania

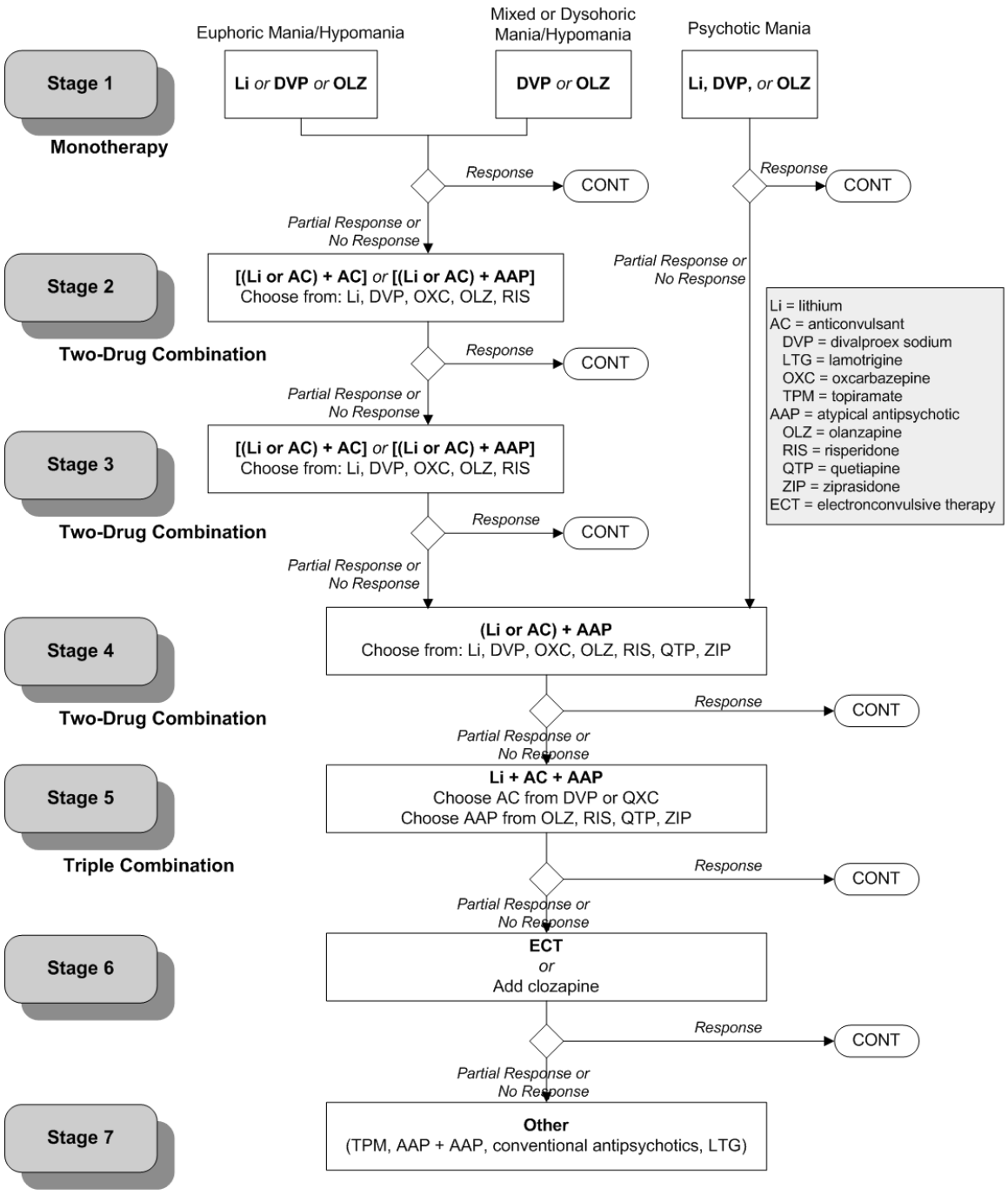
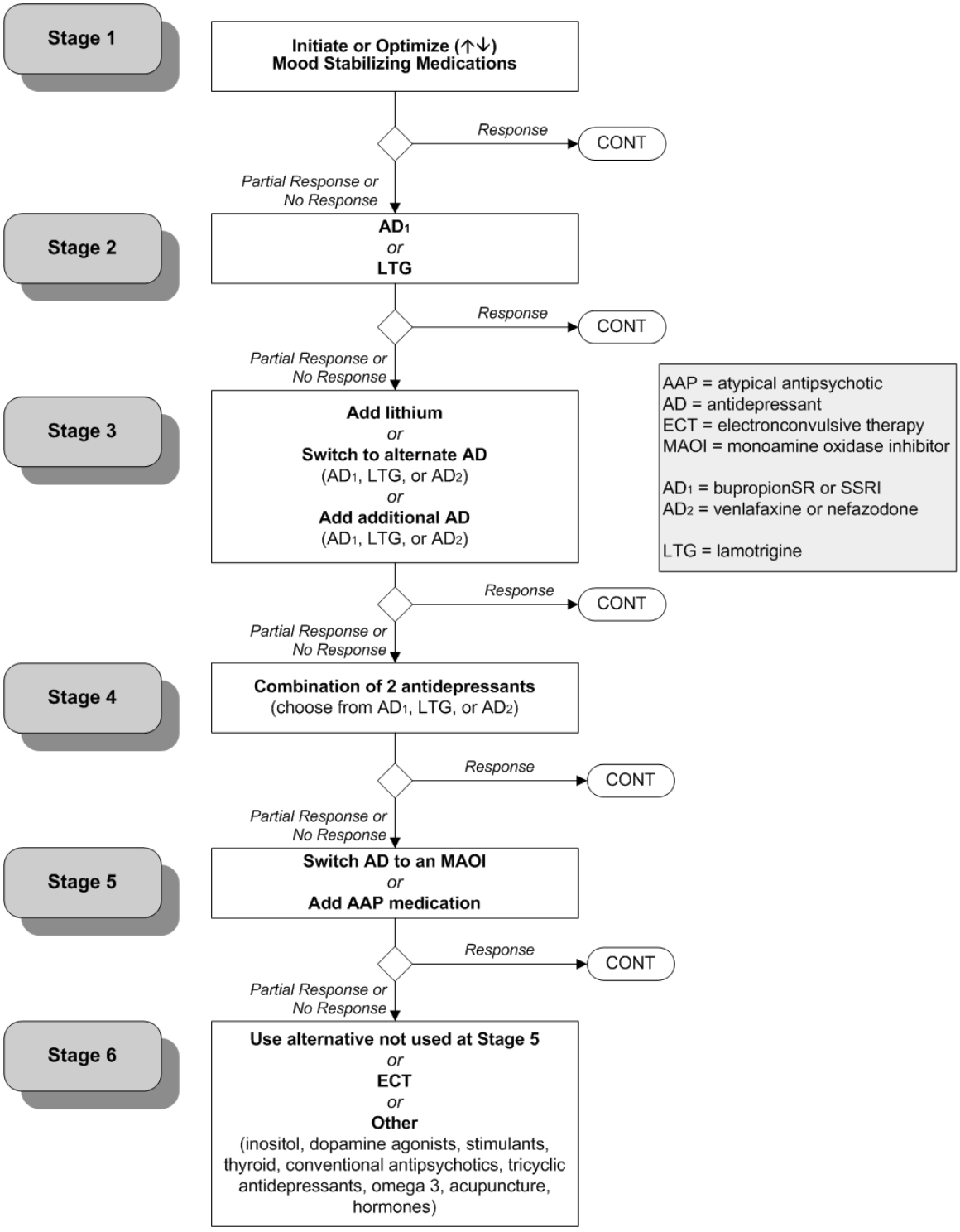


EXHIBIT 2

Algorithm for the Treatment of Depression in Bipolar Disorder*



*To be used in conjunction with primary treatment algorithm.

Description of Algorithm Stages[1]

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 (Li) or divalproex sodium (DVP) 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 two weeks after initiating lithium or divalproex sodium the patient be receiving the minimum target dose. If possible, we recommend a serum level five 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., four weeks), it is generally safe to gradually increase DVP and, more cautiously, Li if no side effects develop.

Target serum levels are provided in the Medications and Dosing section (see Exhibit 5, Summary of Recommended Doses of Medication Used for Acute Phase Treatment of Hypomania/Mania, page 19). 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 µg/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

[1]T. Suppes, E. B. Dennehy, A. C. Swann, C. Bowden, J .Calabrese, R. Hirschfeld, P. E. Keck, G. Sachs, M. L. Crismon, M. Toprac, and S. P. Shon. "Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000," *Journal of Clinical Psychiatry* (2002): 288–99.

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 and 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.

Stage 1

All the options for Stage 1 include monotherapy with lithium, divalproex, or olanzapine (see Exhibit 1, page 6). 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 or adverse events, increased tolerability, and less physician supervision required. Therefore, the combination is lithium or anticonvulsant (Li or AC) + AC, or (Li or AC) + AAP (atypical antipsychotic medication).

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 lithium or anticonvulsant (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 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

Electroconvulsive therapy (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 A).

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.

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" bipolar major depressive episode (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 (see Exhibit 2, page 7) 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 antimanic medications, using the algorithm for treatment of mania/hypomania. 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; the sustained release version of bupropion is recommended, 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 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 two 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 a monoamine oxidase inhibitor (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.

Critical Decision Points

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.

Exhibits 3 and 4 summarize the actions to be taken at each CDP.

EXHIBIT 3

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

CDP	Clinical status	Plan
Week 1 (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.

EXHIBIT 4
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 Bipolar Disorder Symptom Scale (BDSS).

CDP		Symptoms							
				Mild to moderate			Severe		
		NA	1	2	3	4	5	6	7
Week 1: 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 Medications, Dosage, and Side Effects Management section of this manual. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all CDPs.

CDPs 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. Clinicians may evaluate the pattern and severity of symptoms by reviewing the BDSS worksheet (see page 56). 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 antimanic 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 physician's office or be contacted by office 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 CDPs.

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.

CDP 1, Week 1

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.

In addition, 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 next 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 worksheet. The rating of side effect severity may be entered on the worksheet as well.

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 six 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.

EXHIBIT 5

Summary of Recommended Doses of Medications Used for Acute Phase Treatment of Mania/Hypomania*

Type/Class	Medication	Usual target dose	Usual maximum recommended dose (level)	Recommended administration schedule
	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.

EXHIBIT 6

Doses of Medications Used for Acute Phase Treatment of Bipolar Depression*

Type/Class	Medication	Usual target dose	Usual maximum recommended dose (level)	Recommended administration schedule
SSRIs	Citalopram	20–40 mg/day	60 mg/day	QD
	Fluoxetine	20 mg/day	80 mg/day	QD
	Fluvoxamine	150–250 mg/day	250 mg/day	QD
	Paroxetine	20 mg/day	60 mg/day	QD
	Sertraline	50 mg/day	200 mg/day	QD
Anticonvulsant	Lamotrigine	200** mg/day	600 mg/day	QD
Others	Bupropion $_{SR}$	300 mg/day	400 mg/day	BID (*200 mg maximum in each dose)*
	Nefazodone	300–600 mg/day	600 mg/day	QD
	Venlafaxine	150 mg/day	375 mg/day	BID or TID
	Venlafaxine XR	75 mg/day	225 mg/day	QD

*Doses used for maintenance treatment may be lower.
Please refer to Appendix A, Medications Descriptions, for instructions regarding initiation of this medication, due to risk of serious side effects associated ***with rapid titration*. For information on drug interactions, see Appendix C.

EXHIBIT 7
Side Effect Management and Recommendations*

Side effect	Recommendations*
GI Upset	—Administer medication with food and large quantities of liquid.
	—Consider lowering dose, if possible.
	—Use sustained release preparations of medications when available.
	—Some data suggest that this side effect can be successfully treated with H_2 blockers (e.g., cimetidine, ranitidine).
Tremor	**Enhanced physiologic tremor**—A fine tremor of approximately 8–10 Hz; made worse with outstretched hands.
	—Check blood levels of medication.
	—Decrease dose, divide dose, or change to slow release preparation of the medication.
	—Propranolol can be given at 20–30 mg TID.
	Parkinsonian tremor – Coarse tremor at rest of approximately 4–6 Hz.
	—Decrease dose, divide dosing, use QHS dosing, or switch to alternate medication.
	—Pharmacological treatments include benztropine 1–2 mg BID, amantadine 100 mg BID or TID, and diphenyhydramine 25–50 mg BID or TID.
Sedation	—Change dosing to QHS.
	—Substitute a less sedating alternative medication.
Extrapyramidal Symptoms (EPS)	—Usually seen with typical antipsychotics.
	—Treat tremor as suggested above.
	—Reduce dose of antipsychotic medication.
	—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.
	—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.
Tardive Dyskinesia	—Prescribe antipsychotics in the lowest dose necessary for the shortest time possible.
	—Consider alternatives for mood stabilization and control of agitation.
	—Use atypical antipsychotic medications.
	—Some evidence that vitamin E given in high doses (>1,000 units per day) may decrease some symptoms of tardive dyskinesia for some patients.
Insomnia	—Use QAM dosing, or divided dosing as early in the day as possible.
	—Use QHS dosing for any potentially sedating medications.
	—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.
Sexual Dysfunction	—Add yohimbine at 4–7.5 mg, TID, 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.

*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.

EXHIBIT 8

Common Side Effects for Medications in the Algorithm for Hypomania/Mania

Medication	Common side effects*
Lithium	Tremor, drowsiness, nausea/vomiting, polyuria, muscle weakness, thirst, dry mouth, cognitive impairment
Anticonvulsants	
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
Atypical Antipsychotics	
Clozapine	Sedation, anticholinergic effects, hypotension, weight gain, hypersalivation, constipation, nausea, 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.

EXHIBIT 9

Common Side Effects for Medications in the Algorithm for Treatment of Depression in Bipolar Disorder

Medication	Common side effects*
SSRIs Citalopram Fluoxetine Paroxetine Sertraline Fluvoxamine	Dizziness, dry mouth, insomnia, agitation, nausea, sexual dysfunction, headache
Bupropion $_{SR}$	Headache, agitation, weight loss, insomnia, nausea
Lamotrigine	Headache, nausea, dizziness, ataxia, somnolence, rhinitus, rash
Nefazodone	Dizziness, headache, nausea, somnolence, insomnia
Venlafaxine XR	Dizziness, somnolence, insomnia, decreased appetite, anxiety, headache, nausea, sexual dysfunction
MAOIs 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.

Overlap and Taper Guidelines

Considerable evidence in patients with bipolar disorder suggests 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 1200 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 (≥ 50 μg/mL). At this point, the lithium could then be tapered at 300 mg per one to two 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 hand, 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.

Continuation and Maintenance Guidelines

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 three months at the dose effective during the acute phase. Patients should be evaluated at least every three months during continuation treatment (if possible, every 1–2 months).

Importantly, once the patient is 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 percent per week and not before three 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 two

manic episodes, or one 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 six 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 three 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 percent 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 eight months of medication discontinuation; therefore, patients should be evaluated every two to four 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.

MODIFICATIONS FOR INPATIENT USE

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 CDPs are set at two-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 for inpatients. 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.

In addition, 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.

INPATIENT TO OUTPATIENT TRANSITION

The transition between inpatient and outpatient care is often unsuccessful. Most inpatient clinicians have dealt with the frustration of discharging a patient only to see him or her return to the hospital within a few weeks as a result of not receiving outpatient follow-up and/or not filling prescriptions. Managed care's insistence on brief stays further aggravates the problem by forcing clinicians to discharge patients before they are truly stabilized. By the same token, outpatient clinicians must constantly revise their treatment plans when their long-term treatment intentions are not followed by the inpatient physician. The following three strategies may improve transitions between the two treatment settings:

1. **Document the treatment plan.** It is imperative that all clinicians document the rationale behind treatment decisions and outline the expected treatment plan. This would include detailing expected changes in medications, such as "I expect Mr. Doe will discontinue use of Ambien for sleep once manic symptoms are controlled by increased dosing of olanzapine and divalproex into recommended therapeutic ranges." Inpatient clinicians may want to start notes to their outpatient colleagues with "transfer" rather than "discharge" (I am *transferring* the acute care of this patient…) because the former term implies a continuation of care while the latter suggests a termination.

2. **Ensure that patients leave the hospital with enough medication to see them through to the first follow-up appointment.** If administrative policies prevent adequate supplies of medication from being dispensed, these policies need to be challenged. The future availability of long-acting second generation antipsychotics may help resolve this problem.

3. **Establish communication between the inpatient and outpatient treatment teams.** Physicians working in both arenas should get to know each other and brainstorm about ways to improve coordination between the two settings. Two possible strategies for improving communication are (1) having a team member (on each side) whose job it is to coordinate and follow up on transfers and (2) organizing quarterly meetings with key inpatient and outpatient staff members.

Appendix A:
Medication Descriptions

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 BID 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 human chorionic gonadatropin urine test (HCG) if appropriate**,** and an electrocardiogram (ECG) if the patient is more than 50 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 three months. Serum creatinine, BUN, and TSH should be drawn every six 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_2 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 complete blood count (CBC) with platelets, and a 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 μg/mL, 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, 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 six 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 every 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 μg/mL 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 six months.

Drug Interactions

Carbamazepine can induce the metabolism of many psychotropics including lamotrigine, divalproex, benzodiazepines, antipsychotics, and tricyclic antidepressants, and frequently prescribed nonpsychotropics including doxycycline, phenytoin, corticosteroids, theophylline, 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, and 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 gonadatropin (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 percent).

Risperidone

Start-up and Dosing

The effective dosage in bipolar disorder is not known. 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. 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 per day. 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, which can cause up to a 50 percent 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 percent of patients receiving clozapine. An additional side effect is seizures, which is a dose-dependent side effect reported in about 3–4 percent 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^3 or if the granulocyte count drops to less than 1000 $mm.^3$ 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 µg/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, dofetilidine, 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. Carbamazepine has also 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, which were reported in 1.5 percent of patients receiving this medication. The concurrent use of carbonic anhydrase inhibitors such as acetazolimide 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 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 percent of patients receiving lamotrigine and which in some cases can become severe and life threatening (<1 percent). 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 four weeks, then the dose can be increased by 10–20 mg to a maximum dose of 80 mg per day.

Common Side Effects

Common side effects include headache, nervousness, insomnia, somnolence, nausea, diarrhea, dry mouth, and weight loss.

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.

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.

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 percent at dosages greater than 450 mg per. 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.

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. 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, and isoproproteronol. 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 Medications, Dosage, and Side Effects Management section. These medications should not be administered along with serotonin selective reuptake inhibitors or stimulants.

Appendix B:
Process Measures

Brief Bipolar Disorder Symptom Scale

Critical Decision Points and Tactics for the Treatment of Bipolar Disorder

BDSS/CDP Worksheet

Scoring Criteria for Overall Symptom and Side Effect Ratings

Patients with a diagnosis of Bipolar I disorder may 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.[2] The 10-item version assesses hostility, elevated mood, grandiosity, excitement, motor hyperactivity, depressed mood, anxiety, emotional withdrawal, blunted affect, and unusual thought content.

Physicians can use the worksheet (see page 60) 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.

[2]J. E. Overall and D. R. Gorham. "Introduction - the Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling." *Psychopharmacol Bulletin* 24 (1988): 97–99.

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 a household object 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 patients' statements about themselves, not their 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.

5vModerately 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:** Sadness, unhappiness, anhedonia, preoccupation with depressing topics (can't attend to TV, conversations due to depression), hopelessness, and 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? Have they 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 do you experience 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 unique 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/her), ideas of persecution (people may mistreat him/her). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in his/her or patient'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 nonproductive 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 appears preoccupied or smiles 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; appears 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 during 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 patient displays appropriate facial expressions and tone of voice that are within normal limits.

3—Mild
Emotional range overall is diminished; patient is 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):	Explain here if validity of assessment is questionable:
☐ Patient	☐ Symptoms possibly drug-induced
☐ Parents/Relatives	☐ Underreported due to lack of rapport
☐ Mental Health Professionals	☐ Underreported due to negative symptoms
☐ Chart	☐ Patient uncooperative
☐ Difficult to assess due to formal thought disorder	
Confidence in assessment:	Other: _____
☐ (Rate on a scale of 1–5, where 1=Not confident at all, and 5=Very confident.)	

CRITICAL DECISION POINTS 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.

		SYMPTOMS							
		Mild		Mild to moderate			Severe		
Critical decision point	**Clinical status**	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Week 1: 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.

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 (from1–7): _____

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								

		SYMPTOMS							
		Mild		Mild to moderate			Severe		
Critical decision points and tactics*		**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Week 1: CDP1	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 Medications, Dosing, and Side Effects Management section of this manual. Intolerable, unmanageable side effects may warrant changing to a different stage of treatment. Tolerability should be evaluated at all CDPs.

Appendix C:
*Drug Interactions**

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

Medication	Interacting medication	Effect
	Nefazodone	Increased levels of clozapine
Olanzapine	Carbamazepine	May get a 50% increase in the clearance of olanzapine
	Fluvoxamine	Increased levels of olanzapine and quetiapine
Quetiapine	Carbamazepine	Decreased levels of quetiapine
	Nefazodone	Increased levels of quetiapine
	Phenytoin	Decreased levels of quetiapine
Risperidone	SSRIs	Enhanced side effects of risperidone
Ziprasidone	Carbamazepine	Decreased levels of ziprasidone
SSRIs		
Citalopram	MAOIs	Risk of serotonin syndrome – possibly death
Fluoxetine	Benzodiazepines	Increased levels of benzodiazepines
	Carbamazepine	Increased levels of carbamazepine
	Clozapine	Increased levels of clozapine
	Divalproex Sodium	Increased levels of divalproex sodium
	Haloperidol	Increased levels of haloperidol
	TCAs	Increased levels of TCAs
Fluvoxamine	Carbamazepine	Increased levels of carbamazepine
	Clozapine	Increased levels of clozapine
	Imipramine	Increased levels of imipramine
	Olanzapine	Increased levels of olanzapine
	Quetiapine	Increased levels of quetiapine
	TCAs	Increased levels of TCAs
Paroxetine	TCAs	Increased levels of TCAs
Sertraline	TCAs	Increased levels of TCAs
Bupropion $_{SR}$	MAOIs	Increased risk of hypertensive crisis
Lamotrigine	Carbamazepine	Decreased levels of lamotrigine
	Divalproex Sodium	Increased levels of lamotrigine
Nefazodone	Alprazolam, Triazolam, Lorazepam	Highly increased levels of these benzodiazepines
	Clozapine	Increased levels of clozapine
	Haloperidol	Increased levels of haloperidol
	MAOIs	Increased levels of MAOIs
	Quetiapine	Increased levels of quetiapine
Venlafaxine XR	MAOIs	Increased risk for neuroleptic malignant-like syndrome, hypertensive crisis, or a serotonin-like syndrome
Topiramate	Carbamazepine	Decreased levels of topiramate
	Divalproex Sodium	Decreased levels of divalproex sodium and topiramate
Ziprasidone	Carbamazepine	Decreased levels of ziprasidone

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