TMAP PROCEDURAL MANUAL

Depression Module
Physician Algorithm Implementation Manual

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❖ *Overview of TMAP*

For patients with severe and persistent mental illnesses (SPMI), medication treatment guidelines, or algorithms, may bring uniformity of treatment, predictability of costs, and quality of care at overall lower health care and social costs. Treatment guidelines may also provide a benchmark against which to monitor care and to evaluate treatment programs.

The potential of these benefits has never been formally evaluated in SPMI patients. In fact, only recently have medication treatment guidelines been sufficiently developed, and accepted consensually, to allow evaluation of their benefits and costs. In addition, studies of medication efficacy have seldom aimed at comparing the benefits of several medication options given either initially, or given sequentially in treatment in the face of partial response or failure to respond. Studies defining paths through the medication maze that are most helpful for particular patient subgroups can add to our knowledge and improve treatment plans.

The Texas Medication Algorithm Project (TMAP) is designed to determine the clinical and economic value of the use of prespecified medication algorithms (ALGO) in combination with clinical support and a prespecified patient/family educational package (ED) in the pharmacologic management of patients with one of three major mental disorders: schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD) each compared with treatment-as-usual (TAU) in the public mental health sector. TMAP has evolved into a unique and productive public-academic partnership among the Department of Psychiatry at UT Southwestern Medical Center, the Texas Department of Mental Health and Mental Retardation (TDMHMR), the UT College of Pharmacy, the Texas Department of Criminal Justice, and the departments of psychiatry at four other Texas medical schools. Its major goal is to improve the quality of treatment to public sector patients, while, hopefully, containing the cost of services over a patient's lifetime involvement with the service system.

Background: In late 1995, TDMHMR decided to develop and implement pharmacotherapeutic algorithms for treatment of the three major disorders most commonly treated in the Texas public mental health system: schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD). This decision was greatly influenced by observations that significant variance existed in the manner in which these conditions were treated by physicians across the state. Additionally, changes in health care financing had dictated that methods be implemented to contain health care costs while retaining or improving the quality of care.

Managed care organizations in both the private and public mental health sectors are adopting, and in some cases mandating, the use of guidelines and algorithms in patient care. Since inadequate data currently exist to support the hypothesis that pharmacotherapeutic algorithms improve the outcomes of patients with severe mental

disorders, TDMHMR initiated an evaluation of the use of algorithms in treating patients in the Texas public mental health system (Phases 1 and 2 of TMAP).

TMAP is unique in several ways. The algorithms were developed for specific use in the public mental health sector. From the onset, their development included the input from providers in the public sector and from patients and families receiving treatment. An important benefit of this latter participation has been the development and adoption of educational materials that provide information to patients and families on the specific disorder causing their symptoms, on the medication sequence recommended by the algorithms, medication side effects, and methods that patients and families can use to manage symptoms and side effects.

Phase 1: The first algorithm developed, major depressive disorder, relied on the formal consensus conference method. A consensus panel convened that included national experts, Texas public mental health sector practitioners who were to implement the algorithm, patients, family members, and Phase 2 pilot site administrators.

Schizophrenia and bipolar algorithms were developed based upon the expert consensus guidelines from the Tri-University Project (Frances et al., 1996; Kahn et al., 1996). These guidelines relied on a modified RAND Corporation method where a questionnaire with a 9-point scale was used to elicit consensus from a large panel of experts on a variety of clinical questions.

TMAP held two conferences – one for bipolar and one for schizophrenic disorders – at which the Tri-University guideline authors presented their draft guidelines to an audience of TMAP participants including other academic experts, TDMHMR practitioners who had volunteered to implement one of these two algorithms, families, and patients. At the end of these conferences, the TMAP module co-directors for these two algorithms elicited feedback on the guidelines from the practitioners who were to implement the algorithms. This feedback led to modification of the Tri-University guidelines and translating them into algorithmic form. These bipolar and schizophrenia algorithms were then implemented in TMAP Phase 2.

Each algorithm is multi-staged. Each stage describes a treatment strategy. There are two algorithms for major depressive disorder — one for psychotic and one for nonpsychotic depression. The former has four stages or steps, while the latter has seven. The schizophrenia algorithm has four treatment stages, as well as a side effect algorithm and an algorithm for managing co-existing symptoms with adjunctive medications. For bipolar disorder, there is a seven-stage algorithm for the manic phase and a six-stage algorithm for the depressed phase.

Each algorithm includes the particular medication(s) or medication class(es) recommended at each stage (i.e., the strategies), as well as the relevant tactics (i.e., the preferred oral doses or serum concentration ranges, the time to remain at the dose, common side effects, and how to evaluate them). In the tactics, each algorithm focuses on key decision points regarding whether to continue the medication unchanged,

modify the dose, discontinue the medication and begin a new medication, or augment the first medication with a second medication. The algorithm tactics also recommend the frequency of visits required for proper evaluation.

The algorithms identify treatment strategies at each stage that are relatively equivalent in their expected efficacy and medical safety as determined by the scientific literature and/or expert clinical judgment. The earlier treatment stages in each algorithm tend to be simpler in implementation and the later stages more complicated and more demanding of patient adherence. The earlier stages tend to have fewer potential significant side effects than the later stages, which tend to have higher medical risk. The early stages are also based more upon scientific evidence while the later stages depend more on expert consensus. When multiple strategies at a given stage are equivalent (i.e., one alternative seems as valuable as another), these strategies are presented to clinicians and patients as options. The patient/family educational materials, by providing knowledge about symptoms and side effects, help patients collaborate with their physicians in making informed choices with respect to treatment options defined in the algorithms. It is hoped that such efforts will increase patients' adherence with the selected treatments.

Phase 2: Fifteen separate sites (7 inpatient and 8 outpatient) and 36 physicians participated in Phase 2. While the general rule was for each site to enroll patients in only one algorithm, three sites enrolled patients in multiple algorithms. At each site, for each algorithm, there were two participating physicians whose goal was to enroll 10 patients into the algorithm they had been assigned. Physicians were encouraged to enroll any patient for whom they were rather certain of the primary diagnosis for which the algorithm was intended and for whom they judged a change in the medication (not simply dose) was indicated to treat the primary syndrome (i.e., schizophrenia, bipolar, or major depressive disorder). Thus, patients beginning medication treatment and those already taking a medication that was not producing a satisfactory effect were eligible.

The methodology for Phase 2 was consistent with the primary objective of determining the feasibility of implementation. Patients entered the algorithm over a six-month open enrollment period, and were followed for up to four months of treatment with the algorithm.

Data collection instruments and procedures were developed and refined, as were project management and physician training processes.

Phase 2 enrollment closed April 7, 1997, with 235 enrolled. These patients were followed through August 7, 1997, after which final data analyses and publications were completed. Final adjustments in this Phase 3 protocol based on Phase 2 data analysis were completed by December 1, 1997.

Phase 3: Phase 3 will evaluate the clinical and economic impact of medication treatment algorithms for the three most common disorders treated in the public mental health sector: SCZ, BPD, and MDD, each compared with TAU in representative clinics

of the TDMHMR care system in 7 geographical sites across the state of Texas. (See Table 1 for a table showing all TMAP clinic sites and the different groups of study patients in each.) Subject entry will occur over a 9-month period, with follow-up of each patient occurring for at least one year after entry into either ALGO + ED or TAU cells. Research outcome evaluations will occur at baseline and every 3 months thereafter for all ALGO and TAU patient groups. These assessments will collect measures of symptoms, level of functioning, clinician and patient satisfaction, mental health and medical service utilization, and interim contacts with the civil or criminal justice systems and the welfare systems.

Patients must be at least 18 years old. Patients eligible to enter ALGO or TAU are those with the requisite clinical diagnosis (SCZ, BPD, or MDD) for whom their physicians and they decide that medication initiation or a change in medication (not simply dosage adjustment) is clinically indicated. We anticipate the enrollment of approximately 1,755 subjects into the study. Patients eligible to enter ALGO or TAU will have the study described to them by their physician or another clinical staff member. Patients who provide written informed consent will be enrolled in the study.

Data Collection: Clinical data will be gathered every 1-4 weeks for all patients enrolled in an algorithm (ALGO). A Medical Record Review will provide additional data by extracting information from the clinical record that will provide a gauge to the degree to which the physicians followed or approximated the recommendations in the ALGO. The Structured Clinical Interview for DSM-IV-Clinician Version will be conducted with patients who fail to respond to treatment to assess the accuracy of their diagnoses. Research outcome data will be gathered quarterly from all patients (ALGO and TAU). Utilization and cost data will also be gathered every 3 months on all subjects. All data will be sent to Dallas for data entry.

The activities and methods developed in each of the three phases of TMAP are illustrated in Table 2.

References

Frances A, Docherty JP, Kahn DA: The expert consensus guideline series, treatment of schizophrenia. J Clin Psychiatry 1996; 57 (suppl. 12B): 1-58.

Frances A, Docherty JP, Kahn DA: The expert consensus guideline series, treatment of bipolar disorder. J Clin Psychiatry 1996; 57 (suppl. 12A): 1-88.

Kahn DA, Carpenter D, Docherty JP, Frances A: The expert consensus guideline series: Treatment of bipolar disorder. J Clin Psychiatry 1996; 57 (suppl. 12A): 1-88.

Table 1.

TMAP Clinic Sites by Study Groups

	Algorithm + ED			TAU-ALGO			TAU-nonAlgo		
	MDD	SCZ	BPD	MDD	SCZ	BPD	MDD	SCZ	BPD
Tropical									
Edinburg			✓	✓	✓				
Brownsville							✓		✓
Harlingen	✓					✓			
El Paso									
East Valley		✓							
Central								✓	✓
Houston									
Ripley		✓		✓					
North West	✓					✓			
Midcity							✓	✓	✓
Bayshore	✓				✓				
Southeast			✓	✓					
Lubbock									
City		✓				✓			
San Antonio									
Zarzamora		✓				✓			
Commerce			✓		✓				
San Pedro							✓	✓	✓
Tri County									
Combined (Cleveland, Huntsville, Liberty							✓	✓	✓
Conroe	✓				✓				
Tyler									
Andrews			✓	✓					

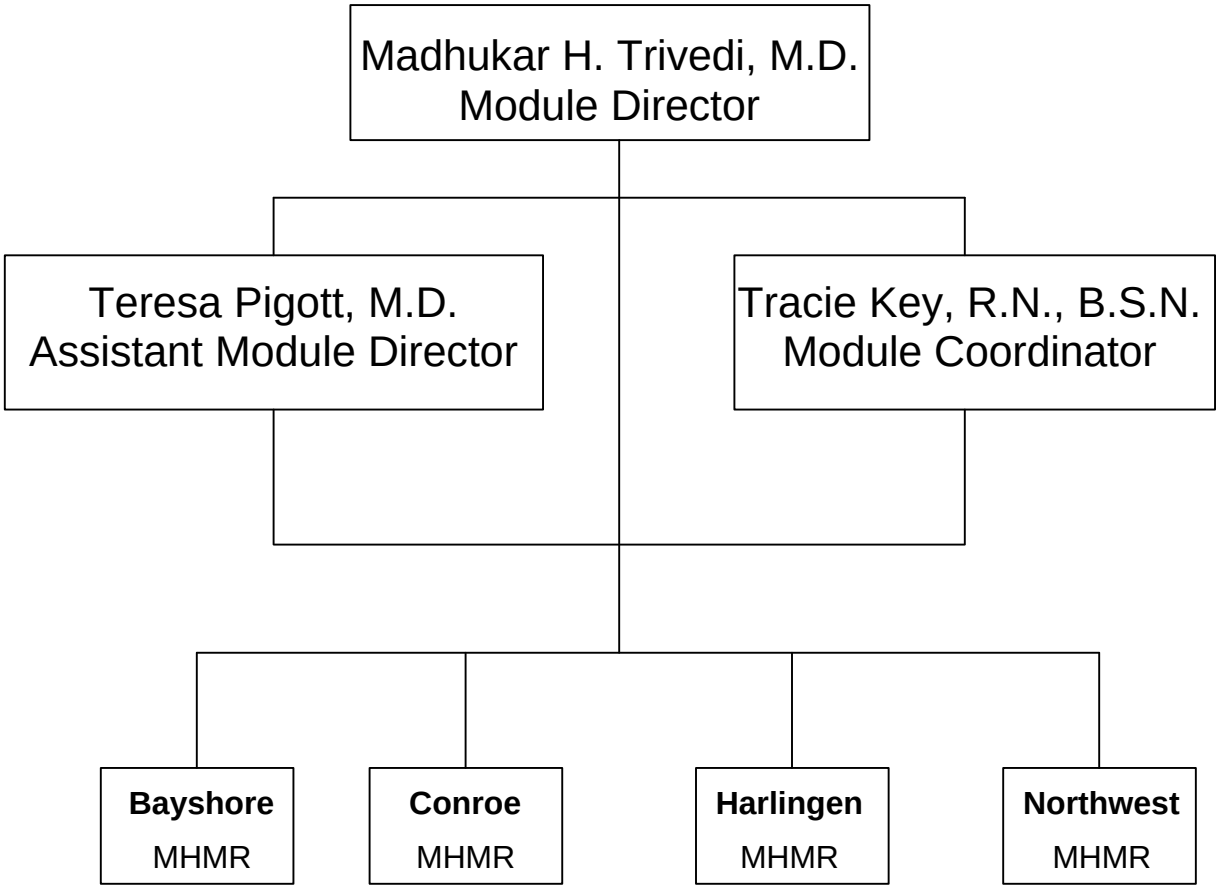
Table 2.
Three Phases of TMAP

Phase	Activity	Method
1	Develop the three medication algorithms.	– Develop TMAP's administrative structure. – Hold consensus conferences to develop algorithms. – Distribute draft algorithms to module co-directors for analysis and suggested revision. – Finalize algorithms for Phase 2 feasibility testing.
2	Evaluate the feasibility of using the algorithms in the TDMHMR system.	– 8 outpatient and 7 inpatient pilot sites enroll patients into an algorithm. – Two physicians at each site aim to enroll 10 patients into the algorithm they are using. – Identify preferred clinical instruments to implement the algorithms (e.g., symptom rating scales or global ratings). – Develop training program for practitioners on algorithms, medications, and instruments. – Develop mechanism for ongoing consultation. – Pilot test patient/family education materials.
3	Prospective, comparative evaluation of the clinical and economic impact of the treatment algorithms as compared to treatment as usual.	– Ensure algorithms are implemented by pretrial training, clinical prompting, chart audits, and clinical consultations. – Only outpatient clinics enter patients. (Once entered, patients remain in algorithm should they become inpatients.) – At least 8 physicians to implement each algorithm. – Enroll patients in each algorithm based upon power analyses. – Enrollment over 9 months. – At least 12-month follow-up for each patient. – Evaluate outcomes including symptom, level of functioning, clinician and patient satisfaction, service utilization, and cost.

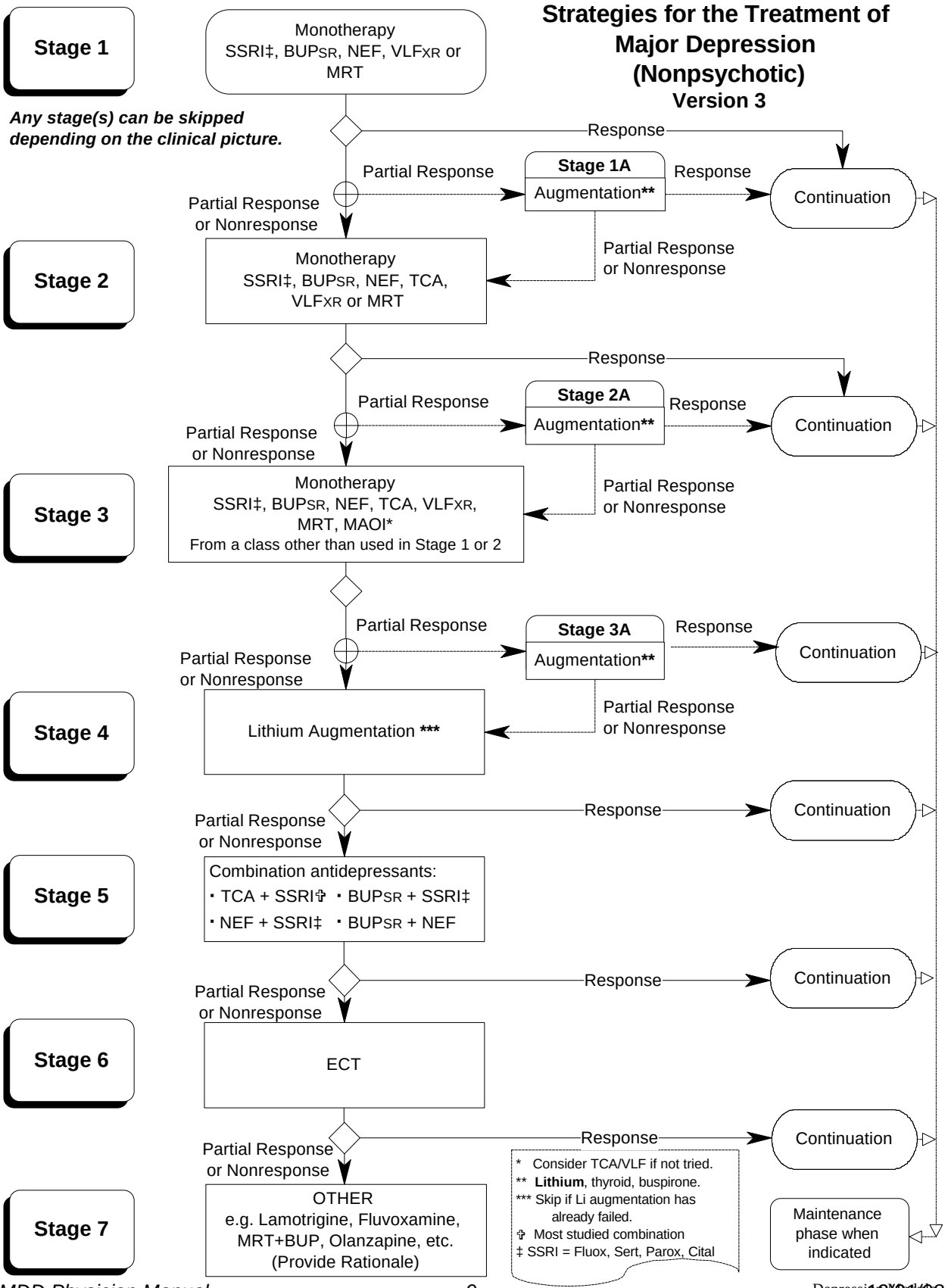
❖ *Administrative Structure — Depression Module*

Texas Medication Algorithm Project

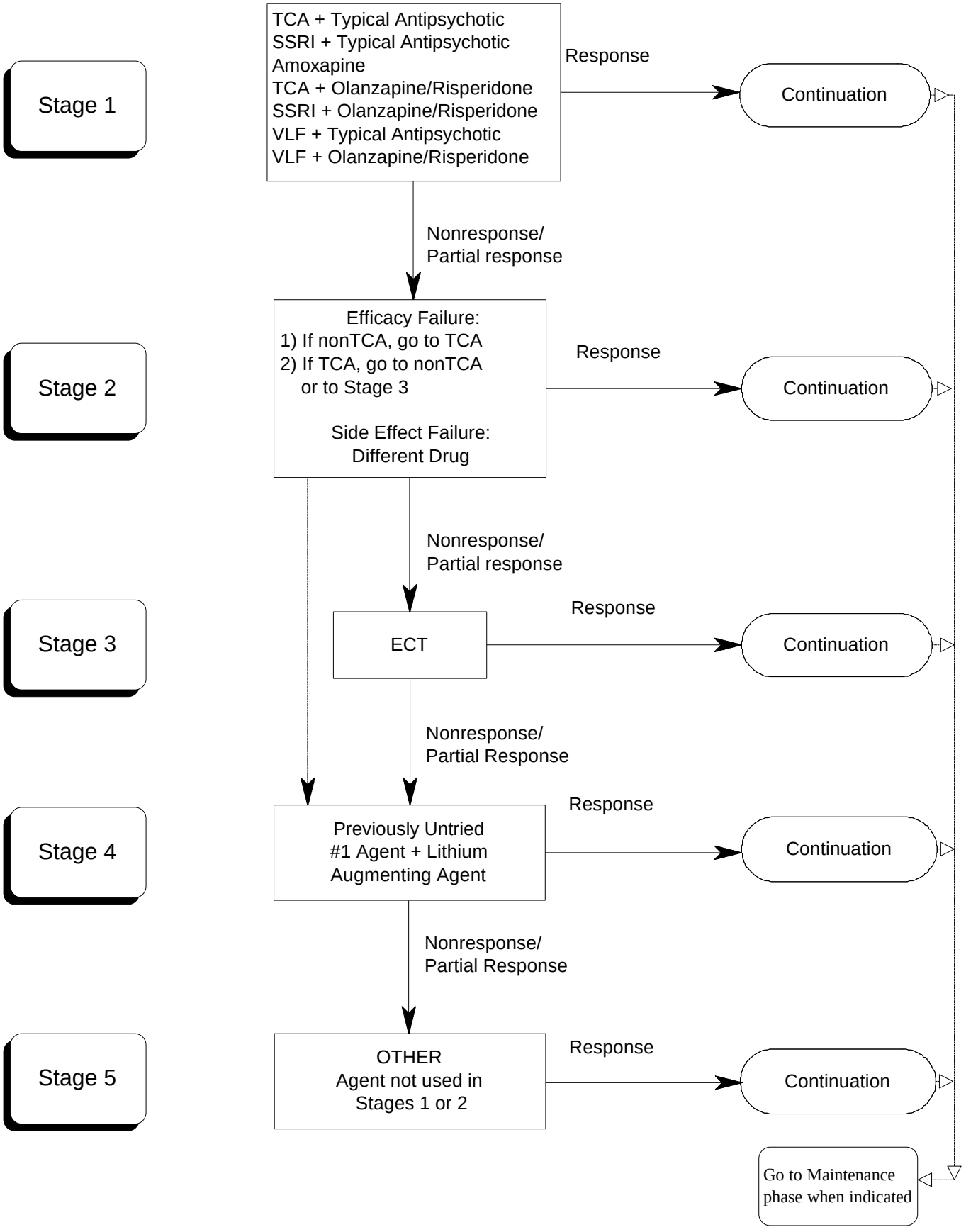
Depression Algorithm Structure



❖ *The Depression Algorithms*



Strategies for the Treatment of Major Depression (Psychotic)



Treatment Algorithms for Depression

At a Glance

At-a-Glance
Depression Medication Algorithm

Visit Frequency: Weekly for the first 4 weeks of each stage, then every 2 weeks until 75% improvement is maintained for 4 weeks.

Assessment Frequency: Done at each visit.

Duration of Acute Treatment: At least 75% for 4 weeks, then move to continuation phase. (See CDP Table)

Response:

Non-response	(<25% improvement)
Minimal response	(25-50% improvement)
Partial response	(50-75% improvement)
Full response	(75-100% improvement)

Criteria for Medication Change: Anything less than 75% improvement or full response may require a medication change.

Evaluations: At each visit an MD assessment of core symptom severity, overall functional impairment, side effect severity, other symptoms. CC assessment using inventory of depressive symptoms (clinician reported and self-reported) and the 4 items of the brief positive and negative symptom scales and patient global self-rating of symptom severity and side effects.

Medication Switching: Discontinue or taper according to table on page ( ) or guide on page ( ).

Medication Doses: See Tables 1 – 5 or information on medications pages ( ).

Table 1: Antidepressant Dosing Used for Acute Phase Treatment of Depression

Type/Class	Medication	Target Dose (Level)	Maximum Dose (Level)	Recommended administration schedule
SSRI	Fluoxetine	20	40-80	qAM
	Paroxetine	20-30	40-60	qAM
	Sertraline	50-100	150-200	qAM
	Citalopram	20	60	qD
TCA	Amitriptyline	150-200	300	qHS
	Clomipramine	100-150	250	qHS
	Desipramine	150 (>125ng/ml)	300 (>**?**200ng/ml)	qHS
	Imipramine	150 (IMI+DMI>200 ng/ml)	300 (200-400 ng/ml)	qHS
	Nortripytline	75-100 (50-150 ng/ml)	150 (50-150 ng/ml)	qHS
Others	Amoxapine	200-300	400	qHS
	Bupropion SR	200-300	400	bid $\leq$ 200 mg/dose
	Bupropion	225-300	450	bid-tid $\leq$ 150mg/dose
	Mirtazapine	30	45	qHS
	Nefazodone	200-400	600	bid
	Venlafaxine	150-225	375	bid-tid
	Venlafaxine XR	75-150	225	qD
MAOIs	Phenelzine	45-60	90-120	qd-tid
	Tranylcypromine	30-40	60-80	qd-tid

Table 2: Augmentation Dosing for Inadequate Response

Type/Class	Medication	Target Dose (Level)	Maximum Dose (Level)	Recommended administration schedule
Augmentation for inadequate response	Lithium	600-1200 (0.4-0.6 mEq/L)	1200-1800 (0.8-1.0 mEq/L)	bid
	T3	25-50 mg	50 micrograms	qAM
	Buspirone	5-30	45-60	bid-tid
	Amphetamine	5-30	60	qAM
	Methylphenidate	5-15	40-60	bid

Table 3: Antipsychotic Dosing for Treatment of Psychotic Depression

Type/Class	Medication	Target Dose (Level)	Maximum Dose (Level)	Recommended administration schedule
Atypicals	Olanzapine Risperidone	10-15 2-4	20 6-8	qHS bid
High potency	Haloperidol	5-10	15-20	qHS
Medium potency	Perphenazine	8-16	24	qHS

Table 4: Dosing of Medications for Treatment of Associated Symptoms of Depression

Associated Symptom	Options	Medication	Usual Dose range, mg/day	Schedule
Insomnia	Medium-acting BZD	Lorazepam (example only) Clonazepam	0.5-2 0.5-2.0	qHS; taper after a few weeks or as soon as possible
Anxiety or panic attacks	Short- or medium-acting BZD	Lorazepam (example only) Alprazolam Clonazepam	0.5-4 .75-4.0 1.5-3.0	q4-6h as needed throughout day
Anxiety, if BZD contraindicated	Serotonin 1A agonist	Buspirone (example only)	15-60	bid-tid
Severe agitation	BZDs	See above Propranolol	See above 10-30 gd	See above

Table 5: Dosing of Medications for Treatment Emergent Side Effects

Treatment Emergent Side Effect	Options	Medication	Usual Dose range, mg/day	Schedule
Insomnia due to antidepressant (esp. SSRI, BUP, VLF)	Medium-acting BZD	See above	See above	See above
	Small dose of sedating AD added to primary treatment	Trazodone AMI Mirtazapine	25-100 25-50 15	qHS qHS qHS
EPS from APs	Anticholinergic	Benztropine	2-4	qHS-bid

Note: BZDs are best avoided in patients with prior substance dependence or disorder or at risk for substance abuse (nonaddicting agents such as zolpidem, ambien, or buspirone may be preferred).

Table 6: Strategies for Acute Treatment Phase of Major Depressive Episodes

Stage	Psychotic Depression	Non-Psychotic Depression
Stage 1	♦ TCA[1] + AP[2] (A-B evidence)[3] ♦ SSRI + AP (B-C evidence) ♦ Amoxapine (B evidence) ♦ VLF + AP (C evidence)	♦ SSRI[4] ♦ Bupropion (BUP) ♦ Nefazodone (NEF) ♦ Venlafaxine (VLF)
Stage 2	Efficacy failure: ♦ If non-TCA used in stage 1, switch to TCA ♦ If TCA used, go to stage 3 Side-effect failure: switch classes, or consider staying with a class if contrasting side effect profile available: ♦ SSRI caused agitation: may try another starting at a very low dose ♦ TCA caused sedation or severe anticholinergic effects: If tertiary TCA (IMI, AMI), consider (secondary DMI, NT)	Efficacy failure: switch to another antidepressant ♦ If on SSRI, may consider another SSRI or different class ♦ If worsening severity since start of tx, consider TCA or VLF Side-effect failure: switch classes, or consider staying within class if contrasting side effect profile available or expected: ♦ SSRI caused agitation: may try another starting at a very low dose
Stage 3	♦ ECT	♦ Monotherapy with an antidepressant from a different class ♦ If atypical sx, consider a MAOI or SSRI ♦ TCA caused sedation or severe anticholinergic effects: If started with tertiary TCA (IMI, AMI), consider secondary (DMI, NT) or SSRI, BUP,VLF
Stage 4	♦ Previously untried level[1] treatment + lithium	♦ Previously untried level[1] treatment + lithium
Stage 5	♦ Other	♦ Antidepressant combinations (e.g., TCA + SSRI, SSRI + Wellbutrin, SSRI + Nefazodone
Stage 6	N/A	♦ ECT If patient refuses ECT or does not respond, go to next stage or repeat an earlier stage with different agent
Stage 7	N/A	♦ Other

[1] Acceptable TCAs for psychotic depression: amitriptyline (AMI), clomipramine (CMI), desipramine (DMI), imipramine (IMI), or nortriptyline (NT).

[2] Antipsychotic (AP): either a high potency antipsychotic (e.g., haloperidol) or medium potency antipsychotic (e.g., perphenazine) are recommended. See Table 3 for suggested dose ranges.

[3] Evidence level: A = controlled clinical trials; B = open trials and retrospective data analyses; C = clinical consensus and/or case reports.

[4] Acceptable antidepressants for stage 1: Discuss treatment options with the patient and depending on the prior treatment history, patient's clinical presentation, life style, and personal preferences, etc., assess the relative advantages of stage 1 medications and make an initial treatment selection. SSRIs FDA-approved for depression include: fluoxetine (Flu), paroxetine (Prx), and sertraline (Sert).

Table 7: Tactics for Acute Phase Treatment of Major Depression: Within each strategy stage, approaches to conducting a therapeutic trial with an antidepressant

Critical Decision Point	Clinical Status	Plan[1]
Week 0 (CDP # 1)	♦ Symptomatic	♦ Initiate medication; adjust dose to lower end of therapeutic dose range or serum level
Week 4 (CDP # 2)	♦ Full Response	♦ Continue current dosage
	♦ Partial Response[2]	♦ Continue current dosage ♦ Increase dose
	♦ Minimal or Non-Response	♦ Increase dose[3] ♦ Go to the next stage
Week 6 (CDP # 3)	♦ Full Response	♦ Go to continuation phase if full response sustained for at least two weeks. Otherwise, continue current dosage.
	♦ Partial Response	♦ Maximize dose ♦ Augment with lithium or alternative augmenting agent
	♦ Non-response or minimal response	♦ Augment with lithium or alternative augmenting agent ♦ Go to the next stage
Week 8 (CDP # 4)	♦ Full Response	♦ Go to continuation phase
	♦ Partial Response	♦ Augment with lithium or alternative augmenting agent ♦ Go to the next stage
	♦ Non-response or minimal response to lithium augmentation for 2-3 weeks	♦ Discontinue and go to the next stage
Week 10 (CDP # 5)	♦ Full Response)	♦ Go to continuation phase
	♦ Partial Response	♦ Adjust dose ♦ Go to the next stage
	♦ Non-response or minimal response	♦ Go to the next stage
Week 12 (CDP # 6)	♦ Full Response	♦ Go to continuation phase
	♦ Partial Response	♦ Go to the next stage

[1] For patients showing minimal or no response, total trial should not exceed 4-8 weeks. For patients with a partial response the trial may last up to 12 weeks to increase and dose and implement augmentation strategy.

[2] With partial response, the clinician and patient assess both the absolute degree of improvement and the rate of improvement. No or minimal improvement is <25% improvement in overall symptoms, partial response is 25-49% improvement in symptoms, and response is 50% or greater improvement.

[3] In patients with psychotic depression, dose increases may include the antidepressant, the antipsychotic, or both.

Table 8: Guidelines for Combining and Switching Between Antidepressant Medications

The following principles apply in determining the tactics of switching antidepressant medications depending on the reasons for switching and duration of exposure to the first agent.

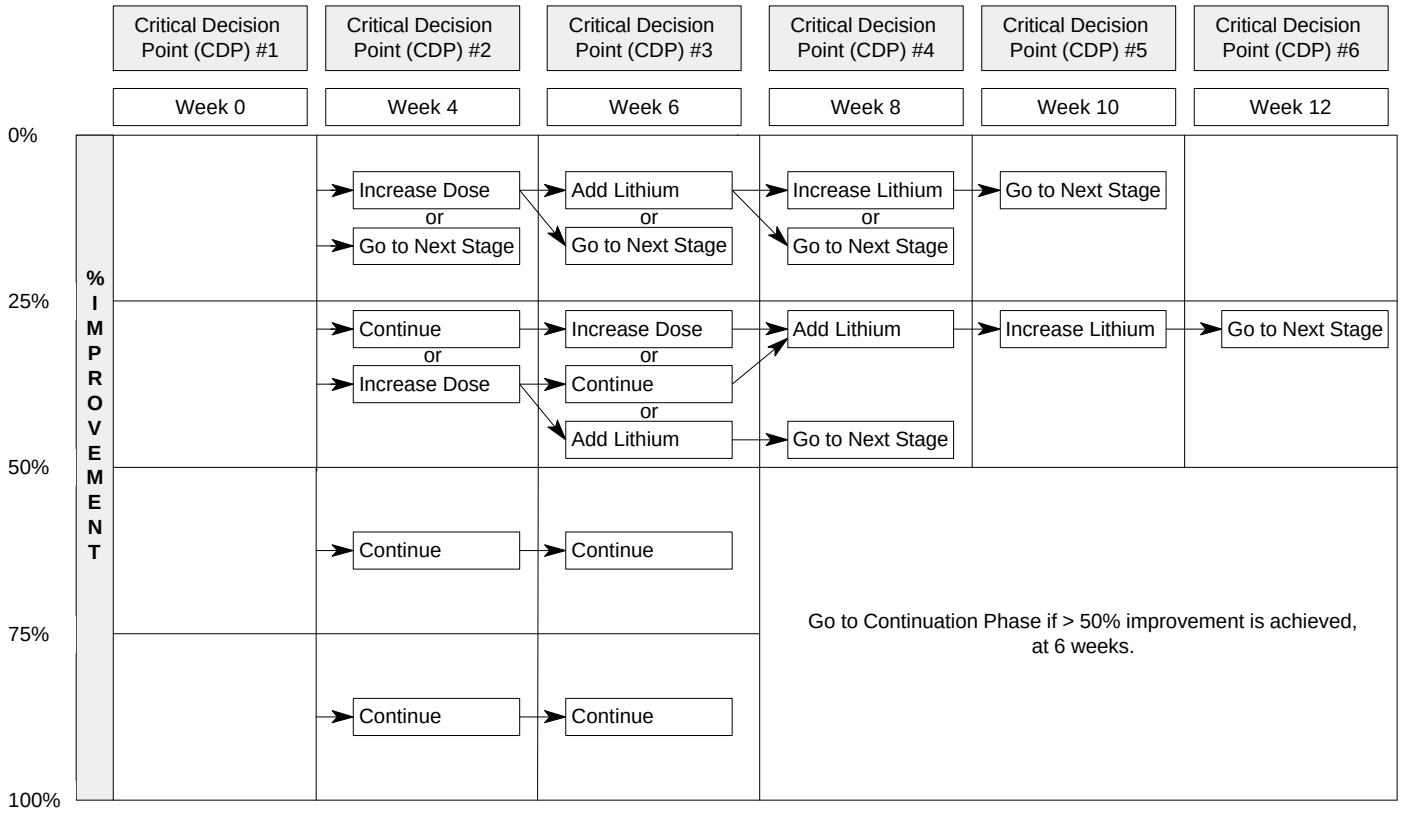
- If the first antidepressant is being discontinued due to intolerance following a brief exposure (< 5 days), the first drug can be stopped and the second drug started.
- If the first drug is being discontinued after a longer exposure (> 7 days), due to symptomatic breakthrough, or inadequate response, then the first drug should be tapered and the second drug started gradually (**notable exception being a switch from an MAOI**).

FROM	TO	PLAN
SSRI	SSRI	• Discontinue SSRI #1 and begin SSRI # 2 • Taper SSRI # 1 and initiate SSRI # 2
SSRI	TCA Bupropion	• Discontinue SSRI and begin TCA or bupropion • Taper SSRI and initiate TCA or bupropion gradually as tolerated to therapeutic dose range[1]
SSRI	Nefazodone Venlafaxine	• Discontinue SSRI and begin nefazodone or venlafaxine • Taper SSRI and initiate nefazodone or venlafaxine gradually as tolerated to therapeutic dose range
SSRI	MAOI	• **Discontinue SSRI. After a 5 week washout period for fluoxetine or a 2 week washout period for sertraline or paroxetine, MAOI therapy can safely be initiated.**
TCA Venlafaxine Nefazodone Bupropion	TCA	• Discontinue TCA # 1 (or venlafaxine, nefazodone, bupropion) by taper and then initiate TCA # 2 • Taper TCA # 1 (or venlafaxine, nefazodone, bupropion) while initiating TCA # 2 gradually as tolerated to therapeutic dose range.
TCA Venlafaxine Nefazodone Bupropion	SSRI	• Taper and discontinue TCA (or venlafaxine, nefazodone, bupropion) and then initiate SSRI • Taper TCA (or venlafaxine, nefazodone, bupropion) while initiating SSRI at a low dose
TCA Venlafaxine Nefazodone Bupropion	Nefazodone Venlafaxine Bupropion	• Discontinue TCA and initiate nefazodone, venlafaxine, or bupropion • Taper and discontinue TCA (or venlafaxine, nefazodone, bupropion) to initiate nefazodone, venlafaxine, or bupropion gradually as tolerated to therapeutic dose range
TCA	MAOI	• **Discontinue TCA. After a 2 week washout, MAOI therapy can be safely initiated.**
MAOI	MAOI	• **Discontinue MAOI # 1. After a 2 week washout, therapy with MAOI # 2 (or TCA, venlafaxine, nefazodone, or bupropion) can be safely initiated.**

[1] Both the TCAs and bupropion are associated with significant toxicity at elevated plasma concentrations. Since SSRIs increase the plasma concentrations of TCAs and bupropion, caution is indicated when co-administering these agents or when therapy with bupropion or a TCA is undertaken in close proximity to cessation of an SSRI.

Critical Decision Points for Major Depressive Disorder

Tactics for the Treatment of Major Depression (Nonpsychotic)



Non-Psychotic Algorithm Critical Decision Points

Stage 1, Week 0, Critical Decision Point (CDP) # 1

Trial of a Single Antidepressant Time Frame-4 weeks

Inclusion Criteria:

Patients entering Stage 1 of the algorithm should have a major depressive disorder of sufficient severity to merit medication treatment and a.) have not been on any antidepressant medication for the current episode of MDD **or** b.) have been tried on an inadequate duration or dose of antidepressant medication prior to evaluation.

Treatment Options:

Recommended medications are:

1. Selective Serotonin Reuptake Inhibitors (SSRIs) - fluoxetine, paroxetine, sertraline, citalopram
2. Bupropion, bupropion SR
3. Nefazodone
4. Venlafaxine or venlafaxine XR

****TCAs are not included in Stage 1 due to their relatively less favorable side effect profile, narrow safety margin and potential toxicity and risk of lethality in overdose.**

(See page for further information on side effects and dosing)

Treatment options should be discussed with the patient. Factors such as the patient's clinical presentation, life style, and personal preferences should be considered when a specific antidepressant is chosen.

Antidepressant Switching Tactics:

Because of the possibility of drug interactions, care should be taken when switching from one antidepressant to another. Please refer to page ( ) for guidelines concerning switching from one antidepressant to another.

Stage 1, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable

Non-Psychotic Algorithm Critical Decision Points (continued)

side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 1, Week 4, Critical Decision Point (CDP) # 2

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Gradually increase dose as tolerated for an additional 2 weeks***

2. If *symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Gradually increase dose as tolerated for an additional 2 weeks***

3. If *symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated for an additional 2 weeks***

4. If *symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***

5. If *symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Go to the next stage***

6. If *symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 1, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Strongly consider augmenting (see rules for augmenting on page)***
    - ***Go to the next stage***

Non-Psychotic Algorithm Critical Decision Points (continued)

2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***If dosage was not increased at Week 4, increase dosage***
    - ***If dosage was increased at Week 4, augment or continue with current treatment***

3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Increase dosage***
    - ***Consider augmentation***

4. If *symptoms have improved (75-100%), and side effects are acceptable*
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Continue current dosage and address side effects***
    - ***Decrease dosage and continue for 2 additional weeks***
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 1, Week 8, Critical Decision Point (CDP) # 4

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Increase augmentation***
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Augment if not done previously***
    - ***Go to the next stage***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase dosage***
    - ***Consider augmentation***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*
    - ***Go to the continuation phase***

Non-Psychotic Algorithm Critical Decision Points (continued)

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 1, Week 10, Critical Decision Point (CDP) # 5

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase augmentation***
    - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 1, Week 12, Critical Decision Point (CDP) # 6

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
   - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
   - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable:*
   - ***Go to the continuation phase***

5. If *symptoms have improved (25-50%) and side effects are not acceptable:*
   - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 2, Week 0, Critical Decision Point (CDP #1)

Trial of an alternative antidepressant Time Frame ( )

Inclusion Criteria:

Patients may enter the study having failed a trial of an antidepressant, either due to intolerance of side effects or lack of efficacy. These patients, by definition, must enter the algorithm at Stage 2 or later (e.g., if a patient has been taking Prozac and this medication was unsuccessful). If the patient's medication trial and failure was with a TCA, he/she would begin at Stage 3, as TCAs are first an option at Stage 2.

Stage 2 includes patients who did not improve clinically during Stage 1 due to: a) lack of full response; or b) inability to adequately tolerate side effects. Patients may enter the algorithm at Stage 2 if their previous history of response (previous positive response to TCA) or other factors (intolerance to previous Stage 1 antidepressants, etc.) suggest that Stage 1 is not appropriate.

Non-Psychotic Algorithm Critical Decision Points (continued)

Treatment Options:

- If the patient did not have a full response with an SSRI or did not receive an SSRI during Stage 1, consider either: a) an SSRI, b) a different SSRI, c) bupropion SR, d) nefazodone, e) venlafaxine XR, or f) mirtazapine.
- If the patient has prominent symptoms of atypical depression, consider an SSRI if not used during Stage 1 [level A evidence].
- If an SSRI was used during Stage 1, consider a tricyclic antidepressant (TCA). If a TCA is unlikely to be tolerated or is contraindicated, consider a different SSRI.
- If Stage 1 treatment was unsuccessful primarily because of intolerable side effects, consider selecting an antidepressant from a different class with a contrasting side effect profile

If treatment history or other factors (suicidality, etc.) indicate that adequate trial(s) with monotherapy as outlined in Stages 1 and 2 are unlikely to be of benefit or are not clinically indicated, skipping to more complex stages of treatment (3, 4, or 5) is recommended and encouraged.

Antidepressant Switching Tactics:

Because of the possibility of drug interactions, care should be taken when switching from one antidepressant to another. Please refer to page ( ) for guidelines concerning switching from one antidepressant to another.

Stage 2, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 2, Week 4, Critical Decision Point (CDP) # 2

1. If *symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Increase dosage***
    - ***Go to the next stage***

Non-Psychotic Algorithm Critical Decision Points (continued)

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase dosage***
    - ***Continue with current treatment***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Continue current dosage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Continue current dosage***

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Continue current dosage and address side effects***
    - ***Decrease dosage and continue***
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 2, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consider augmentation***
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***If dosage not increased at Week 4, increase dosage***
    - ***If dosage was increased at Week 4, augment or continue with current treatment***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Continue current dosage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Go to continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Continue current dosage and address side effects***
    - ***Decrease dosage and continue for 2 additional weeks***

Non-Psychotic Algorithm Critical Decision Points (continued)

- ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 2, Week 8, Critical Decision Point (CDP) # 4

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Increase augmentation***
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
   - ***Augment if not done previously***
   - ***Go to the next stage***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
   - ***Increase dosage***
   - ***Consider augmentation***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*
   - ***Go to continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
   - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 2, Week 10, Critical Decision Point (CDP) # 5

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase augmentation***
    - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 2, Week 12, Critical Decision Point (CDP) # 6

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***

Non-Psychotic Algorithm Critical Decision Points (continued)

5. If *symptoms have improved (25-50%) and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 3, Week 0, Critical Decision Point (CDP) #1

Trial of an Antidepressant from a Different Class Other Than Used in Stage 1 or 2

Inclusion Criteria

Stage 3 is for patients from Stage 2 who: a) did not have a full response, or b) were unable to tolerate side effects. Depending on a patient's current condition(s) or past treatment history, a patient may enter the algorithm at Stage 3.

Treatment options

1. Monotherapy with an antidepressant from a different class from those used in Stages 1 and 2. (e.g., classes include SSRI, TCA, MAOI, or bupropion, nefazodone, venlafaxine, or mirtazapine.
2. If the patient had worsening or severe, persistent depressive symptoms, consider either a TCA or venlafaxine. Some data suggest that TCAs [level B evidence] and perhaps venlafaxine [level B-C evidence] may be more effective antidepressants in severely depressed or treatment-resistant patients. The secondary amine TCAs (desipramine and nortriptyline) are generally preferred over the tertiary amines (e.g., amitriptyline, imipramine) due to relatively last side effects [level A evidence]. TCA dosage should be titrated as tolerated to achieve a steady-state serum concentration within the ranges specified in Table 3.

Antidepressant Switching Tactics:

Because of the possibility of drug interactions, care should be taken when switching from one antidepressant to another. Please refer to page ( ) for guidelines concerning switching from one antidepressant to another.

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 3, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 3, Week 4, Critical Decision Point (CDP) # 2

1. If *symptoms have improved (0-25%), and side effects are acceptable*:
   - ***Increase dosage***
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
   - ***Increase dosage***
   - ***Continue with current treatment***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
   - ***Continue current dosage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
   - ***Continue current dosage***

5. If *symptoms have improved and side effects are unacceptable:*
   - ***Continue current dosage and address side effects***
   - ***Decrease dosage and continue***
   - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic: 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 3, Week 6, Critical Decision Point (CDP) # 3

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Strongly consider augmenting (see rules for augmenting on page)***
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects acceptable:*
   - ***If dosage was not increased at Week 4, increase dosage***
   - ***If dosage was increased at Week 4, augment or continue with current treatment***

3. If *symptoms have moderately improved (50-75%), and side effects acceptable*:
   - ***Continue current dosage***

4. If *symptoms have robustly improved (75-100%), and side effects acceptable*:
   - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
   - ***Continue current dosage and address side effects***
   - ***Decrease dosage and continue for 2 additional weeks***
   - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 3, Week 8, Critical Decision Point (CDP) # 4

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Increase augmentation***
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
   - ***Augment if not done previously***
   - **Go to the next stage**

Non-Psychotic Algorithm Critical Decision Points (continued)

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase dosage***
    - ***Consider augmentation***
4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 3, Week 10, Critical Decision Point (CDP) # 5

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase augmentation***
    - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for one month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 3, Week 12, Critical Decision Point (CDP) # 6

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
   - ***Increase augmentation***

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
   - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable:*
   - ***Go to the continuation phase***

5. If *symptoms have improved (25-50%) and side effects are not acceptable:*
   - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 0, Critical Decision Point (CDP) # 1

Trial of Lithium Augmentation (if not already tried) (time frame 2-4 weeks)

Inclusion Criteria

Stage 4 includes patients from Stage 3 who: a) did not have a full response, or b) were unable to tolerate side effects. Patients may enter or skip to Stage 4 if their previous history or current condition suggests that Stage 4 is most clinically appropriate.

Treatment Options

1. If the patient did not have a full response to any of the monotherapies and particularly if lithium augmentation has not yet been attempted (1A, 2A or 3A), Stage 4 should be completed prior to beginning Stage 5.
2. At least one attempt at lithium augmentation should be initiated (unless contraindicated) before proceeding to combination antidepressant medication

Non-Psychotic Algorithm Critical Decision Points (continued)

therapy, because the evidence is stronger supporting the efficacy of lithium augmentation as compared to antidepressant combination (fluoxetine and desipramine).

If the patient fails an adequate trial of lithium augmentation (or is unable to tolerate lithium), alternative augmenting agents such as T3, buspirone, and methylphenidate should be strongly considered. Methylphenidate should not be used in conjunction with MAOIs. The serum level of the TCA must be monitored closely when methylphenidate augmentation is utilized.

For Stage 4, the new antidepressant and the augmenting agent should be initiated simultaneously.

Referral to an OB/GYN or Primary Care Physician to assess the new hormone follow-up replacement therapy should be considered in all peri- and post-menopausal women with major depressive disorder.

Antidepressant Switching Tactics:

Because of the possibility of drug interactions, care should be taken when switching from one antidepressant to another. Please refer to page ( ) for guidelines concerning switching from one antidepressant to another.

Stage 4, Weeks 1 – 3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 4, Week 4, Critical Decision Point (CDP) # 2

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Gradually increase antidepressant dose as tolerated and continue for an additional 2 weeks and increase the dose of lithium to serum levels of 0.8-1.2 mEq/L.***

******A gradual dose increase is critical for the Stage 4 antidepressants since response is enhanced by titration within a therapeutic dose range.***

***Non-Psychotic Algorithm Critical Decision Points* (continued)**

2. *If symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Gradually increase antidepressant dose as tolerated and continue for an additional 2 weeks and increase the dose of lithium to serum levels of 0.8-1.2 mEq/L.***

    ****** A gradual dose increase is critical for the Stage 4 antidepressants since response is enhanced by titration within a therapeutic dose range.***
3. *If symptoms have moderately improved (50-75%), and side effects are acceptable:*
    - ***Continue current dosage***
    - ***Gradually increase the dose(s) as tolerated***
4. *If symptoms have robustly improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***
5. *If symptoms have improved and side effects are unacceptable:*
    - ***Continue current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. Go back to CDP #1 if beginning a trial of a second medication.***
    - ***Go to next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 4, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Maximize the antidepressant dose and attain lithium serum levels of 0.8-1.2 mEq/L***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Maximize the antidepressant dose and attain lithium serum levels of 0.8-1.2 mEq/L***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Continue with current dosage(s)***
    - ***Gradually increase the antidepressant dose***

Non-Psychotic Algorithm Critical Decision Points (continued)

- ***If already at maximum dose of the antidepressant, increase the dose of lithium to serum levels of 0.8-1.2 mEq/L***

4. *If the symptoms have robustly improved (75-100%), and side effects are acceptable:*
   - ***Go to continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
   - ***Continue current dosage(s) and address side effects***
   - ***Decrease dosage(s) and continue***
   - ***Go to the next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
   - ***Increase lithium as above to maximal plasma concentration***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
   - ***Increase lithium as above to maximal plasma concentration***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
   - ***If patient is at maximal tolerable therapeutic dose, consider an alternative augmenting agent***
   - ***Continue with current dosage***
4. *If the symptoms have robustly improved (75-100%), and side effects are acceptable:*
   - ***Go to the continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
   - ***Continue with current dosage and address side effects***
   - ***Decrease dosage(s) and continue***
   - ***Switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***

Non-Psychotic Algorithm Critical Decision Points (continued)

- ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Increase lithium dose to optimal plasma concentration***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Increase lithium dose to optimal plasma concentration***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Maximize the antidepressant dose, increase dose to achieve a lithium steady-state serum concentration of 0.8-1.2 mEq/L or the maximal therapeutic dose for the selected augmentation strategy***
    - ***If the patient is receiving the maximal therapeutic lithium or alternative augmentation agent dose, go to the next stage***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***
5. *If the side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 5, Week 0, Critical Decision Point (CDP) # 1

Trial of Combination Antidepressants (time frame 4-8 weeks)

Inclusion Criteria

Stage 5 includes patients who did not have a full response during Stage 4 or who had intolerable side effects.

Treatment Options

Antidepressant combination therapy (TCA + SSRI) may be considered if patients have failed to respond in previous stages. If a TCA or SSRI is being used as monotherapy, consider a TCA/SSRI combination [level B evidence]. Both antidepressants should be initiated simultaneously. Since the SSRIs, particularly fluoxetine and paroxetine, may inhibit the metabolism of TCAs, close monitoring of TCA serum concentrations should occur during TCA/SSRI combination treatment [level A evidence]. Because of norfluoxetine's long elimination half-life, maximum effects of fluoxetine on elevation of the TCA serum concentrations may not be observed for 4-6 weeks. If a TCA is added to an SSRI, it will not take this long. Maximal enzyme inhibition will have already occurred and time to steady state is dependent on the particular TCA used. The goal is to obtain two serial levels that are essentially the same. Since evidence for the efficacy of other antidepressant combinations are derived entirely from case series, they are not recommended at this stage. A patient may actually go through Stage 5 twice, trying a primary and an alternative combination if necessary.

> In general, because of the potential for drug interactions, antidepressant combination treatment should be used carefully, and patients monitored closely. The goal of combination antidepressant regimens is to combine medications to theoretically enhance clinical response.

Considerable care is required to obviate potential drug interactions associated with combined regimens. Algorithm Appendix 3 found on page ( ) is provided as a guideline for the tactic of antidepressant combinations. Other treatment tactics included in Stage 5 are identical to those outlined in Stage 4.

Stage 5, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 5, Week 4, Critical Decision Point (CDP) # 2

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue with current dose***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Go to the next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 5, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***
    - ***Consider switching to an alternative combination. Return to CDP # 1.***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Go to the next stage***

Non-Psychotic Algorithm Critical Decision Points (continued)

- ***Consider switching to alternative combination. Return to CDP # 1.***

3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
    - ***Increase to maximum therapeutic dose and continue to monitor for an additional 2 weeks***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Go to the next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 5, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***

Non-Psychotic Algorithm Critical Decision Points (continued)

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Go to the next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 5, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Consult with the Module Director***
    - ***Go to the next stage***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***

Non-Psychotic Algorithm Critical Decision Points (continued)

- ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
- ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 5, Week 12, Critical Decision Point (CDP) #6

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Go to the next stage***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Go to the next stage***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Go to the next stage***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

A patient could make two attempts at Stage 5, but should consider ECT or Stage 7.

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 6, Week 0, Critical Decision Point (CDP) # 1

Trial of Electroconvulsive Therapy (ECT) Time Frame

Inclusion Criteria

Stage 6 includes patients who did not have a full response during Stage 4 or 5 or who were unable to tolerate side effects. Depending on a patient's current condition or past treatment history, a patient may initially enter the algorithm at Stage 6. For example, a severely depressed patient with significant risk of suicide should be considered for (initial entry at Stage 6) treatment with ECT.

Treatment Options

Stage 6 treatment is electroconvulsive therapy (ECT). If the patient refuses ECT, ECT is unavailable, or is contraindicated, go to Stage 7.

As cognitive side effects are generally less severe compared with bilateral ECT, treatment may begin with right unilateral ECT. However, before declaring a patient resistant to ECT, a course of bilateral ECT should be considered. The electrical dose of right unilateral ECT should be at least 2.5 times the initial seizure threshold, while bilateral ECT should be dosed no more than 1.5 times the initial threshold. ECT should be terminated when patients are in full remission or fail to sustain response over 1-2 treatments. With either ECT modality, at least 6-10 ECT treatments should be attempted before declaring a patient resistant to treatment. **(Note: Avoid ECT when the patient is taking lithium because CNS lithium toxicity may ensue.)**

Stage 7, Week 0, Critical Decision Point (CDP) # 1

Trial of Alternative Mood Stabilizers (Time Frame – 2 to 4 weeks at **therapeutic** dose)

Inclusion Criteria

Stage 7 includes patients who fail to fully respond during Stages 1-6 or who are unable to tolerate side effects.

Treatment Options

Stage 7 includes the alternatives not used previously during earlier Stages (e.g., lamotrigine or one of the newer antidepressants). It also includes other antidepressant combinations (not included in Stage 5) that are more speculative than those previously discussed in earlier stages. Alternative augmenting agents such as T3, buspirone, and methylphenidate are also included in Stage 7. At Stage 7, combinations of

Non-Psychotic Algorithm Critical Decision Points (continued)

antidepressants or antidepressants plus an alternative augmenting agent are preferable to a monotherapy not previously tried. **Even though Stage(s) can be skipped in the algorithm, Stage 7 is most likely to be indicated for those patients who have already failed to respond to multiple earlier stages in the algorithm.**

Antidepressant Switching Tactics:

Because of the possibility of drug interactions, care should be taken when switching from one antidepressant to another. Please refer to page ( ) for guidelines concerning switching from one antidepressant to another.

Stage 7, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 7, Week 4, Critical Decision Point (CDP) # 2

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue with current dose***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Consult with the Module Director***

Non-Psychotic Algorithm Critical Decision Points (continued)

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Consult with the Module Director***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 7, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consider switching to an alternative medication. If beginning a trial of an antidepressant, return to CDP # 1.***
    - ***Consult with the Module Director***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consider switching to an alternative medication. If beginning a trial of an antidepressant, return to CDP # 1.***
    - ***Consult with the Module Director***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated for an additional 2 weeks***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Consult with the Module Director***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Consult with the Module Director***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Algorithm Critical Decision Points (continued)

Stage 7, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consult with the Module Director***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consult with the Module Director***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***If patient is at maximum tolerable therapeutic dose, consult the Module Director***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Consult with the Module Director***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Consult with the Module Director***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 7, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consult with the Module Director***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consult with the Module Director***

Non-Psychotic Algorithm Critical Decision Points (continued)

3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***If patient is at maximum tolerable therapeutic dose, consult the Module Director***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Continue with current dosage and address side effects***
    - ***Decrease dosage(s) and continue***
    - ***Consider switching to an alternative medication. If beginning a trial of a second antidepressant, go back to CDP # 1***
    - ***Consult with the Module Director***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Consult with the Module Director***

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 7, Week 12, Critical Decision Point (CDP) # 6

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Consult with the Module Director***
2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***Consult with the Module Director***
3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Consult with the Module Director***
4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***
5. *If the symptoms have improved and side effects are unacceptable:*
    - ***Consult with the Module Director***
6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Consult with the Module Director***

Non-Psychotic Algorithm Critical Decision Points (continued)

Return to clinic:

If >50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

MDD Psychotic Algorithm Critical Decision Points

Stage 1, Week 0, Critical Decision Point (CDP) # 1

Inclusion Criteria

The patient entered into the algorithm at stage 1 is most likely either experiencing his/her first episode of major depression complicated by psychotic features or has previously responded to a Stage 1 regimen during a past episode.

Treatment Options

The options for Stage 1 are:

- A tricyclic antidepressant (TCA) [amitriptyline, clomipramine, desipramine, imipramine, or nortriptyline] plus an antipsychotic [level A evidence], or
- A Serotonin Selective Reuptake Inhibitor (SSRI) plus an antipsychotic or venlafaxine XR plus an antipsychotic, [level B evidence], or
- Amoxapine [level A evidence].

Stage 1, Weeks 1 – 3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 1, Week 4, Critical Decision Point (CDP) # 2

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
   - ***Gradually increase dose as tolerated for an additional 2 weeks***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
   - **Gradually increase dose as tolerated for an additional 2 weeks**

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
   - ***Continue current dosage***
   - ***Gradually increase dose as tolerated for an additional 2 weeks***

Psychotic Algorithm Critical Decision Points (continued)

4. If *symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***

5. If *symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Go to the next stage***

6. If *symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 1, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Strongly consider augmenting (see rules for augmenting on page)***
    - ***Go to the next stage***

2. *If symptoms have improved (25-50%), and side effects are acceptable:*
    - ***If dosage was not increased at Week 4, increase dosage***
    - ***If dosage was increased at Week 4, augment or continue with current treatment***

3. *If symptoms have improved (50-75%), and side effects are acceptable:*
    - ***Increase dosage***
    - ***Consider augmentation***

4. *If symptoms have improved (75-100%), and side effects are acceptable*
    - ***Go to the continuation phase***

5. *If symptoms have improved and side effects are unacceptable:*
    - ***Continue current dosage and address side effects***
    - ***Decrease dosage and continue for 2 additional weeks***
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Psychotic Algorithm Critical Decision Points (continued)

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 1, Week 8, Critical Decision Point (CDP) # 4

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Increase augmentation***
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Augment if not done previously***
    - **Go to the next stage**

2. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase dosage***
    - ***Consider augmentation***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are unacceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 1, Week 10, Critical Decision Point (CDP) # 5

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have minimally improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

Psychotic Algorithm Critical Decision Points (continued)

3. If *symptoms have moderately improved (50-75%), and side effects are acceptable*:
    - ***Increase augmentation***
    - ***Go to the next stage***

4. If *symptoms have robustly improved (75-100%), and side effects are acceptable*:
    - ***Go to the continuation phase***

5. If *symptoms have improved and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 1, Week 12, Critical Decision Point (CDP) # 6

1. If *symptoms have improved (0-25%), and side effects are acceptable:*
    - ***Go to the next stage***

2. If *symptoms have* minimally *improved (25-50%), and side effects are acceptable:*
    - ***Increase augmentation***

3. If *symptoms have* moderately *improved (50-75%), and side effects are acceptable*:
    - ***Go to the next stage***

4. If *symptoms have* robustly *improved (75-100%), and side effects are acceptable:*
    - ***Go to the continuation phase***

5. If *symptoms have* improved *(25-50%) and side effects are not acceptable:*
    - ***Go to the next stage***

6. *If the symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Psychotic Algorithm Critical Decision Points (continued)

Stage 2, Week 0, Critical Decision Point (CDP) #1

Trial of an alternative antidepressant plus an antipsychotic Time Frame ( )

Inclusion Criteria

Stage 2 includes patients who did not have a full response at Stage 1 or who were unable to tolerate side effects. Patients may enter the algorithm at Stage 2 if their history of response during previous depressive episodes suggests that Stage 1 is not appropriate. If the patient's clinical presentation dictates a need for more immediate clinical response (e.g., emergent suicidality) or if the patient has a history of previous response to ECT, entry at Stage 3 should be considered.

Treatment Options

1. Patient did not have full response at Stage 1.
    a) If the patient received a TCA during Stage 1 and did not respond, consider venlafaxine with an antipsychotic or proceed to Stage 3 (ECT).
    b) If an SSRI was the antidepressant used in Stage 1, consider a TCA with an antipsychotic.
    c) If amoxapine was the antidepressant used in Stage 1, consider a TCA with an antipsychotic.
2. If the patient did not respond during Stage 1 due to intolerable side effects, select an antidepressant from a different class from the previous choice and with a contrasting side effect profile (e.g., from a TCA to a SSRI). If a patient is unable to tolerate two different antidepressants from distinct chemical classes, consider proceeding to Stage
3. The tactics for drug treatment in Stage 2 are essentially the same as those outlined in Stage 1. Patients should be initiated with doses of antidepressants at the lower end of the therapeutic range and the dosage gradually increased as tolerated if response is not attained. Patients should be seen and monitored frequently during the initial month. At Week 4, if full response is absent, response and medication tolerability should be assessed. Further assessments at subsequent critical time points on a 2-week basis should be completed to assess for dosage increase as outlined in treatment tactics (See Table 2).

Stage 2, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms,

Psychotic Algorithm Critical Decision Points (continued)

functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 2, Week 4, Critical Decision Point (CDP) #2

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
   - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

2. *If symptoms have* improved *(25-50%), and side effects are acceptable*:
   - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

3. *If symptoms have* improved *(50-75%), and side effects are acceptable*:
   - ***Continue current dosage***
   - ***Gradually increase dose as tolerated to a maximal therapeutic range***

4. *If symptoms have* improved *(75-100%), and side effects are acceptable:*
   - ***Continue current dosage***

5. *If symptoms have* improved *and side effects are unacceptable*:
   - ***Continue current dosage and address side effects***
   - ***Decrease dose and continue for 2 additional weeks***
   - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
   - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 2, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
   - ***If the antidepressant dose was maximized at week 4, go to the next stage***
   - ***If the antidepressant dose was not maximized at week 4, increase the dose to the maximum therapeutic level (monitor serum concentration for TCAs)***

Psychotic Algorithm Critical Decision Points (continued)

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***If the antidepressant dose was maximized at week 4, go to the next stage***
    - ***If the antidepressant dose was not maximized at week 4, increase the dose to the maximum therapeutic level (monitor serum concentration for TCAs)***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated to a maximal therapeutic range***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 2, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Go to the next stage***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Go to the next stage***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue at maximal doses for 2 additional weeks***

4. *If symptoms have* improved *(75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

Psychotic Algorithm Critical Decision Points (continued)

5. *If symptoms have* improved *and side effects are unacceptable*:
    - ***Go to the next stage***

6. *If symptoms have not improved* and *side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 2, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Go to the next stage***

2. *If symptoms have* improved *(25-50%), and side effects are acceptable*:
    - ***Go to the next stage***

3. *If symptoms have improved (50-75%),* and *side effects are acceptable*:
    - ***Go to the next stage***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

5. *If symptoms have improved and side effects are* unacceptable:
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects* are *unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 3, Week 0, Critical Decision Point (CDP) # 1

Inclusion Criteria

Stage 3 includes patients who did not have a full response at Stage 2 or who were unable to tolerate side effects. Patients may enter the algorithm at Stage 3 if their current condition, associated features, or history of response during a previous

Psychotic Algorithm Critical Decision Points (continued)

depressive episode suggest that Stage 1 or 2 is not appropriate or is contraindicated. If the patient's clinical presentation warrants a more immediate clinical response (e.g., emergent suicidality) or history of previous response to ECT, entry at Stage 3 should be considered.

Treatment Options

- Stage 3 treatment is electroconvulsive therapy (ECT).

As cognitive side effects are generally less severe compared with bilateral ECT, treatment may begin with right unilateral ECT. However, before declaring a patient resistant to ECT, a course of bilateral ECT should be considered. The electrical dose of right unilateral ECT should be at least 2.5 times the initial seizure threshold, while bilateral ECT should be dosed no more than 1.5 times the initial threshold. ECT should be terminated when patients are in full remission or fail to sustain response over 1-2 treatments. With either ECT modality, at least 6-10 ECT treatments should be attempted before declaring a patient resistant to treatment. **(Note: Avoid ECT when the patient is taking lithium because CNS lithium toxicity may ensue.)**

- In general, any antidepressant or antipsychotic medication should be discontinued before initiating ECT.
- If a patient does not give informed consent for ECT, fails to respond to ECT, or ECT is not available, proceed ⇒ Stage 4.

Stage 4, Week 0, Critical Decision Point (CDP) # 1

Trial of an alternative antidepressant not previously tried plus augmentation

Inclusion Criteria

Stage 4 includes patients from Stage 3 who: a) did not have a full response, or b) were unable to tolerate side effects. Patients may enter or skip to Stage 4 if their previous history or current condition suggests that Stage 4 is most clinically appropriate.

If the patient did not have a full response to any of the combinations in Stages 1 or 2, Stage 4 should be completed prior to beginning Stage 5.

Treatment Options

At least one attempt at lithium augmentation should be initiated (unless contraindicated) before proceeding to Stage 5. Both the antidepressant and the augmenting agent should be started simultaneously.

Psychotic Algorithm Critical Decision Points (continued)

If the patient fails an adequate trial of lithium augmentation (or is unable to tolerate lithium), alternative augmenting agents such as T3, buspirone, and methylphenidate should be strongly considered. Methylphenidate should not be used in conjunction with MAOIs. The serum level of the TCA must be monitored closely when methylphenidate augmentation is utilized.

> If therapeutic serum levels are not available, consider an augmenting agent other than lithium or skipping Stage 4.

Stage 4, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Stage 4, Week 4, Critical Decision Point (CDP) #2

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
   - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

2. *If symptoms have* improved *(25-50%), and side effects are acceptable*:
   - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

3. *If symptoms have* improved *(50-75%), and side effects are acceptable*:
   - ***Continue current dosage***
   - ***Gradually increase dose as tolerated to a range of 0.4-0.8 mEq/L for lithium and to the therapeutic range appropriate to the antidepressant***

4. *If symptoms have* improved *(75-100%), and side effects are acceptable:*
   - ***Continue current dosage***

5. *If symptoms have improved and* side *effects are unacceptable*:
   - ***Continue current dosage and address side effects***
   - ***Decrease dose and continue for 2 additional weeks***
   - ***Go to the next stage***

Psychotic Algorithm Critical Decision Points (continued)

6. *If symptoms have not improved and* side *effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic: 2 weeks

Stage 4, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***If the antidepressant dose was already maximized at week 4, increase the lithium dose so that serum levels between 0.8-1.2 mEq/L are attained***
    - ***If the dose was not maximized at week 4 and the patient is currently tolerating the antidepressant, the dose should be increased to the usual maximum dose (monitor serum concentration for TCAs)***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***If the antidepressant dose was already maximized at week 4, increase the lithium dose so that serum levels between 0.8-1.2 mEq/L are attained***
    - ***If the dose was not maximized at week 4 and the patient is currently tolerating the antidepressant, the dose should be increased to the usual maximum dose (monitor serum concentration for TCAs)***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***If the antidepressant dose was maximized at week 4, continue current dosage for an additional 2 weeks***
    - ***Maximize the antidepressant dose within the therapeutic range and the lithium dose should be increased to 0.8-1.2 mEq/L for an additional 2 weeks***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Consider switching medications if side effects are attributable to a particular medication***
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Psychotic Algorithm Critical Decision Points (continued)

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Go to the next stage***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Go to the next stage***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue at maximal doses for 2 additional weeks***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Go to the next stage***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Go to the next stage***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Go to the next stage***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

Psychotic Algorithm Critical Decision Points (continued)

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 5, Week 0, Critical Decision Point (CDP) # 1

Trial of an agent not previously used in Stages 1 or 2

Inclusion Criteria

Stage 5 includes patients who fail to fully respond during Stages 1-4 or who are unable to tolerate side effects.

Treatment Options

Stage 5 includes the alternatives not used previously during earlier Stages (e.g., lamotrigine or one of the newer antidepressants). It also includes antidepressant combinations. Alternative augmenting agents such as T3, buspirone, and methylphenidate are also included in Stage 5. **Even though Stage(s) can be skipped in the algorithm, Stage 5 is most likely to be indicated for those patients who have already failed to respond to multiple earlier stages in the algorithm.**

Stage 5, Weeks 1-3

This week is for assessment of symptoms and tolerability only; no changes in dosage are required at this time. The study coordinator will evaluate depressive symptoms, functioning and side effects. If at this time the patient is experiencing unacceptable side effects, the study coordinator will report to the physician for any necessary intervention, i.e., dosage change, medication change.

Return to clinic: 1 week

Psychotic Algorithm Critical Decision Points (continued)

Stage 5, Week 4, Critical Decision Point (CDP) #2

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Increase antidepressant dose to a maximal therapeutic level and continue for two additional weeks***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue current dosage***
    - ***Gradually increase dose as tolerated to a maximal therapeutic range***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Consult module director***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Consult module director***

Return to clinic: 2 weeks

Stage 4, Week 6, Critical Decision Point (CDP) # 3

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***If the antidepressant dose was maximized at week 4, consult the module director***
    - ***If the dose was not maximized at week 4, increase the dose to the usual maximum dose (monitor serum concentration for TCAs)***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***If the antidepressant dose was maximized at week 4, consult the module director***
    - ***If the dose was not maximized at week 4, increase the dose to the usual maximum dose (monitor serum concentration for TCAs)***

Psychotic Algorithm Critical Decision Points (continued)

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***If the antidepressant dose was maximized at week 4, continue current dosage for an additional 2 weeks***
    - ***Maximize the antidepressant dose within the therapeutic range and continue for an additional 2 weeks***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Continue current dosage***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Consider switching medications if side effects are attributable to a particular medication***
    - ***Consult the module director***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Consult the module director***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 8, Critical Decision Point (CDP) # 4

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Consult the module director***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Consult the module director***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Continue at maximal doses for 2 additional weeks***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Continue current dosage and address side effects***
    - ***Decrease dose and continue for 2 additional weeks***
    - ***Consider switching medications if side effects are attributable to a particular medication***
    - ***Consult the module director***

Psychotic Algorithm Critical Decision Points (continued)

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Consult the module director***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Stage 4, Week 10, Critical Decision Point (CDP) # 5

1. *If symptoms have improved (0-25%), and side effects are acceptable*:
    - ***Go to the next stage***

2. *If symptoms have improved (25-50%), and side effects are acceptable*:
    - ***Go to the next stage***

3. *If symptoms have improved (50-75%), and side effects are acceptable*:
    - ***Go to the next stage***

4. *If symptoms have improved (75-100%), and side effects are acceptable:*
    - ***Go to continuation phase***

5. *If symptoms have improved and side effects are unacceptable*:
    - ***Go to the next stage***

6. *If symptoms have not improved and side effects are unacceptable:*
    - ***Go to the next stage***

Return to clinic:

If > 50% improvement for 1 month, return in 4 weeks, otherwise return in 2 weeks

Non-Psychotic Depression Algorithm Implementation

Introduction:

Study Rationale:

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

It is assumed that a comprehensive psychiatric evaluation, as well as a complete general medical history and relevant diagnostic tests are completed prior to entry into any treatment algorithm. Some patients may not be appropriate for entry into the algorithms. In addition, patients may enter the algorithms at different stages depending upon their specific clinical features and previous treatment histories. For example, patients may enter stage 2 or 3 if they have already failed to respond to an adequate trial of another antidepressant monotherapy.

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

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

General Medical Principles Guiding Algorithm Implementation:

1. The ultimate goals in the acute phase of treatment (0 -12 weeks) are achieving symptomatic remission and full return of psychosocial functioning. The prevention of relapse and recurrence are the essential goals of the continuation and maintenance phases of treatment.
2. The treatment options recommended at the various points in the algorithms are based upon available data from: (a) controlled clinical trials [level A evidence]; (b) open trials and retrospective data analyses [level B evidence]; and (c) case reports and clinical consensus [level C evidence]. The later stages in the algorithm involve more complicated single or combined regimens, while the earlier stages involve simpler more routine medications in terms of safety, ease of use, side-effect profiles etc.
3. A patient's previous response to antidepressant treatments should always be considered when selecting the point of entry into an algorithm. If a patient responded well to a specific pharmacotherapy or other treatment intervention during a previous episode of depression, the same treatment should be used again. Similarly, if a patient failed to respond, or was unable to tolerate an adequate trial of a specific medication during a previous episode of depression, that medication is not recommended for the current or future depressive episodes.
4. An adequate discussion between the clinician and the patient regarding available treatment options and information concerning specific medications (including expected results, routine dosing strategies, possible side effects, drug interactions, potential toxicity, as well as potential effects in overdose) is essential. Medication selection should be dependent on these factors. When these considerations suggest that several medications are equivalent, patient preference becomes paramount and should define the particular option selected. It has been well documented that patient participation during this process is likely to enhance compliance to the chosen treatment option.
5. Eligibility and point of entry into the algorithm for an individual patient should be determined by the physician based upon a review of relevant psychiatric factors (e.g., symptom severity, suicidality, comorbidity, etc.), medical status (e.g., concomitant medications or illnesses, age, etc.), and prior treatment history. **A rationale should provided when a patient enters the algorithm at a later point/stage or when stages in the algorithm are skipped.**
6. At the beginning of each stage, follow-up visits are recommended weekly for 4 weeks or until an improvement in symptoms has been noted to optimize treatment outcomes by: a) encouraging patient adherence with treatment and b) rapidly identifying and correcting potential problems or adverse events associated with treatment.
7. Response to a medication is enhanced by ensuring an adequate treatment trial of at least 4-8 weeks of administration at the recommended dosage range. However, if a

patient fails to respond to an adequate dosage of a specific medication for 4-6 weeks or has an unsatisfactory or partial response by weeks 6-8, an alternative treatment plan is recommended. The duration of a treatment trial may be extended to 8-12 weeks if an augmentation strategy has been instituted in patients with a partial response.

8. Continuation phase treatment is recommended to prevent relapse for all patients with major depressive disorder that achieve a satisfactory clinical response, preferably symptom remission.
9. Maintenance phase treatment is recommended for patients with major depressive disorder who have had at least: a) three episodes of major depression; or b) have experienced two episodes of major depression and have additional factors that contribute to an increased risk of recurrence, such as comorbid anxiety disorder or substantial residual functional impairment.
10. A SCID should be considered:
    a) to confirm a diagnosis.
    b) to reconfirm the diagnosis if there has been no response after 3 months.
    c) if comorbid psychiatric conditions are present.
    d) If patient has failed on two different classes or stages of medications.
11. Adequate documentation should be completed for each algorithm stage and treatment choice or critical decision points. If algorithm stages are skipped or if treatment deviates from the algorithms, the rationale behind the decision should be adequately documented.
12. While the algorithms are independent of treatment settings, the present protocol applies only to outpatient treatment. In the event of hospitalization during the implementation of the algorithm, all attempts must be made to encourage inpatient psychiatrists to adhere to the algorithm if possible. Finally, patients must be re-entered into the algorithm following discharge from the hospital.
13. At baseline and throughout treatment, possible psychosocial interventions, including psychotherapy, should be considered to optimize treatment. The protocol allows for the addition of psychotherapy if clinically indicated based on individual patient situations.
14. Adjunctive medications prescribed for the treatment of associated symptoms such as anxiety or treatment emergent side effects should be discontinued once these symptoms resolve. The rationale for their use should be carefully documented. The continued indication for these medications should be re-assessed on a regular basis.

Acute Treatment Phase

The algorithm begins after the patient has received a thorough baseline evaluation and is appropriately diagnosed with Major Depressive Disorder. Since all of the commercially available antidepressants are equally efficacious, selection of a specific medication should be a treatment choice based on individual factors such as the expected side-effect profile, potential toxicity, concomitant medications and comorbid general medical conditions.

> *The goal of acute phase treatment is to achieve full symptomatic remission as well as a return to the previous level of psychosocial function. There is evidence that the expected improvement in psychosocial functioning may well continue during the continuation phase of treatment.*

A thorough understanding of the emphasis on range of response is essential. Moreover, the goal of symptom remission for each individual patient requires consideration of the following:

(1) a single week of improvement may not represent a stable effect. Changes in tactical steps are recommended only after an adequate duration has elapsed on the current treatment. Progression to the continuation phase is contingent upon the response being stable. Therefore, it is crucial for the clinician to monitor and reevaluate the patient for several weeks following the first week of the response. This will ensure the stability of improvement and that the goal of full remission is attained.

(2) Recall that the aim of treatment is remission — not just partial response. Although, not all patients can obtain full remission, every effort must be made to ensure maximal response for each patient. Therefore, once a response occurs, further tactical (e.g., dose increases) or strategic (e.g., addition of psychotherapy or rehabilitative services) options may be needed before partial response is accepted as commensurate with maximal therapeutic benefit.

Non response (<25% improvement) indicates that the patient is essentially unchanged or response is clinically negligible

Minimal response (25 - 50% improvement) indicates that a clinical response is apparent, but substantial depressive symptoms remain so that this is not a satisfactory endpoint.

Partial response (50-75% improvement) indicates that the patient has achieved substantial improvement, but has yet to reach a full response.

Full Response ($\geq$ 75% improvement in baseline symptoms) indicates that patients have improved significantly compared to baseline. Once this full response is stabilized

(at least 2 visits with ≥75% improvement) patients may enter the continuation phase of treatment. However, continuation phase must not begin prior to 6 – 8 weeks after acute phase treatment was initiated.

Remission indicates an absence of symptoms, an essential return to a pre-morbid level of functioning.

Randomized controlled trials have consistently demonstrated similar efficacy between the commercially available antidepressants for the treatment of major depressive disorder. Hence, the selection of a first line agent is based on factors other than efficacy including safety, tolerability, and ease of use. All of the medications listed in Stage I are potential first line agents as determined by their: equivalent efficacy, favorable side effect profile, ease of use, safety in overdose, and relatively minimal patient attrition rates due to treatment emergent side effects. All of these factors should enhance the efficacy, tolerability and compliance to the prescribed antidepressant medication during Stage 1. The only exceptions are when superior efficacy has been documented in a subgroup of major depressive disorder (e.g., SSRIs and MAOIs for atypical depression).

Monitoring:

Most studies suggest that patients seen more often during the initial period of treatment (e.g., every 1-2 weeks for the initial 7-8 weeks of medication) have a more favorable outcome than patients seen on a less frequent basis. Several factors are likely to contribute to this finding. Treatment-emergent side effects are more likely to occur early in treatment. Failure to address such effects can result in poor compliance to the medication. Additionally, frequent visits during the initial phase permit more time for observation of a potential worsening of symptoms or the emergence of suicidality. Additional complicating factors can be identified and more opportunity to conduct global assessments and to make necessary dose adjustments also result. In this way, optimal treatment can be provided which is more likely to ensure a favorable outcome. Finally, this also provides an opportunity to offer encouragement and provide education to the depressed patient as well as appropriate family members or significant others.

Patients should be monitored closely for treatment-emergent side effects during the initial phase of treatment. Early intervention enhances patient adherence with the treatment plan. Both the patient and the family should be advised to promptly contact the clinic if substantial side effects occur. Patients should also be monitored for possible worsening of depressive symptoms, particularly the emergence of suicidality. If a rapid remission of depressive symptoms occurs within the first 3 weeks, appropriate positive reinforcement to continue with treatment is essential to reduce relapse and recurrence from premature termination of the medication.

Inclusion Criteria

Patients may be entered into the algorithm if one of the following criteria is met:

- Initial antidepressant treatment for current depressive episode
- Insufficient response to an adequate trial of an antidepressant
- Intolerable side effects with current antidepressant

The initial algorithm stages focus on monotherapy with antidepressant medications associated with favorable risk-benefit ratios. Each algorithm stage has multiple choices and acceptable alternatives. Within each strategic stage, there are critical decision points designed to guide the tactics of treatment.

Continuation Phase Treatment

1. 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 6 to 9 months at the dose effective during the acute phase. Patients should be evaluated at least once every 3 months during continuation treatment (preferably every 1-2 months). For initial episodes of major depression, medication tapering and discontinuation should be considered after the continuation period is completed. If previous depressive episodes have occurred, maintenance treatment should be considered. When discontinuing the antidepressant, the dosage should be tapered no more rapidly than 25% per week and not before 6-8 months of full remission have occurred. Tapering and discontinuation usually can be completed over a 2-3 month period. Patients should be educated concerning the signs and symptoms of recurrence of depressive symptoms. A new depressive episode is most likely to occur within the first 8 months of medication discontinuation; therefore, patients should be evaluated every 2 to 4 months during that period. 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).

2. Patient received ECT during acute phase:

Continuation treatment with an antidepressant is recommended after the initial treatment phase of ECT is completed. Selecting an antidepressant that the patient has not previously received or one that the patient has responded to during a previous episode of depression is generally recommended. However, if necessary,

a previously ineffective antidepressant may be used in combination with lithium. Dosing, duration of treatment, monitoring, and medication tapering are as above.

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

Maintenance Phase Treatment

Patients experiencing an initial episode of major depression have at least a 50% chance of having a second episode, and by the third episode of major depression, there is a 90% chance of recurrence. Therefore, all patients having a third depressive episode and some patients experiencing a second episode should be evaluated for maintenance antidepressant treatment.

Indications for Maintenance Medication

Feature	**Strength of Indication**
1. Three or more episodes of major depression	Very strongly recommended
2. Two episodes of major depressive disorder, and one or more of the following:	
a) Family history of bipolar disorder	Strongly recommended
b) History of recurrence within 1 year after previously effective medication was discontinued	Strongly recommended
c) A family history of recurrent major depression	Strongly recommended
d) Early onset (before age 20) of the first depressive episode	Strongly recommended
e) Depressive episodes were severe, sudden, or life-threatening within the past 3 years	Strongly recommended

(from the AHCPR Guidelines (1993), Vol. 2, page 111.)

Maintenance medication should be continued at full therapeutic doses and, as in the continuation phase, the regimen associated with symptom remission is recommended. The optimal duration of maintenance treatment has not been established, but depending on risk factors, is generally between one year past continuation phase and lifetime administration.

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 major depressive disorder. The patient's personal preference as well as the risk factors for recurrence should be considered in the decision process.

Psychotic Depression Algorithm Implementation

Acute Treatment Phase

The algorithm begins with the assumption that the patient has received an adequate baseline evaluation and has a primary diagnosis of major depressive disorder with psychotic features. (A DSM-IV checklist for major depressive disorder is attached for reference.) In psychotic depression, antidepressant/antipsychotic combinations have consistently demonstrated efficacy over antipsychotic or antidepressant medication alone. In patients with chronic or concomitant serious medical conditions and/or on multiple medications, an antipsychotic alone may be initiated and then followed by the addition of an antidepressant as tolerated. The treatment regimen selected should be based upon individual patient characteristics and the medication's relative tolerability, safety, need for dosage adjustment, patient compliance, potential drug interactions, patient's age, medical status, and patient preference. TCAs are the only antidepressants that have been systematically evaluated in more than one randomized controlled clinical trial and found to be effective for patients with psychotic depression when combined with an antipsychotic (level A evidence). Amoxapine is the only monotherapy agent that has demonstrated efficacy in patients with psychotic depression (level A evidence in one controlled trial). The tertiary amine TCAs, amitriptyline and imipramine, are listed as first line agents since a positive relationship between their serum concentrations and response in psychotic depression (when co-administered with an antipsychotic) has been demonstrated.

Although scant data exist for their efficacy in psychotic depression (level C evidence), SSRIs and venlafaxine are included when combined with an antipsychotic medication due to their superior side effect profile and the fact that psychotic depression is often complicated with chronic medical conditions and is associated with a high risk of suicide. Preliminary data suggest that venlafaxine may be more effective in severely depressed or treatment-resistant patients (level B evidence), and it has relatively few relevant drug interactions in comparison to the SSRIs.

Medium to high potency typical antipsychotics (e.g., haloperidol or perphenazine) are specifically recommended due to their relatively decreased risk of orthostatic hypotension, EKG changes, and anticholinergic effects as compared with the low potency antipsychotics such as chlorpromazine or thioridazine. These factors may be particularly important in patients receiving concomitant medications on an ongoing basis for chronic medical conditions. The atypical antipsychotic medications olanzapine and risperidone are also options at this stage due to their decreased risk of T.D. and, especially in the case of olanzapine, little to no EPS.

Patients evaluated more frequently during the acute treatment phase are likely to have more favorable outcomes than those monitored less closely. Antidepressant side

effects are more likely to occur early in treatment with subsequent deleterious impact on compliance with treatment. More frequent visits permit the clinician to monitor for evidence of worsening of symptoms, emergent suicidality, or complicating conditions. They also provide an opportunity to offer critical encouragement and positive reinforcement to the patient. This may be particularly essential for patients with psychotic depression who often have substantial associated psychosocial impairment and low self-esteem and often are receiving complicated medication regimens.

If the patient's clinical presentation warrants ECT (e.g., emergent suicidality or previous response to ECT), skipping stages 1 and 2 to enter at Stage 3 should be considered.

Monitoring

Patients should be closely monitored for the emergence of side effects, especially during the initial treatment period. Patients and families should be advised to contact the clinic promptly if side effects occur so that compliance to treatment is enhanced. Monitoring for the possible worsening of depressive symptoms, as well as the emergence of suicidality and other features is also essential. Patients demonstrating a rapid remission in depressive symptoms within the first three weeks should receive appropriate positive reinforcement and education to facilitate their continued compliance with the prescribed treatment to help prevent recurrence or relapse.

In psychotic depression, antidepressant/antipsychotic combinations have consistently demonstrated efficacy over antipsychotic or antidepressant medication alone. In patients with chronic or concomitant serious medical conditions and/or on multiple medications, an antipsychotic alone may be initiated and then followed by the addition of an antidepressant as tolerated. The treatment regimen selected should be based upon individual patient characteristics and the medication’s relative tolerability, safety, need for dosage adjustment, patient compliance, potential drug interactions, patient's age, medical status, and patient preference. TCAs are the only antidepressants that have been systematically evaluated in more than one randomized controlled clinical trial and found to be effective for patients with psychotic depression when combined with an antipsychotic (level A evidence). Amoxapine is the only monotherapy agent that has demonstrated efficacy in patients with psychotic depression (level A evidence in one controlled trial). The tertiary amine TCAs, amitriptyline and imipramine, are listed as first line agents since a positive relationship between their serum concentrations and response in psychotic depression (when co-administered with an antipsychotic) has been demonstrated.

Although scant data exist for their efficacy in psychotic depression (level C evidence), SSRIs and venlafaxine are included when combined with an antipsychotic medication due to their superior side effect profile and the fact that psychotic depression is often complicated with chronic medical conditions and is associated with a high risk of suicide. Preliminary data suggest that venlafaxine may be more effective in severely depressed or treatment-resistant patients (level B evidence), and it has relatively few relevant drug interactions in comparison to the SSRIs.

Medium to high potency typical antipsychotics (e.g., haloperidol or perphenazine) are specifically recommended due to their relatively decreased risk of orthostatic hypotension, EKG changes, and anticholinergic effects as compared with the low potency antipsychotics such as chlorpromazine or thioridazine. These factors may be particularly important in patients receiving concomitant medications on an ongoing basis for chronic medical conditions. The atypical antipsychotic medications olanzapine and risperidone are also options at this stage due to their decreased risk of T.D. and, especially in the case of olanzapine, little to no EPS.

Patients evaluated more frequently during the acute treatment (e.g., every week) phase are likely to have more favorable outcomes than those monitored less closely. Antidepressant side effects are more likely to occur early in treatment with subsequent deleterious impact on compliance with treatment. More frequent visits permit the clinician to monitor for evidence of worsening of symptoms, emergent suicidality, or complicating conditions. They also provide an opportunity to offer critical encouragement and positive reinforcement to the patient. This may be particularly essential for patients with psychotic depression who often have substantial associated psychosocial impairment and low self-esteem and often are receiving complicated medication regimens.

If the patient's clinical presentation warrants ECT (e.g., emergent suicidality or previous response to ECT), skipping stages 1 and 2 to enter at Stage 3 should be considered.

A TCA should be titrated as rapidly as tolerated to a dosage expected to attain serum concentration within the usual therapeutic range. This can generally be accomplished over a one or two week period for TCAs. It takes approximately 5 days after a dose change to achieve a steady-state or plateau TCA serum concentration. (See table 3.)

Although the dose response curve for SSRIs is reasonably flat, side effects generally increase with dose escalation. Therefore, SSRI dose is generally initiated at the lower end and dose titration is generally reserved for poorly responding patients. (See Table 3.) Although some patients will respond at 75 mg daily of venlafaxine XR, response rates increase with dose increases within the therapeutic range. Venlafaxine should be initially titrated up to 150 mg daily as tolerated. Doses of venlafaxine XR up to 225 mg daily have been beneficial in severely depressed patients, but side effects also increase with dose escalation. Amoxapine has a definite dose response curve. Dose titration is indicated to minimize side effects and to increase the likelihood of attaining both antidepressant and antipsychotic therapeutic effects. Amoxapine’s dose should be titrated to at least 200 mg daily.

Initial antipsychotic doses recommended for haloperidol are 5-10 mg daily; for perphenazine, 24-36 mg daily; 10-20 mg daily for olanzapine; and 2-6 mg daily for risperidone.

Continuation Phase Treatment

1. 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 6 to 9 months at the dose effective during the acute phase. Patients should be evaluated at least once every 3 months during continuation treatment (preferably every 1-2 months). For initial episodes of major depression, medication tapering and discontinuation should be considered after the continuation period is completed. If previous depressive episodes have occurred, maintenance treatment should be considered. When discontinuing the antidepressant, the dosage should be tapered no more rapidly than 25% per week and not before 6-8 months of full remission have occurred. Tapering and discontinuation usually can be completed over a 2-3 month period. Patients should be educated concerning the signs and symptoms of recurrence of depressive symptoms. A new depressive episode is most likely to occur within the first 8 months of medication discontinuation; therefore, patients should be evaluated every 2 to 4 months during that period. 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).

No systematic studies regarding the optimal duration of antipsychotic treatment during the continuation phase have been reported. It is recommended that the acute phase antipsychotic at the same dose be maintained at least for 1-2 months and then slowly tapered over the continuation phase. The duration of antipsychotic treatment should be limited to the minimum duration indicated in order to reduce the risk of tardive dyskinesia. If a patient is receiving a TCA, the serum concentration should be monitored, and the dose adjusted as necessary to maintain the level with the recommended therapeutic window (with and without the neuroleptic co-administered).

2. Patient received ECT during acute phase:

Continuation treatment with an antidepressant is recommended. It is preferable to select an antidepressant that the patient has not received or one that the patient has responded to during a previous episode of depression. However, if necessary, a previously ineffective antidepressant may be used in combination with lithium. Dosing, duration of treatment, monitoring, and medication tapering are as above.

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

Maintenance Phase Treatment

Recommendations for maintenance phase treatment are the same as those suggested for patients with major depressive disorder without psychotic features.

Glossary of Terms

Efficacy: the ability of a drug to demonstrate statistical superiority over placebo in a randomized, controlled clinical trial conducted in subjects with an identified illness.

Effectiveness: the clinical response to a medication in an individual patient.

Full Response: (≥ 75% improvement in baseline symptoms), indicating that the patient has essentially returned to their baseline or premorbid level of function. No further revisions in the strategy or tactics are indicated when a full response is attained.

Partial response: (50-75% improvement), indicating that patients have achieved substantial improvement, but have yet to reach a full response.

Minimal response: (25-50% improvement), indicating that a clinical response is apparent, but substantial depressive symptoms remain so that this is not a satisfactory endpoint. A change in tactic and perhaps strategy is indicated at this time.

Non Response: (<25% improvement), indicating that the patient is essentially unchanged or the response is clinically negligible. A change in tactic may be indicated, but a change in strategy is more likely indicated and/or necessary

Remission: Indicates an absence of symptoms, an essential return to a pre-morbid level of functioning for a period of 2 months or longer.

Strategic Choices in treatment: What strategy? When? (e.g., whether to give a TCA or ECT).

Tactical Choices in treatment: How to use a selected strategy.

Critical Decision: Time when an additional tactic or change in strategy is necessary.

Adherence: The diligence and degree to which a patient complies to the recommended prescription (in terms of drugs taken and their respective doses and timing, not taken, and the dosage).

Algorithm Appendix 1: DSM-IV Criteria for Major Depressive Disorder

Criteria for Major Depressive Episode

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

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. Symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Algorithm Appendix 1 (continued)

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Diagnostic criteria for 296.2x Major Depressive Disorder, Single Episode

A. Presence of a single Major Depressive Episode.

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, A Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode):

Severity/Psychotic/Remission Specifiers
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset

Diagnostic criteria for 296.3x Major Depressive Disorder, Recurrent

A. Presence of two or more Major Depressive Episodes.

Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

***Algorithm Appendix 1* (continued)**

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode)

Severity/Psychotic/Remission Specifiers
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery)
With Seasonal Pattern

Algorithm Appendix 2: Guidelines for Beginning Antidepressant Therapy and Dosing

Citalopram: an SSRI that is a very effective inhibitor on neuronal serotonin reuptake. Absorption is fast, almost complete, and unaffected by food. Bioavailability is 80% with a half-life of 35 hours. Citalopram is 80% protein bound with a low potential for interaction with drugs metabolized by the CYP2D6 system. Should not be used with MAOIs. Much less cardiotoxic than tricyclic and tetracyclic antidepressants.

Dosing

- Initial dose 20 mg
- Target Dose is 20 – 40 mg
- Maximum daily dose is 60 mg
- Maximum dose for patients >65 years of age is 40 mg qd
- Half-life is 35 hours
- Increase by 10 mg increments

Side Effects

- dizziness
- headache
- sleep disturbances
- dry mouth
- nausea

Fluoxetine: an SSRI that inhibits CNS neuron uptake of serotonin but not of norepinephrine. Uses include major depression, obsessive-compulsive disorder and bulimia nervosa. **Should not be used with MAOIs or with highly protein-bound drugs.** Fluoxetine also increases the half-life of diazepam and tricyclic antidepressant levels. It is metabolized in the liver with a half-life of 2 – 7 days.

Dosing

- Dosing begins at 20 mg qAM
- Target dose is 20 – 40 mg qd
- Maximum daily dose is 80 mg qd.
- Increase dose by 10-20 mg increments

Side Effects

- headache
- insomnia
- anxiety
- nausea
- sexual dysfunction

Algorithm Appendix 2 (continued)

Paroxetine: an SSRI that inhibits CNS neuron uptake of serotonin but not of norepinephrine or dopamine. Uses include major depression, obsessive-compulsive disorder and panic disorder. Paroxetine is metabolized through the liver with a half-life of 21 hours. Protein binding capacity is 95%. **Should not be used with MAOIs. May cause severe side effects with highly bound protein drugs. Paroxetine may also decrease digoxin levels and increase theophylline levels. It may also increase bleeding when given in combination with Warfarin.**

Dosing

- Dosing begins at 20 mg qAM
- Target dose is 20-30 mg qd
- Maximum daily dose for is 50 mg qd
- Increase by 10 mg increments

Side Effects

- headache
- insomnia
- agitation
- nausea
- sexual dysfunction

Sertraline: an SSRI that inhibits serotonin reuptake in the CNS, increases action of serotonin but does not effect dopamine or norepinephrine. Uses include major depression and obsessive-compulsive disorder. Sertraline peaks in 5 – 9 hours reaching a steady state in 1 week. It is 99% plasma protein binding with a half-life of 1 – 4 days. It is also extensively metabolized and excreted in urine. **May cause fatal reactions when used in combination with MAOIs. May also cause altered lithium levels when combined with lithium. Taking with food decreases the time required to reach peak plasma levels.**

Dosing

- Initial dose 50 mg qam
- Target dose 50-100 mg
- Maximum daily dose is 200 mg

Side Effects

- headache
- insomnia
- agitation
- nausea
- diarrhea
- sexual dysfunction

Algorithm Appendix 2 (continued)

Bupropion SR: an antidepressant that inhibits the reuptake of dopamine, serotonin and norepinephrine. Uses include major depression and smoking cessation. Onset of medication is 2 – 4 weeks with a half-life of 12 – 14 hours. Bupropion is metabolized by the liver and reaches a steady state in 1 week. Contraindicated in seizure disorder and eating disorders. Use cautiously in patients with renal and hepatic disease, recent MI or cranial trauma.

Dosing

- Initial dose 100 to 150 mg qam
- Target dose is 300 mg qd
- Maximum daily dose is 200 mg bid
- Half-life is 21 hours.
- **Do not give to patients with history of seizures**

Side Effects

- headache
- restlessness
- insomnia
- agitation
- nausea
- weight loss
- decreased libido

Bupropion (immediate release)*:* an antidepressant that inhibits the reuptake of dopamine, serotonin and norepinephrine. Uses include major depression and smoking cessation. Onset of medication is 2 – 4 weeks with a half-life of 12 – 14 hours. Bupropion is metabolized by the liver and reaches a steady state in 1 week. Contraindicated in seizure disorder and eating disorders. Use cautiously in patients with renal and hepatic disease, recent MI or cranial trauma.

Dosing

- Initial dose is 75 mg tid
- Target dose is 300-375 mg qd
- Maximum daily dose is 450 qd
- Half-life is 8 – 24 hours

Side Effects

- headache
- insomnia
- agitation
- nausea
- weight loss
- decreased libido

Algorithm Appendix 2 (continued)

Nefazodone: An antidepressant that selectively inhibits serotonin uptake by the brain, potentiates behavorial changes and occupies central S-H2 receptors. Used for major depression. Metabolized in the liver extensively to metabolites. Peaks in 1 – 3 hours with a half-life of 2 – 4 hours. Increases the effect of CNS depressants. Possible fatal reaction when used with antihistamines. Increases plasma concentrations of benzodiazepines. **Possible hypertensive crisis when combined with MAOIs.** Drug use and smoking can increase metabolism and decrease effects. Use cautiously in patients with cardiovascular disease or seizure disorder.

Dosing

- Initial dose is 100 mg bid
- Target dose is 300-600 mg qd
- Maximum daily dose is 300 mg bid
- Food delays absorption and decreases bioavailability by 20%
- Half-life is 2-4 hours

Side Effects

- dizziness
- somnolence
- headache
- insomnia
- nausea
- decreased libido

Venlafaxine XR: Potent inhibitor of neuronal serotonin and norepinephrine uptake and a weak inhibitor of dopamine. Extensively metabolized in the liver to an active metabolite with 87% of drug recovered in the urine. 27% protein binding with a half-life of 48 hours. **May cause hyperthermia, rigidity, rapid fluctuations of vital signs and mental status changes when used with MAOIs.** Use cautiously in patients with mania, hypertension or seizure disorder.

Dosing

- Initial dose is 37.5 mg qd
- Target dose is 75-150 mg qd
- Maximum daily dose is 225 mg qd
- Use with caution in patients with hypertension and monitor blood pressure
- Half-life is 48 hours

Side Effects

- dizziness
- anxiety
- somnolence
- headache
- insomnia
- nausea
- decreased appetite

Algorithm Appendix 2 (continued)

Venlafaxine: Potent inhibitor of neuronal serotonin and norepinephrine uptake and a weak inhibitor of dopamine. Extensively metabolized in the liver to an active metabolite with 87% of drug recovered in the urine. 27% protein binding with a half-life of 48 hours. **May cause hyperthermia, rigidity, rapid fluctuations of vital signs and mental status changes when used with MAOIs.** Use cautiously in patients with mania, hypertension or seizure disorder.

Dosing

- Initial dose is 37.5 mg bid
- Target dose is 150-225 mg qd
- Maximum daily dose is 375 mg bid
- Half-life is 5 hours. The half life of its metabolite, ODV, is 11 hours.
- Use with caution with patients with hypertension.

Side Effects

- dizziness
- anxiety
- somnolence
- headache
- insomnia
- nausea
- decreased appetite

Amitriptyline: Tricyclic antidepressant that blocks reuptake of norepinephrine, serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Onset within 45 minutes with peak in 2 – 12 hours. Metabolized by the liver with a half-life 10 – 50 hours. Contraindicated in the recovery phase of myocardial infarction. **Use cautiously in severe depression and suicidal patients. Also use cautiously in patients with cardiac disease, renal disease and hyperthyroidism.** Possible hyperpyretic crisis, convulsions or hypertensive episode when given with MAOIs.

Dosing

- Initial dose is 75 mg qhs
- Target dose is 150 mg qhs
- Maximum daily dose is 300 mg qhs
- Effective plasma levels for amitriptyline are 110-250 ng/ml.
- Half-life is 31-46 hours

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- dry mouth
- insomnia
- nausea

Algorithm Appendix 2 (continued)

Clomipramine: Tricyclic antidepressant that potently inhibits serotonin uptake and increases dopamine metabolism. Uses include, major depression, dysphoria, phobias, anxiety, agoraphobia and obsessive-compulsive disorder. Use cautiously in patients with seizure disorder and suicidal ideations. Extensively bound to tissue and plasma proteins. Half-life is 21 hours for the parent compound and 36 hours for metabolites.

Dosing

- Initial dose is 25 mg qhs
- Target dose of 100 mg should be reached by gradually increasing the dose to 100 mg over the first 2 weeks. Doses can be increased as quickly as 4 days apart if necessary.
- Maximum daily dose is 250 mg qhs
- Effective plasma levels for clomipramine are 80-100 ng/ml

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- dry mouth
- insomnia
- nausea

Desipramine: Tricyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings increasing the action of norepinephrine and serotonin in the nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants. **Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs. Do not break, crush or chew.**

Dosing

- Initial dose is 100 mg qhs
- Target dose is 150 mg qhs
- Maximum daily dose for this medication is 300 mg qhs
- Effective plasma levels for this medication are 125-300 ng/ml.
- Half-life is 12-24 hours.

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- insomnia
- nausea

Algorithm Appendix 2 (continued)

Imipramine: Tricyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants. **Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs. Do not break, crush or chew.**

Dosing

- Initial dose is 50 mg qhs
- Target dose is 150 mg qhs. Doses can be increased every 4 days if necessary.
- Maximum daily dose is 300 mg qhs
- Effective plasma levels for this medication are 200-350 ng/ml.
- Half-life is 11-25 hours

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- dry mouth
- insomnia
- nausea

Nortriptyline: Tricyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants. **Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs. Do not break, crush or chew.**

Dosing

- Initial dose is 25 mg qhs
- Target dose is 75-100 mg. Doses can be increased every 7 days if necessary.
- Maximum daily dose is 150 mg qhs
- Effective plasma levels for this medication are 50-150 ng/ml.
- Half-life is 18-44 hours

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- dry mouth
- insomnia
- nausea

Algorithm Appendix 2 (continued)

Amoxapine: Tetracyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. **Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants.** Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs.

Dosing

- Initial dose is 50 mg tid
- Target dose is 300 mg and can eventually be dosed once per day, at HS.
- Maximum daily dose is 600 mg qd.
- Effective plasma levels are 200-500 ng/ml.
- Half-life is 30 hours

Side Effects

- sedation
- anticholinergic effects
- dizziness
- anxiety
- dry mouth
- insomnia
- nausea

Mirtazapine: Tetracyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. **Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants.** Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs.

Dosing

- Initial dose is 15 mg qhs
- Target dose is 30 mg qd
- Maximum daily dose is 45 mg
- Half-life is 20-40 hours

Side Effects

- dizziness
- drowsiness
- diarrhea
- dry mouth
- increased appetite

Algorithm Appendix 2 (continued)

Phenelzine: MAOI antidepressant that increases concentrations of endogenous epinephrine, norepinephrine, serotonin, and dopamine in storage sites in the central nervous system by inhibiting MAO. Increased concentrations reduce depression. Contraindicated in hypertension, elderly, CHF, severe hepatic disease, pheochromocytoma, severe renal disease and severe cardiac disease. Increases hypotension when given with thiazide diuretics. Possible toxicity when given with sumatriptan, sulfonamide. Increased hypoglycemic effect with antidiabetics.

Dosing

- Initial dose is 15 mg bid
- Target dose is 45-60 mg qd
- Maximum daily dose is 90 mg qd
- PATIENTS NEED TO BE CAUTIONED TO AVOID TYRAMINE-RICH FOODS AND OF DRUG INTERACTIONS SUCH AS EPINEPHRINE, AMPHETAMINES, DOPAMINE, ETC. AS A HYPERTENSIVE CRISIS CAN OCCUR.

Side Effects

- restlessness
- insomnia
- dizziness
- weakness
- blurred vision
- arrythmias
- diarrhea

Tranylcypromine: MAOI antidepressant that increases concentrations of endogenous epinephrine, norepinephrine, serotonin, and dopamine in storage sites in the central nervous system by inhibiting MAO. Increased concentrations reduce depression. Contraindicated in hypertension, elderly, CHF, severe hepatic disease, pheochromocytoma, severe renal disease and severe cardiac disease. Increases hypotension when given with thiazide diuretics. Possible toxicity when given with sumatriptan, sulfonamide. Increased hypoglycemic effect with antidiabetics.

Dosing

- Initial dose is 10 mg qd in divided doses
- Target dose is 20 - 30 mg qd in divided doses
- Maximum daily dose is 40 mg qd
- PATIENTS NEED TO BE CAUTIONED TO AVOID TYRAMINE-RICH FOODS AND OF DRUG INTERACTIONS SUCH AS EPINEPHRINE, AMPHETAMINES, DOPAMINE, ETC. AS A HYPERTENSIVE CRISIS CAN OCCUR.

Side Effects

- restlessness
- insomnia
- dizziness
- weakness
- blurred vision
- arrythmias
- diarrhea

***Algorithm Appendix 2* (continued)**

Fluvoxamine: Miscellaneous antidepressant that inhibits the CNS neuron uptake of serotonin but not of norepinephrine. Increased CNS depression with alcohol, barbiturates, and benzodiazepines. Increased toxicity with tricyclic antidepressants, theophylline, and lithium. Although this medication is an SSRI, the current FDA indication is for the treatment of Obsessive/Compulsive Disorder. It is currently being used investigationally for the treatment of depression.

Dosing

- Initial dose is 50 mg qd
- Target dose is 100-200 mg qd
- Maximum daily dose is 300 mg
- Half-life is 13.6-15.6 hours

Side Effects

- headache
- insomnia
- anxiety
- nausea
- sexual dysfunction

Algorithm Appendix 3: Guidelines for Augmentation Therapy and Dosing

Guidelines for Beginning Augmentation Therapy and Dosing

Lithium: Antimanic that may alter sodium, potassium ion transport across cell membrane in nerve or muscle cells and may balance biogenic amines of norepinephrine and serotonin in CNS areas involved in emotional responses. Contraindicated in hepatic disease, renal disease, brain trauma, and severe cardiac or renal disease. Increased toxicity with indomethacin, diuretics, nonsteroidal antiinflammatories.

Dosing

- Initial dose for augmentation is 600 mg/day and should be adjusted to reach plasma level of 0.5 - 0.8 mEq/L

Side Effects at Therapeutic Blood Level

- fainting
- drowsiness
- nausea/vomiting
- tremor
- muscle weakness
- thirst

Buspirone: Antianxiety agent that acts by inhibiting the action of serotonin. May also be used in augmentation therapy due to increased effects when used with psychotropic drugs. Use cautiously in elderly patients and patients with impaired hepatic/renal functioning. Increased ALT when combined with trazodone. Do not use with MAOIs.

Dosing

- Initial dose is 5 mg bid
- Maximum daily dose is 20 mg tid

Side Effects

- dizziness
- insomnia
- nervousness
- nausea/vomiting
- dry mouth

Algorithm Appendix 4: Guidelines for Beginning Antipsychotic Therapy and Dosing

Haloperidol: Neuroleptic antipsychotic that depresses cerebral cortex, hypothalmus and limbic system that control activity and aggression. Also blocks neurotransmission produced by dopamine at the synapse. Contraindicated in alcohol and barbiturate withdrawal states, Parkinson's disease, angina, epilepsy, and urinary retention. Possible toxicity when combined with epinephrine or lithium.

Dosing

- Initial dose is 1-2 mg qhs
- Target dose is 5-10 mg qhs
- Maximum recommended dose is 15-20 mg qhs
- Contraindicated in patients with hypertension and cardiac disease

Side Effects

- headache
- drowsiness
- nausea/vomiting
- seizures
- orthostatic hypertension
- cardiac arrest

Perphenzine: Neuroleptic antipsychotic that depresses cerebral cortex, hypothalmus and limbic system that control activity and aggression. Also blocks neurotransmission produced by dopamine at the synapse. Possible toxicity when combined with epinephrine.

Dosing

- Initial dose is 4 mg qhs
- Target dose range is 8-16 mg qhs
- Maximum recommended dose is 24 mg qhs

Side Effects

- headache
- nausea/vomiting
- seizures
- cardiac arrest
- orthostatic hypertension

***Algorithm Appendix 4* (continued)**

Olanzapine: Neuroleptic antipsychotic that may mediate antipsychotic activity by both dopamine and serotonin type 2 antagonist. Also, may antagonize muscarinic receptors, histaminic and alpha-adrenergic receptors. Use cautiously in patients with hypertension, hepatic disease, cardiac disease and in elderly patients.

Dosing

- Initial dose is 5 mg qhs
- Target dose range is 10 - 15 mg qhs
- Maximum recommended dose is 20 mg qhs

Side Effects

- headache
- nausea/vomiting
- insomnia
- agitation/nervousness
- dizziness

Quetiapine: Neuroleptic antipsychotic that functions as an antagonist at multiple neurotransmitter receptors in the brain. Use cautiously in the elderly and in patients with hepatic disease, seizures, or dementia. Decreased clearance when combined with cimetidine. Increased clearance when combined with phenytoin, thioridazine, barbiturates, and glucocorticoids. Decreased clearance of lorazepam, levodopa, and dopamine agonists.

Dosing

- Initial dose is 25 mg bid
- Incremental increases of 25 mg bid – tid on days 2 and 3 to a dose of 300 – 4 mg qd given bid – tid
- Half-life $\geq$ 6 hrs

Side Effects

- Headache
- Seizures
- Dizziness
- Nausea
- Anorexia
- Constipation

Algorithm Appendix 4 (continued)

Risperidone: Neuroleptic antipsychotic that may mediate through both dopamine type 2 and serotonin type 2 antagonism. Contraindicated in seizure disorders. Extensively metabolized by the liver to active metabolite. Plasma protein binding 90%.

Dosing

- Initial dose is 1 mg qhs
- Target dose range is 2-4 mg qhs
- Maximum recommended dose is 6-8 mg qhs
- If the patient experiences EPS, consider adding Benztropine 2-4 mg to counteract this.

Side Effects

- Headache
- Drowsiness
- Insomnia
- Anxiety
- Nausea
- Anorexia
- constipation

Note for all antipsychotic medications: Once psychotic symptoms have remitted, maintain the patient on the lowest necessary dose to maintain remission for a period of 3 months. After 3 months of no psychotic symptoms, gradually taper the patient off the antipsychotic medication over a period of 2 weeks.

Algorithm Appendix 5: Guidelines for Switching Antidepressants

Switching From an SSRI

1. SSRI/#1 to SSRI/#2:
    - discontinue SSRI/#1 and then start SSRI/#2

    -or-
    - decrease SSRI/#1 to initiate SSRI/#2 to taper and discontinue SSRI/#1

Case Example: If patient. is on 40 mg po qam of fluoxetine: a) stop the fluoxetine and start paroxetine (or sertraline) the next day; or b) decrease the fluoxetine to 20 mg per day and add in paroxetine 20 mg (or sertraline 50 mg) per day for 1-3 days and discontinue the fluoxetine.

2. SSRI to TCA or bupropion:
    - discontinue SSRI and then start TCA or bupropion

    -or-
    - decrease SSRI to initiate TCA or bupropion at low dose to taper and discontinue SSRI, while gradually increasing TCA or bupropion as tolerated to therapeutic dose range.*

* Both the TCAs and bupropion are associated with significant toxicity at elevated plasma concentrations. Since SSRIs increase the plasma concentrations of TCAs and bupropion (paroxetine > fluoxetine > sertraline > citalopram), caution is indicated when co-administering these agents or when therapy with bupropion or a TCA is undertaken in close proximity to cessation of an SSRI.

Case Example: If pt. is on 40 mg po qam of fluoxetine: a) stop the fluoxetine and start nortriptyline (or other TCA) or bupropion the next day; or b) decrease the fluoxetine to 20 mg po qam and add in nortriptyline (25 mg po qhs or another TCA) or bupropion (50-75 mg po qd) for 1-3 days to discontinue fluoxetine and increase nortriptyline or bupropion as tolerated to therapeutic dose range.

3. SSRI to nefazodone or venlafaxine:
    - discontinue SSRI and then start nefazodone or venlafaxine

    -or-
    - decrease SSRI to initiate nefazodone (50-100 mg po qhs) or venlafaxine (37.5-75 mg po qd) to taper and discontinue SSRI, while gradually increasing nefazodone or venlafaxine as tolerated to therapeutic dose range.

Case Example: If patient is on 40 mg po qam of fluoxetine: a) stop the fluoxetine and start nefazodone (50-100 mg po qhs) or venlafaxine (37.5-75 mg po qd) the next day;

Algorithm Appendix 5 (continued)

or b) decrease the fluoxetine to 20 mg po qam and add in nefazodone (50-100 mg po qhs) or venlafaxine (37.5-75 mg po qd) for 1-3 days to discontinue fluoxetine and increase nefazodone and venlafaxine as tolerated to therapeutic dose range.

4. SSRI to MAOI:
    - discontinue SSRI and then after a 5 week washout period for fluoxetine or after a 2 week washout period (sertraline or paroxetine), MAOI therapy can be safely initiated.

Switching from TCA, Venlafaxine, Nefazodone, or Bupropion

1. TCA/#1 (or venlafaxine, nefazodone, or bupropion) to TCA/#2:
    - discontinue TCA/#1 (or venlafaxine, nefazodone, or bupropion) by taper and then start TCA/#2

    -or-
    - decrease TCA/#1 (or venlafaxine, nefazodone, or bupropion) to initiate TCA/#2 to taper and discontinue TCA/#1 (or venlafaxine, nefazodone, or bupropion), while gradually increasing TCA#2 as tolerated.

Case Example: If patient. is on 100 mg po qhs of nortriptyline (or venlafaxine, nefazodone, or bupropion): a) taper and then discontinue the nortriptyline (or venlafaxine, nefazodone, or bupropion) and start the other TCA the next day; or b) decrease the nortriptyline (or venlafaxine, nefazodone, or bupropion) and add in doxepin (50-100 mg po qhs or other TCA) for 1-3 days and then taper and discontinue the nortriptyline (or venlafaxine, nefazodone, or bupropion).

2. TCA (or venlafaxine, nefazodone, or bupropion) to SSRI:
    - taper and discontinue TCA (or venlafaxine, nefazodone, or bupropion) and then start SSRI

      -or-
    - decrease TCA (or venlafaxine, nefazodone, or bupropion) to initiate SSRI at low dose to taper and discontinue TCA (or venlafaxine, nefazodone, or bupropion).

Case Example: If patient. is on nortriptyline (or venlafaxine, nefazodone, or bupropion): a) taper and discontinue the nortriptyline (or venlafaxine, nefazodone, or bupropion) and start fluoxetine (or other SSRI) the next day; or b) decrease the nortriptyline (or venlafaxine, nefazodone, or bupropion) and add in fluoxetine (20 mg po qam or another SSRI) for 1-3 days to taper and discontinue nortriptyline (or venlafaxine, nefazodone, or bupropion).

Algorithm Appendix 5 (continued)

3. TCA (or venlafaxine, nefazodone, or bupropion) to nefazodone, venlafaxine, or bupropion:
    - discontinue TCA (or venlafaxine, nefazodone, or bupropion) and then start nefazodone, venlafaxine, or bupropion
      -or-
    - decrease TCA (venlafaxine, nefazodone, or bupropion) to initiate nefazodone (50-100 mg po qhs), venlafaxine (37.5-75 mg po qd), or bupropion (37.5-50 mg po qd) to taper and discontinue TCA (venlafaxine, nefazodone, or bupropion), while gradually increasing nefazodone, venlafaxine, or bupropion as tolerated to therapeutic dose range.

Case Example: If patient is on nortriptyline (or venlafaxine, nefazodone, or bupropion): a) stop the nortriptyline (or venlafaxine, nefazodone, or bupropion) and start nefazodone (50-100 mg po qhs), venlafaxine (37.5-75 mg po qd), or bupropion (37.5-50 mg po qd) the next day; or b) decrease the nortriptyline (or venlafaxine, nefazodone, or bupropion) and add in nefazodone (50-100 mg po qhs), venlafaxine (37.5-75 mg po qd), or bupropion (37.5-50 mg po qd) for 1-3 days to discontinue nortriptyline (or venlafaxine, nefazodone, or bupropion) and increase nefazodone, venlafaxine, or bupropion as tolerated to therapeutic dose range.

4. TCA to MAOI:
    - discontinue TCA and then after a 2 week washout period, MAOI therapy can be safely initiated.

Switching from an MAOI

1. MAOI/#1 to MAOI/#2, SSRI, TCA, venlafaxine, bupropion, nefazodone:
    - discontinue MAOI/#1 and then after a 2 week washout period, therapy with MAOI/#2 (or SSRI, TCA, venlafaxine, or nefazodone) can be safely initiated.

❖ *Physician Responsibilities*

Primary Responsibilities

TMAP primary responsibilities for physicians include the following:

- Identify patients for the Algorithm and coordinate their entry into the Algorithm with the assistance of the Clinical Coordinator.
- Develop, in collaboration with the patient, a specified plan of action that adheres to the Algorithm to the highest degree consistent with good medical care and patient acceptance.
- Follow Algorithm guidelines and Critical Decision Point guidelines as provided.
- Communicate with Directors and Clinical and Module Coordinators as needed for the successful management of the Algorithm.
- Initiate and participate in the patient and family education program.
- Complete appropriate forms and assessments as required.
- Communicate with hospital physicians as needed when an Algorithm study patient is hospitalized.
- Each physician has the ultimate responsibility and complete authority regarding all aspects of patient care.
- Physicians must judge the suitability of the Algorithm for each individual patient, and are responsible for implementing it to the best of their ability.

Hospitalized Patient Physician Responsibilities

The hospitalization of a TMAP patient presents special concerns for the TMAP clinic physician. Every effort must be made to keep patients in the algorithm by contacting the hospital physician as soon as a patient is admitted in order to discuss the treatment plan.

The clinical coordinator is responsible for providing local and area state hospitals with a weekly updated list of TMAP patients and the patients will be instructed to present their TMAP ID cards in the event of an emergency room visit or admission to a hospital.

The clinic physician can help ensure that TMAP patients remain in the algorithm by

- Being sensitive to changes in a patient's mental status that might indicate a need for hospitalization.
- Communicating concerns regarding patient status to the clinical coordinator.
- Reinforcing the use of the TMAP ID card with patients and their families.
- Contacting hospital physicians as soon as possible and as often as needed to maintain hospitalized patients in the algorithm.

Patient/Family Education Program Physician Responsibilities

The physician is responsible for initiating the patient/family education program. By providing information on diagnosis and medications to the patient during the patient's entry into the algorithm, the physician sets the tone for patient participation. The information given by the physician is then reinforced by the clinical coordinator who guides the patient and family through the levels of the education program.

The physician will assist with the education program as needed. The Patient Education Plan Guidebook gives the physician an in depth explanation of the education program and the physician's responsibilities for its implementation.

❖ *Patient Recruitment*

MDD Algorithm Patient Recruitment

1. Patients are recruited by physicians with the help of the CC.

2. Patients are eligible to participate in TMAP if:

   - the physician deems the patient to have major depressive disorder.
   - the patient is sufficiently symptomatic for medication treatment.
   - the patient is intolerant or is insufficiently responsive to current medication such that a medication initiation or change (not a simple dosage change) is needed.

3. Patients deemed eligible for the algorithm by physicians will have the treatment and evaluation procedures explained to them either by the physician or the CC.

4. Physicians will enroll 45 patients per CC whom they believe are eligible and suitable to be treated with the assigned medication algorithm.

5. The TMAP Intake Form is to be completed by the CC using information obtained from the physician, patient, and medical records as needed.

❖ *Informed Consent*

Instructions on Obtaining Informed Consent

The CC obtains and uses the Informed Consent Form specific to his/her clinic. The CC places an original copy of this site-specific Informed Consent Form in Appendix F of this manual.

✍ Please note that informed consent must be obtained from the patient before any study procedures are performed.

Before asking the patient to sign the consent form, the CC:

- Explains the purpose and requirements of the study. It is important that the patient understand the time involved in the quarterly evaluations, patient/family education, and the research assessments.
- Reads the informed consent form out loud to the patient.
- Asks the patient at the end of each paragraph if s/he has any questions.
- Makes sure the patient understands that he/she will remain a study participant if hospitalized.
- Answers any questions from the patient.

Who can sign the consent forms:

- patients 18 and older
- patients who do not have a guardian
- the guardian of a patient (with written consent of the patient)

Who cannot sign the consent forms:

- family members may not sign for the patient (unless they have proof of guardianship)
- patients who have a guardian

The patient signs three (3) identical consent forms. One is given to the patient, one is filed in the patient's clinic chart, and the other is filed in the patient's study chart.

❖ *Process Measures*

Physician Administered Assessments

The physician rates the patient at each visit using a scale of 0=not ill, to 7=extreme. The rating scale is found on the Clinical Record Form and the numerical results are recorded on that form. The areas assessed are Core symptom Severity, Overall Functional Impairment, and Other Symptoms, which includes Associated Symptom Severity and Overall Side Effect Severity.

Clinical Coordinator Administered Assessments

Prior to the Physician seeing the patient, the Clinical Coordinator administers the Patient Global (Self-Report), the Symptom Severity, the Side Effects, the IDS-C, the IDS-SR, and the 4 Item BPRS. The results of these assessments are recorded on the Physician Review Form.

❖ *Data Collection*

Intake Form (Appendix G)

1. The Intake Form is to be completed by the physician. The CC reviews the form for accuracy and completeness and faxes it to the TMAP Data Center.
2. The physician documents the following identifying information:

   - **Local Case #**
   - **MHMR Physician Code**
     (or first 4 digits of the physician's Social Security number)
   - **Component/Clinic #**
   - **Date of Visit** (i.e., date intake procedures initiated)
   - Note: Write in the month, day, year (e.g., 3/1/98)
   - **Age**
   - **Gender**
   - **Ethnic or Racial Group** (check one only)
   - **Principal Diagnosis** (i.e., DSM-IV Axis Code).

     This diagnosis should coincide with the disease-specific module under consideration (i.e., major depressive disorder, schizophrenia, or bipolar disorder).
   - **Age of Onset** (pertains to principal diagnosis).
   - **Other Current Diagnoses**
     Not including principal diagnosis (i.e., other comorbid Axis I conditions using the DSM-IV Axis I code).
   - **Alcohol/Substance Problem**
     (Clinician rating within last six (6) months).
   - **Axis III**
     (Record general medical conditions that the patient is currently receiving treatment for. Check all that apply.)

✍ Note there is no need to document Axis IV.

- **Have any family members been treated for: Depression, Schizophrenia, Bipolar, Alcohol Abuse, Drug Abuse, Suicide?**
  (Father, Mother, Sister(s), Bother(s), Son(s), Daughter(s))

- **Number of Psychiatric Hospitalizations**
  (Past Year, Past 5 Years, Lifetime)

- **TMAP Group**
  Check only one: ALGO+ED, TAU ALGO, TAU-nonALGO

- **Module**
  Check only one: MDD, BPD, SCZ

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

- **Medication**
  List name of medication, either generic or brand name.

- **Current**
  Check Yes or No if this is a current medication.

- **Dose**
  List the highest daily dose taken during the past two years.

- **Frequency**
  How often taken, daily dosage, scheduled or prn.

- **Weeks On**
  How many weeks in the past two years was the medication taken?

- **Responded**
  (Full, Partial, None, Unknown)

- **Date Visit #1 is Scheduled For**
  Record in numbers, e.g., August 3 would be 8/3/98.

Patient Perception of Benefits of Care (Appendix H)

The CC completes this form at intake on all patients recruited into the study.

Demographic Questionnaire (Appendix I)

The CC completes this form at intake on all patients recruited into the study.

Clinical Record Form (Appendix J)

- **Service Activity Code:**
  Service activity or billing code for this visit.

- **Site/Clinic #:**
  Your site number for this project.

- **Physician Code:**
  Your code number.

- **Start Time:**
  Please indicate the time you started spending time with this patient.

- **Stop Time:**
  Indicate the time you finished providing care for this patient, including your progress note.

  Note: Please use 24-hour clock.

- **Duration:**
  The difference between stop time and start time in minutes.

- **Primary Current Dx:**
  Please check the patient's primary Axis I diagnosis for which the algorithm is being used.

Physician Ratings

Each of the symptom clusters is rated on a 7-point scale (from "no symptoms" to "extremely severe"). The rating is based on your impression of the patient at this visit, as well as information you have about the patient's clinical status during the week prior to the visit.

- **Core Symptoms:**
  Based upon all available information, your impression of the level of the presence of each of the symptoms in this patient.

- **Other Symptoms:**
  Your rating of other symptoms associated with the patient's disorder, but

not core symptoms of the patient's illness. Rate your impression for each of the specific "other symptoms" listed (irritability, mood lability, insomnia, agitation, anxiety). Under "other," specify and rate any other symptom that you feel is significant.

✏ **Overall Side Effect Severity:**
Your overall rating of side effects from all medications being taken by the patient.

✏ **Overall Functioning:**
Your overall impression of this patient's ability to function on a daily basis. "100" is the highest possible functioning, and "1" is the lowest possible functioning.

Prescription Information

✏ **Medication Name:**
List the names of all psychotropic medications (for the core syndrome, other symptoms, or side effects) the patient is receiving — both **new** medications prescribed at this visit and **continuing** medications. Check the appropriate box. If a medication is being **discontinued**, list the medication name and check the **D/C** box.

List the complete SIG (dose and frequency) for each medication the patient is receiving. If a medication is being titrated or tapered, please outline the schedule. Indicate stop dates, if applicable. Please check whether the medication is for core syndrome **(S)**, other symptoms **(OS)**, or side effects **(SE)**.

✏ **Comments:**
Note any pertinent points about the patient's clinical status (e.g., most prominent symptoms, specific side effects, serum level results, psychosocial stressors, compliance, crisis interventions, ER visits, information given to patient, etc.). If there is insufficient room for all of your comments here, continue on a second **Comments Only** page.

✍ If you are varying from the algorithm, please indicate why.

Algorithm Information (boxed section; page 2 of NCR form only)

✏ **Use of Algorithm:**
Indicate whether you are changing from the recommended algorithm at this visit. If yes, please check the appropriate box indicating why you are varying from the algorithm.

- **Algorithm Stage:**
  Indicate the stage of the algorithm you are using at this visit.

- **Side Effect Algorithm:**
  Indicate whether a "side effect algorithm" is being used (started or discontinued).

- **Other Symptom Algorithm:**
  Indicate whether an "other symptom algorithm" is being used (started or continued).

- **Return to Clinic:**
  The physician should indicate the number of weeks when the patient is to return to the clinic.

- **Physician Signature:**
  Please sign the form.

Physician Review Form (Appendix K)

The Physician Review Form is to be completed by the CC and is presented to the **physician** for **review prior to** his/her **visit with the patient**. The CC should review this form for accuracy and completeness and fax it to the TMAP Data Center.

The CC documents the following information:

- **Local case #**
- **Component/Clinic #**
- **Date of Visit**
- **Visit Number**
- Name of **All Medications In Last Week (Prescription and OTC** [over-the-counter]**)**
- **Was the medication taken as prescribed?**
  For each medication prescribed, check whether the medication was taken as directed. Options include:
  - Mostly yes (includes always taken as prescribed)
  - Sometimes
  - No

- **Clinical Rating Scales**
  Total scores for the appropriate rating scales done at this visit.

- **Overall Patient Global**
  The scores for Overall Patient Global Rating.

  Note: This should be the first question of the interview.

- **Staff Time**
  Staff time for this visit in minutes.

- **Patient/Family Education:** (check yes or no)
  - Done at this visit?
  - Between last visit and this visit?
  - Patient Education Activity Log Completed?

- **Most Recent Drug Levels:**
  Record medication name, date drawn, and serum level.

- **Comments**

- **Termination Visit?**
  Check yes or no. If "No," record Next Appointment Date.

- **Clinical Coordinator Signature**

The CC should first assess the Overall Global Rating and document this score.

Next, the CC should inquire about all medications taken in the last week and document how they were taken as compared to how they were prescribed.

Then the CC should administer the rating scales appropriate for the module and this visit. Total the scores for these rating scales and note them in the respective blanks (some will be empty).

Note: Some of the rating scale blanks will remain empty.

This information is presented to the **physician** for **review prior to** his/her **visit with the patient**.

TMAP Termination Form (Appendix L)

1. The TMAP Termination Form is to be completed by the physician. The CC will review the form for accuracy and completeness and fax it to the TMAP Data Center.
2. The physician should complete the TMAP Termination form at the last or final algorithm visit, *in addition to* the Clinical Record Form.
3. The physician documents the following identifying information:

   - **Local case #**
   - **Component/Clinic #**
   - **Date of Visit**
   - **Visit Number**

   Note: The visit number should be in sequence throughout the algorithm. To ensure valid sequencing of visits, please check previous Clinical Record Form for the correct termination visit number to be entered in the space provided.

   - **Algorithm Termination Reason**
     Check all reasons that apply from the list provided.

     Note that if "Other" is chosen, please write specific reason in the space provided.

   - **Physician Satisfaction Ratings**

     The physician should complete the physician satisfaction scale for each patient at the termination visit.

     The physician satisfaction scale consists of three statements which should be responded to by the physician according to the following scale: Strongly Agree, Agree, Neutral, Disagree, or Strongly Disagree

   - **In using the algorithm with this patient, how would you rate the overall quality of medication treatment?**

     The physician should check the appropriate response: Excellent, Very Good, Good, Substandard, or Unacceptable.

- Following the termination visit, the physician should review the termination form to ensure accuracy of information provided and to make sure they have not missed a section.

- The termination form should be given to the CC to review and fax to the TMAP Data Center within 24 hours.

❖ *Communications*

Important Phone Numbers

Depression Module Director
Madhukar H. Trivedi, M.D.
5959 Harry Hines POB1 Suite 600
Dallas, TX 75390-9101

Office number (214) 648-4282
Fax number (214) 648-4210
To be paged (214) 648-3300
E-mail address: mtrive@mednet.swmed.edu

Depression Module Assistant Director
Teresa Pigott, M.D.
UTMB, Department of Psychiatry
301 University Blvd.
Galveston, TX 77555-0428

Office number (409) 772-2002
Fax Number (409) 772-6771
E-mail address: tpigott@psypo.med.utmb.edu

Depression Module Coordinator
Tracie Key, R.N., B.S.N.
5959 Harry Hines POB1 Suite 600
Dallas, TX 75390-9101

Office number (214) 648-8344
Fax number (214) 648-1044
Pager number (214) 781-4192
E-mail address: tkey@mednet.swmed.edu

Conference Call Schedule

Two teleconferences per week will be scheduled for the project. The teleconferences are designed to be a forum for discussion of the implementation of the algorithm. General and specific questions related to the algorithm may be asked during these time periods. Teleconference times and dates will be at a regular day and time each week and will be scheduled at times as convenient a time as possible for all concerned. The length of each teleconference will vary depending on the type/number of questions, with a maximum time limit of 45 minutes. The teleconference schedules will be revised as needed.

The Depression module teleconference groups will be comprised in the following manner: (1) Dr. Trivedi and/or Dr. Pigott, Tracie Key, and the local Study Psychiatrists; and (2) Tracie Key and the Clinical Coordinators. Other people may be asked or invited to attend, but these staff members should make every effort to participate. *If possible, questions from each site should be faxed to the MC before each teleconference using the "Question and Answer Fax Form."* Unanswered non-urgent questions will be tabled until the next scheduled teleconference.

Teleconference schedule:

Teleconference Group 1
Scheduled for _____ (day of the week)
at _____ (time)

Teleconference Group 2
Scheduled for _____ (day of the week)
at _____ (time)

Calling in:

Call ( ) - and the pin # for our conference call is:
Group 1: _____

Group 2: _____

Question and Response Fax Form (see Appendix M)

This form is for questions to be submitted for the teleconference or for site-specific non-urgent questions. They will be answered as quickly as possible, but as the Module Director and MC both travel, the response may not be immediate. For all urgent questions, please page your MC.

❖ *Data Management*

The TMAP Data Center (TMAP-DC) supports scientific excellence in clinical/mental health services research through reliable, timely, and accurate data management. Specifically, the objectives of the TMAP-DC are designed to ensure that data are: (*a*) accurately and promptly processed, (*b*) documented for use in analysis, (*c*) easily accessible to investigators, (*d*) processed in a standardized operating environment; (*e*) properly backed up, (*f*) secured from improper handling, and (*g*) protective of patient confidentiality.

To accomplish these objectives, TMAP data management personnel function within a standard operating environment. This standard framework promotes efficient data management operations functions and ensures high quality data.

Quality Control

TMAP-DC personnel assist the Module Directors and Outcomes Assessment Team with quality control procedures for TMAP data. TMAP-DC provides routine quality control reports to appropriate TMAP personnel. TMAP-DC monitors the quality of data management activities on a continual basis.

To maintain high quality data, some basic principles are followed:

- Teamwork — Assist and work with each study team member to achieve the goals of the project.
- Adherence to Procedures — Follow procedures as outlined in the TMAP user manuals.
- Data Transfer —Transfer data to the TMAP-DC in a timely manner.
- Communication — Effective communication is critical in resolving data errors and problems with project team members.
- Confidentiality — Ensure confidentiality of all TMAP patients.
- Integrity — Maintain high standards in dealing with the data at all times (e.g., accurate completion of data forms; check data forms prior to transfer to TMAP-DC).

Data Collection and Processing

1. The data are collected according to procedures outlined in the user manuals and recorded on the appropriate forms and measures.

2. Forms and measures identified as data are faxed to the TMAP-DC (see Data Transfer section below).

3. When received, the TMAP-DC reviews each form or measure for completeness and legibility.

4. When a form or measure is incomplete or illegible, the CC is contacted to resolve the problem.

5. After a period of time, data are declared missing when attempts to resolve data problems are unsuccessful.

The data collected (forms and measures) are the basis for all routine reports and data analysis. Persistent problems with completeness and legibility are monitored and reported to appropriate TMAP personnel.

Data Transfer

The CC faxes to the TMAP-DC (within one working day) the completed TMAP data forms and measures associated with the type of data collection point (Intake, Follow-up, etc.) without a cover page.

Contact Person: Brad Witte
Phone: (214) 648-4628
E-mail: bwitte@mednet.swmed.edu

TMAP Data Center Fax Numbers: (214) 648-4632
(214) 648-4633

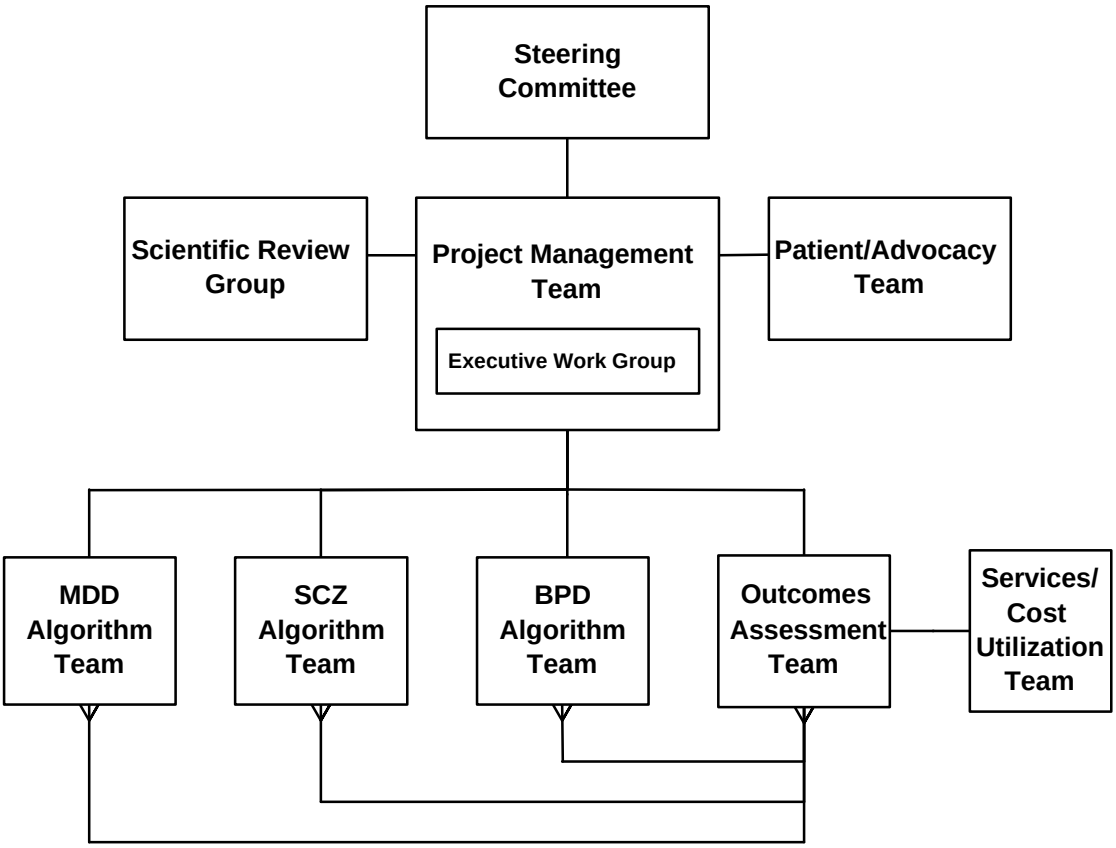
TMAP Data Center Address: UT Southwestern Medical Center
TMAP-DC
6363 Forest Park Road, Suite B225
Dallas, Texas 75235

❖ *Appendix: Table of Contents*

Appendix A

TMAP Administrative Organizational Chart

TMAP Administrative Organizational Chart



Appendix B

TMAP Personnel: Committees and Teams

Texas Medication Algorithm Project

Steering Committee

Texas Medication Algorithm Project

Project Management Team

A. John Rush, M.D., Project Director
University of Texas Southwestern Medical Center at Dallas

M. Lynn Crismon, Pharm. D., Project Co-Director
University of Texas at Austin-College of Pharmacy

Marcia Toprac, Ph.D., Project Co-Director
Texas Department of Mental Health and Mental Retardation

Steven P. Shon, M.D., Project Co-Director
Texas Department of Mental Health and Mental Retardation

Melanie M. Biggs, Ph.D., Co-Director, Outcomes Assessment Team
University of Texas Southwestern Medical Center at Dallas

Michael Kashner, Ph.D., Utilization and Cost Core
University of Texas Southwestern Medical Center at Dallas

Alexander Miller, M.D., Schizophrenia Module Director
University of Texas Health Science Center at San Antonio

Trisha Suppes, M.D., Ph.D., Bipolar Module Director
University of Texas Southwestern Medical Center at Dallas

Alan Swann, M.D., Senior Consultant to Project Management Team
University of Texas Health Science Center at Houston

Madhukar Trivedi, M.D., Depression Module Director
University of Texas Southwestern Medical Center at Dallas

Kathy Shores-Wilson, Ph.D., Co-Director, Outcomes Assessment Team
University of Texas Southwestern Medical Center at Dallas

William V. Rago, Ph.D., Project Management Team Consultant
Texas Department of Mental Health and Mental Retardation

Brad Witte, M.S., Data Center Administrator
University of Texas Southwestern Medical Center at Dallas

Texas Medication Algorithm Project

Executive Work Group

A. John Rush, M.D., Project Director
University of Texas Southwestern Medical Center at Dallas

M. Lynn Crismon, Pharm. D., Project Co-Director
University of Texas at Austin-College of Pharmacy

Marcia Toprac, Ph.D., Project Co-Director
Texas Department of Mental Health and Mental Retardation

Steven P. Shon, M.D., Project Co-Director
Texas Department of Mental Health and Mental Retardation

William V. Rago, Ph.D., Project Management Team Consultant
Texas Department of Mental Health and Mental Retardation

Tex Killion
Texas Department of Mental Health and Mental Retardation

Karla Starkweather
Texas Department of Mental Health and Mental Retardation

Texas Medication Algorithm Project

Scientific Review Group Members

Larry Ereshefsky, Pharm. D.
University of Texas at Austin
Clinical Pharmacy Programs
UT Health Science Center at San Antonio

Mark Bauer, M.D.
Department of VAMC

Charles Bowden, M.D.
Department of Psychiatry
UT Health Science Center at San Antonio

Robert Drake, M.D.
Psychiatric Research Center

Vijay Ganju, Ph.D.
Texas Department of Mental Health and Mental Retardation

William Hargreaves, Ph.D.
Department of Psychiatry
University of California at San Francisco
San Francisco General Hospital

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Tarrant County MHMR

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University of Maryland
Center for Mental Health Services Research

Tuan Nguyen, Ph.D.
MHMRA of Harris County

Harold Sackeim, Ph.D.
NY State Psychiatric Institute

M. Katherine Shear, M.D.
University of Pittsburgh
Medical Center
Western Psychiatric Institute & Clinic

Marvin Shepherd, Ph.D.
UT College of Pharmacy

Texas Medication Algorithm Project

Patient/Advocacy Team

Texas Alliance for the Mentally Ill
- Joe Lovelace, President
- Eldon Baber, Executive Director
- Vicki Olsen, Education Director

Mental Health Association of Texas
- Stella Mullins, Executive Director
- Christine Devall
- Mary Dees
- Jim Lockheed

Depressive/Manic Depressive Association
- Cliff Gay
- Diane Batchelder

Texas Mental Health Consumers
- Mike Halligan, Executive Director

Texas MHMR Consumer Affairs Office
- Cindy Hopkins (Chair)

Others
- Marcia Toprac, Ph.D., TXMHMR (Co-Chair)
- Gus Sicard, Ph.D., Center for Health Care Services

Texas Medication Algorithm Project

Outcomes Assessment Team

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Michael Lay, B.A., Research Administrator
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Marcia Toprac, Ph.D., Consultant
Texas Department of Mental Health and Mental Retardation

Mark Mason, M.S., Statistician
Texas Department of Mental Health and Mental Retardation

Texas Medication Algorithm Project

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MHMRA of Harris County

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Tarrant County MHMR Center

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Texas Medication Algorithm Project

Bipolar Disorder Module

Trisha Suppes, M.D., Ph.D., Director
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Sherwood Brown, M.D., Ph.D., Assistant Director
NIMH Fellow, University of Texas Southwestern Medical Center at Dallas

Ellen Dennehy, Ph.D., Coordinator
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Texas Medication Algorithm Project

Depression Module

Madhukar H. Trivedi, M.D., Director
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Tracie Key, R.N., B.S.N., Coordinator
University of Texas Southwestern Medical Center at Dallas

Texas Medication Algorithm Project

Schizophrenia Module

Alexander Miller, M.D., Director
Professor, University of Texas Health Science Center at San Antonio

John Chiles, M.D., Assistant Director
Professor, University of Texas Health Science Center at San Antonio

Judy Chiles, R.N., Coordinator
San Antonio State Hospital

Appendix C

TMAP Primary Responsibilities for Module Coordinators

TMAP Primary Responsibilities for Module Coordinators include the following:

- Coordinate, facilitate, and supervise the clinical aspects of a specific TMAP module.
- Assist the Module Directors with the interviewing and hiring of Clinical Coordinators.
- Conduct the orientation of Clinical Coordinators.
- Follow monitoring procedures to ensure that the module protocols proceed as outlined in the study protocol.
- Assure the quality of the data through periodic reviews.
- Assure the routine procedures for follow-up and tracking of study participants are implemented.
- Assist the Clinical Coordinators with the implementation of the study.
- Develop and implement a review of patient records and documentation for data collection purposes.
- Interact with the TMAP Data Center, Module Directors, clinical and research personnel and the on site clinic staff as needed to maintain an optimum research project environment.
- Periodically use own vehicle, rental vehicle, commercial airlines, or other suitable transportation to travel to and from clinics and other locations for meetings.
- Participate in weekly phone conferences with clinical coordinators, physicians, and research personnel as needed.
- Keep a log in which to document all communications with all study participants and research personnel, including types of communications, time periods involved and all outcomes.
- Report regularly to the Module Director regarding the progress or problems with the study.
- Advise and monitor the Clinical Coordinator's implementation of the patient and family education program.
- Obtain feedback from physicians and Clinical Coordinators on the usefulness of their respective manuals. Collaborate with other Module Coordinators to revise and edit these manuals as needed.

Appendix D

TMAP Primary Responsibilities for Clinical Coordinators

TMAP Primary Responsibilities for Clinical Coordinators include the following:

- Assisting the physicians in the proper implementation of the Texas Medication Algorithm Project (TMAP).
- Assisting in identifying patients and obtaining informed consent.
- Completing TMAP study forms.
- Ensuring appropriate and complete documentation of all study forms.
- Faxing all study forms to appropriate personnel.
- Communicating with the Module Coordinator on a weekly basis or as often as needed, and the Director of the TMAP Data Center as needed to resolve questions regarding study forms.
- Administering module-specific assessments at every TMAP physician visit, including documenting the section scores on the appropriate forms.
- Assisting the physician and patient with scheduling TMAP appointments.
- Referring patients to their respective caseworkers when they have issues unrelated to TMAP.
- Conducting family and patient education groups with the assistance of a trained mental health consumer, physicians, and other content experts as needed.
- Documenting and faxing to the TMAP Data Center a report of all educational activities.
- Assisting Project Management Team members or designees in coordinating SCID-CV interview appointments and site visits.
- Implementing procedures for increasing the likelihood that patients attend appointments as scheduled (e.g., a postcard and/or telephone call to remind the patient of his/her appointment prior to the visit; stressing with the patient and family at the initial visit of the importance of keeping appointments).
- Specifying and implementing a procedure for following up with patients who do not show for scheduled appointments (e.g., telephone the patient the day they missed an appointment, contact other persons who may be able to help locate the patient so that a new appointment can be scheduled).
- Tracking any patients who may be hospitalized during participation in this project and assisting the treating physicians to follow algorithm guidelines.
- Keeping a log of all communications with other clinical and research personnel and physicians involved in TMAP.

Appendix E

TMAP Terms

TMAP Terms

ALGO - A pre-specified medication algorithm. An algorithm is a rule-based, deductive system operating with inputs, sequences, time frames, and outputs that provide a framework for decision-making. An assumption in this study is that adequate clinical and administrative supports are in place to assure successful implementation of the algorithm. Algorithms have been developed for three major psychiatric disorders for TMAP. These are the major depressive disorder algorithm, the schizophrenia algorithm, and the algorithm for the treatment of bipolar disorder.

ALGO + ED - The combination of an algorithm and patient/family education program that constitutes the major intervention whose effects are being evaluated in this study.

Clinic - An outpatient clinic of the local community mental health and mental retardation (MHMR) center. An MHMR center may have one or more clinics operating under the same local MHMR authority. Medication treatment is a major service provided by clinics in the Texas Department of Mental Health and Mental Retardation's service system.

ED - The patient/family educational program developed or adapted by family members, advocates and members of the TMAP Project Management Team. In this educational package each disorder is addressed in a five-step program that includes: 1) a disorder fact sheet: 2) a symptom and side effect monitoring sheet; 3) introductory information on the disorder and medication treatment, and family support: 4) advanced information on the disorder, medication treatment, and family support and 5) a set of videotapes covering important information for family members and patients on each disorder.

Phase 1 - The first phase of TMAP where the three medication treatment algorithms were developed.

Phase 2 - During the second phase of TMAP, the algorithms developed in Phase 1 were evaluated for feasibility and suitability of implementation in a public sector mental health system that provides services to individuals with serious and persistent mental illness.

TMAP - The Texas Medication Algorithm Project. This project is a unique, collaborative public-academic effort among the Texas Department of Mental Health and Mental Retardation, UT Southwestern Medical Center, UT College of Pharmacy, the Texas Department of Criminal Justice, and four other Texas medical schools. TMAP is composed of three phases.

PMT - The Project Management Team whose members come from the University of Texas Southwestern Medical Center Department of Psychiatry, the University of Texas at Austin College of Pharmacy, the UT Health Sciences Center at San Antonio, UT Health Science Center at Houston, and from the Texas Department of Mental Health and Mental Retardation. The PMT not only facilitates communication among all those

involved in TMAP, but is also responsible for the development and implementation of all aspects of the project. This team oversees all aspects of the Phase 3 protocol, management of the algorithm implementation process, management of data collection, data analysis, and reporting of results.

Site - A clinic that, as part of the evaluation of Phase 3, will either implement one of the three interventions, i.e., ALGO + ED, or will be a control clinic.

TAU - Treatment as usual. In this evaluation TAU is the comparison condition of which there are two groups. The first TAU group includes patients seen by physicians located in a clinic in which no algorithms are used. This is the TAU - nonALGO clinic control group. The second group, TAU - ALGO clinic, consists of patients treated by a physician who is using one of the three algorithms for other patients, but not for them or their disease state.

TMAP Scientific Review Group - A multidisciplinary cadre of national experts on outcomes research who review the evaluation protocol for Phase 3 and provide feedback to the Project Management Team.

TMAP Steering Committee - The 12 member committee, with representatives from the Texas Department of Mental Health and Mental Retardation, the Texas Department of Criminal Justice, the academic institutions participating in TMAP, and patient representatives. The Steering Committee provides general project oversight by reviewing and approving the protocol, periodically monitoring the progress of the project, and making recommendations for any revisions or subsequent, wider implementation of the algorithms.

Appendix F

Informed Consent Form

Appendix G

Intake Form

TMAP ***Intake Form***

_____ Local Case # _____ MHMR Physician Code _____/_____ Component/Clinic # **Date of Visit:** _____/_____/_____ mm dd yy

Coordinator Name: _____ **Coordinator Type:** ☐ Clinical ☐ Research

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

Principal Diagnosis *(DSM-IV Axis I code)*: ____ ____ ____ . ____ ____ → **Age at Onset:** _____

Other current diagnoses <u>not including</u> principal diagnosis:

Axis I: ____ ____ ____ . ____ ____ ____ ____ ____ . ____ ____

Alcohol/Substance Problem *(within last 6 months)*: ☐ *Yes* ☐ *No*

Axis III *(Current General medical conditions, <u>check all that apply</u>)*:

☐ Hypertension ☐ Diabetes ☐ HIV Disease ☐ Closed Head Injury with Loss of Consciousness
☐ Heart Failure ☐ Hypothyroid ☐ Cancer ☐ Head Injury ☐ Ischemic Heart Disease ☐ Arthritis
☐ Chronic Lung Disease ☐ Seizure Disorder ☐ Other Significant Systemic Illness *(specify)*:_____

Have any family members been treated for the following *(please check all that apply)*:

	Depression	Schizophrenia	Bipolar	Alcohol Abuse	Drug Abuse	Suicide
Father						
Mother						
Sister(s)						
Brother(s)						
Son(s)						
Daughter(s)						

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

TMAP Group *(check one)*: ☐ ALGO+ED ☐ TAU ALGO ☐ TAU nonALGO **Disorder** *(check one)*: ☐ *MDD* ☐ *BPD* ☐ *SCZ*

Do Not Complete Medications if a TAU Patient

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

Medication	Current	Dose	Freq.	Weeks on	Response
1.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
2.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
3.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
4.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
5.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
6.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
7.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
8.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
9.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
10.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
11.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
12.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
13.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
14.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*
15.	☐ *Yes* ☐ *No*				☐ *Full* ☐ *Partial* ☐ *None* ☐ *Unknown*

Date Visit #1 is Scheduled For: _____/_____/_____ *(can be the same date as this visit, i.e., Intake)*
mm dd yy

Appendix H

Patient Perception of Benefits of Care Form

TMAP

Patient Perception of Benefits of Care

Patient's Name: _____

Social Security Number: ___ ___ ___ / ___ __ / ___ ___ ___ ___.

Local Case #: _____

Component/Clinic #: _____

Please indicate if you agree with each of the following statements:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If I can get the help I need from a doctor, I believe that I will be much better able to:					
1. manage problems at home:	1	2	3	4	5
2. earn a living or go to school:	1	2	3	4	5
3. enjoy things that interest me:	1	2	3	4	5
4. feel good about myself:	1	2	3	4	5
5. handle emergencies and crises:	1	2	3	4	5
6. get along with my friends:	1	2	3	4	5
7. get along with my family:	1	2	3	4	5
8. control my life:	1	2	3	4	5
9. do things on my own:	1	2	3	4	5
10. make important decisions that affect my life and those of my family:	1	2	3	4	5

Appendix I

Demographic Questionnaire

TMAP

Demographic Questionnaire

Patient's Name: _____

Social Security Number: ___ ___ ___ / ___ __ / ___ ___ ___ ___.

Local Case #: _____

Component/Clinic #: _____

(1) What is your current address?

STREET _____.
STREET _____.
CITY _____.
STATE _____.
ZIP _____.

(2) How long have you lived there?

MONTHS _____.
YEARS _____.

(3) What type of residence is it?

Single Family House-Detached....01
Duplex or Semi-Detached....02
Triplex....03
Quadruplex....04
Apartment....05
Condominium....06
Retirement Complex, Senior Housing....07
Rooming House....08
Room in Private Hotel....09
Nursing Home....10
Residential Care Home....11
Mobile Home....12
Townhouse....13
Alcohol Rehabilitation Center....14
Hospital....15
VA Domiciliary....16
Automobile....17
Homeless....18

(4) What was your address before that?

STREET _____.
STREET _____.
CITY _____.
STATE _____.
ZIP _____.

(5) How long had you lived there?

MONTHS _____.
YEARS _____.

(6) What type of residence was it?

Single Family House-Detached....01
Duplex or Semi-Detached....02
Triplex....03
Quadruplex....04
Apartment....05
Condominium....06
Retirement Complex, Senior Housing....07
Rooming House....08
Room in Private Hotel....09
Nursing Home....10
Residential Care Home....11
Mobile Home....12
Townhouse....13
Alcohol Rehabilitation Center....14
Hospital....15
VA Domiciliary....16
Automobile....17
Homeless....18

(7) How far have you gotten in school?

No School	00
Elementary	01, 02, 03, 04, 05, 06, 07, 08
High School	09, 10, 11, 12
College	13, 14, 15, 16
Post College	17, 18, 19, 20

(A) Did you graduate from High School

Yes	1 (go to Q. 8).
No	0

(B) *If no...* Did you graduate with a G.E.D. (General Equivalency Diploma)?

Yes	1
No	0

(8) What is your current employment status?

Never Employed	01	Full-time Employed	04
Unemployed	02	Self-Employed	05
Part-time Employed	03		

(9) What is your occupation?

Professional, technical, managerial	01	Benchwork	07
Clerical, sales	02	Structural work	08
Service	03	Homemaker	09
Agricultural, fishery, forestry	04	Miscellaneous	10
Processing	05	Military	11
Machine trades	06	Own Business	12

(10) What is your marital status?

Never Married	01	Divorced	04
Married	02	Widowed	05
Separated	03		

(11) What is your date of birth? (__ __ / __ __ / __ __)
mm dd yy

(12) *For the next set of questions, please think about the people who live with you at your current address?*

(A) Does your **spouse** live with you?

Yes	01
No	00

(B) How many **relatives** live with you?

Number of Relatives (include spouse) _____.

(C) How many **friends** live with you?

Number of Friends _____.

(D) *TOTAL*

Total Number at Address _____.

(13) *For the next set of questions, please think about the Friends / Relatives / Spouse who live within 20 miles of your current address?*

(A) Excluding the people who live with you, how many **relatives** live within 20 miles of your current address?

Number of Relatives _____ .

(B) Excluding the people who live with you, how many **friends** live within 20 miles?

Number of Friends _____ .

(C) If separated, does your **spouse** live within 20 miles?

Yes 1
No 0
Inapplicable.....7

(D) *TOTAL*

Total Number within 20 miles (Exclude subject's address) _____ .

(14) As I read each possible source of income, will you tell me if you receive any money each month from each source. Do you receive income from ...

		No	Yes	Refused	Don't Know	$ Per Month
A.	Wages, salaries, tips, commissions	0	1	8	9	
B.	Social Security	0	1	8	9	
C.	Retirement Pension	0	1	8	9	
D.	VA Payments/Armed Forces allotments	0	1	8	9	
E.	Railroad retirement	0	1	8	9	
F.	Interests, dividends, royalties, leases,...	0	1	8	9	
G.	Case contributions from family/friends	0	1	8	9	
H.	Public assistance	0	1	8	9	
I.	SSI/ Blind, Disabled, Age Assistance	0	1	8	9	
J.	Unemployment benefits	0	1	8	9	
K.	VA Disability Benefits	0	1	8	9	

(15) What is the total amount you receive each month before taxes?

Monthly income _____.

(16) Do you receive food stamps

Yes 1
No .....0 (go to Q. 18).

(17) *If yes....* What was the monthly value of the food stamps

Monthly value _____.

(18) Do you own or rent your home?

Own 1
Buying.....2 (go to Q.19).
Renting .....3 (go to Q.19).
Other _____.....4

(19) *If buying or renting* … How much do you pay per month for rent or mortgage payments?

Monthly payments _____.

Appendix J

Patient Clinic Visit

Clinical Record Form

TMAP

Patient Clinic Visit
Clinical Record Form

Date: ____/____/____ Service Activity Code: _______

Site/Clinic #: ______________/______ Physician Code: __________

Start Time: _____:_____ Stop Time: _____:_____ Duration: __________

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

Use for all physician's ratings below:
0=No Symptoms 1=Borderline 2=Mild 3=Moderate 4=Marked 5=Severe 6=Extreme

Core Symptoms: ____ Mania ____ Depression ____ Positive Sx *or* Psychoses ____ Negative Sx

Other Symptoms: ____ Irritability ____ Mood Lability ____ Insomnia ____ Agitation ____ Anxiety

____ Other (specify): ____ **Overall Side Effect Severity:** _____

Is patient presently suicidal? ☐Yes ☐No homicidal? ☐Yes ☐No **Overall Functioning:** _____ (1-100)

Prescription Information

Medication Name	New/ Continuing/ Discontinue	Please provide information on titration, dose, dose frequency, duration the medication is to be taken, start and stop date *(if applicable),* and any other pertinent information describing this medication.	Indication (check all that apply)[1]
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE
	☐ New ☐ Cont. ☐ D/C		☐ S ☐ OS ☐ SE

[1]S=Meds Targeted at core syndrome. OS=Meds targeted at other symptoms. SE=Meds for side effects of S or OS

Are serum levels needed? ☐ Yes ☐ No *(if yes, specify below)*

Comments:____

____

____

____

____

____

Is a change from the algorithm recommended? ☐ Yes ☐ No Algo Stage: _______

If yes, check all that apply:
☐ No options left (ALGO ran out).
☐ Next step not available at this site.
☐ Patient previously failed next *(or 1st)* step.
☐ Next step not acceptable to patient.
☐ Next step not medically safe for this patient.
☐ Other ______________________________

Side effect algo implemented? ☐ Yes ☐ No Other symptom algo implemented? ☐ Yes ☐ No

Return to clinic: ________ weeks **Physician Signature:**________________________________

Appendix K

Patient Clinic Visit

Physician Review Form

TMAP

Patient Clinic Visit
Physician Review Form

_____ _____/_____ **Date of Visit:** _____/_____/_____ **Visit Number:** _____

Local Case # **Component/Clinic #** mm dd yy

All Medications In Last Week (Prescription and OTC)	
Medication Name	Was the medication taken as prescribed?
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No

All Medications In Last Week (Prescription and OTC)	
Medication Name	Was the medication taken as prescribed?
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No
	☐ Mostly Yes ☐ Sometimes ☐ No

Clinical Rating Scales:
POS SX:_____ NEG SX:_____ PANSS-N:_____ BPRS:_____ IDS-C:_____ IDS-SR:_____ Altman:_____

Overall Patient Global *(self report)***:**
Symptom Severity: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 Side Effects: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Staff Time *(for this visit)*: _____ *(in minutes)*

Patient/Family Education:
Done at this visit? ☐ Yes ☐ No Between last visit and this visit? ☐ Yes ☐ No

Patient Education Activity Log Completed? ☐ Yes ☐ No

Most Recent Drug Levels:

Medication Name	Date Drawn	Serum Level

Comments:_____
_____
_____
_____
_____
_____
_____
_____
_____

Termination Visit? ☐ Yes ☐ No If No, Next Appointment Date: _____/_____/_____

Clinical Coordinator Signature: _____

Appendix L

Termination Form

TMAP ***Termination Form***

_____ _____/_____ **Date of Visit:** _____/_____/_____ **Visit Number:** _____
Local Case # **Component/Clinic #** mm dd yy

Termination Type: ☐ Clinical Care ☐ Outcome Assessments

Termination Reason *(check all that apply)***:**

☐ *End of Study* ☐ *Patient Lost to Follow-up*
☐ *Patient Transfer* ☐ *Patient Move*
☐ *Patient Discharge* ☐ *Patient Choice*
☐ *Physician Choice* ☐ *Poor Symptom Response*
☐ *Adverse Effects* ☐ *Treatment No Longer Indicated*
☐ *Diagnosis Change*
☐ *Other* _____

Stop here if this is a termination from the Outcome Measures, continue if this is a termination from clinical care.

Physician Satisfaction Ratings: (*Please check the appropriate response following each statement.)*

	Strongly Agree	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**
1. Following the algorithm was difficult with this patient.	☐	☐	☐	☐	☐
2. Using the algorithm assisted me in making treatment decisions for this patient.	☐	☐	☐	☐	☐
3. I would have liked additional choices in the algorithm stages for this patient.	☐	☐	☐	☐	☐

In using the algorithm with this patient, how would you rate the overall quality of medication treatment?

☐ 1=Excellent ☐ 2=Very Good ☐ 3=Good ☐ 4=Substandard ☐ 5=Unacceptable

Appendix M

Question and Response Fax Form

TMAP ***Question and Response Fax Form***

To: _____ **Madhukar H. Trivedi, M.D.**
Phone # (214) 648-4282
Fax # (214) 648-4210

or _____ **Tracie Key, R.N., B.S.N.**
Phone # (214) 648-8344
Fax # (214) 648-4210

From: _____ **Phone #: (____)**_____

Date: _____ **Fax #: (____)**_____

Question:

_____

_____

_____

_____

_____

_____

_____

_____

_____

****

Researched by: **Trivedi** **Pigott** **Key** **Other:**_____

Response from: **Trivedi** **Pigott** **Key** **Other:**_____

Faxed _____ **Date:** _____ **Called** _____ **Date:** _____

To: _____ **Fax #: (____)**_____

Response:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Module Coordinator Only: Teleconference Agenda __