Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000

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Background: The process and outcome of a consensus conference to develop revised algorithms for treatment of bipolar disorder to be implemented in the public mental health system of Texas are described. These medication algorithms for bipolar disorder are an update of those developed for the Texas Medication Algorithm Project, a research study that tested the clinical and economic impact of treatment guidelines for major psychiatric illnesses treated in the Texas public mental health system (Texas Department of Mental Health and Mental Retardation [TDMHMR]).

Method: Academic clinicians and researchers, practicing clinicians in the TDMHMR system, administrators, advocates, and consumers participated in a consensus conference in August 2000. Participants attended presentations reviewing new evidence in the pharmacologic treatment of bipolar disorder and discussed the needs of consumers in the TDMHMR system. Principles were enumerated, including balancing of evidence for efficacy, tolerability, and safety in medication choices. A set of 7 distinct algorithms was drafted. In the following months, a subcommittee condensed this product into 2 primary algorithms.

Results: The panel agreed to 2 primary algorithms: treatment of mania/hypomania, including 3 pathways for treatment of euphoric symptoms, mixed or dysphoric symptoms, and psychotic symptoms; and treatment of depressive symptoms. General principles to guide algorithm implementation were discussed and drafted.

Conclusion: The revised algorithms are currently being disseminated and implemented within the Texas public mental health system. The goals of the Texas initiative include increasing the consistency of appropriate treatment of bipolar disorder, encouraging systematic and optimal use of available pharmacotherapies, and improving the outcomes of patients with bipolar disorder.

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A complete list of members of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder appears at the end of this article. Special thanks to the Texas Department of Mental Health and Mental Retardation for funding the consensus conference.

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This article describes the process of reviewing, updating, and in some cases, creating treatment algorithms for patients with bipolar I disorder being treated in the public mental health system of Texas. The revised algorithms will be used in the Texas Implementation of Medication Algorithms (TIMA) initiative, which mandates the use of treatment guidelines for major psychiatric disorders in state-funded inpatient and outpatient settings in Texas. Consistent with past methodologies of the Texas Medication Algorithm Project (TMAP), a consensus panel format was utilized to update previous versions of the algorithms.[1–6]

A number of academic psychiatrists and clinical psychopharmacology specialists in the area of bipolar disorder were identified and invited to attend a 2-day conference in

Dallas, Texas, in August 2000. Additionally, administrators of the Texas Department of Mental Health and Mental Retardation (TDMHMR), physicians from community mental health settings, advocates, patients, and family members were invited to join the consensus panel. The first day was devoted to structured presentations and panel discussions regarding the newest research on pharmacologic treatment of bipolar disorder and the goals of various interest groups regarding these algorithms. After conclusion of these presentations, the panel met privately through the evening and throughout the second day to draft the medication algorithms.

When possible, the consensus panel decision process was based on evidence rather than on expert opinion or clinical consensus. The consensus panel used a method similar to that utilized by the Agency for Healthcare Research and Quality (AHRQ) (formerly the Agency for Health Care Policy and Research [AHCPR]) in the development of depression guidelines. A rating system of A, B, or C is used to evaluate the quality of data available to support a recommendation: "A" representing randomized, blinded, and placebo-controlled trials; "B" representing open, controlled trials and/or large case series; and "C" representing early findings on smaller case reports and case series.[7,8] Presentations on new, well-controlled treatment studies were made (including recently presented or in-submission studies) in order to provide the consensus panel with the most current evidence.

Panel decisions were made after weighing various issues, including level of evidence in support of a treatment (both efficacy and effectiveness data), expert opinion, consumer input, and safety and tolerability issues. In particular, safety and tolerability issues directly affected placement of certain treatments in the algorithm. Therefore, for example, the panel may have deliberated and determined that because of safety concerns a "level A" treatment be placed after a treatment with less robust evidence of treatment efficacy. Where the panel could not reach consensus, or there was inadequate evidence to reach a consensus, no opinion was rendered. Rather, where potential treatments had the possibility of equivalent efficacy, or there were no data suggesting superiority, they were included as multiple options within a single stage of treatment.

The panel did not work from a restricted formulary. With the support of the administration of TDMHMR, they were asked to consider all commercially available medications currently used in the treatment of bipolar disorder. The algorithms are flexible so that when equally efficacious medications are available at a given stage, the practitioner is able to make decisions on the basis of individual patient preference, economics, or other practice priorities.

While the goal of this conference was to develop medication algorithms, it is not the intention of these authors to minimize the potential necessity and impact of other therapies, including psychotherapy, psychosocial interventions, and alternative and complementary treatments, in the treatment of bipolar disorder. The value of these and other interventions is recognized by this panel. Future guidelines will most likely include such recommendations as data become available and include more comprehensive treatment recommendations.

When asked to develop a set of algorithms for the treatment of patients with bipolar disorder, the consensus panel developed 7 distinct algorithms for different presentations of the disorder. This article will discuss the initial algorithms and the process by which they were condensed into a summary product of 2 algorithms that are feasible for broad-scale implementation in the public mental health system, with few accompanying supports or resources. General principles derived at the Consensus Conference will first be presented with discussion regarding the philosophy of guideline implementation, as well as specific rules that govern application of these guidelines. The treatment algorithms will then be presented.

TREATMENT ALGORITHMS FOR BIPOLAR DISORDER

The goal of the consensus panel was to integrate available research information and clinical consensus into user-friendly, hierarchical decision trees of medication options for patients with bipolar disorder. The adoption of treatment guidelines in the TDMHMR system is not intended to substitute for clinician judgment or choice, but to provide systematic guidance and structure to the array of potential treatment options for this patient group. The following general principles are intended to disseminate the algorithm philosophy as well as specific implementation strategies endorsed by the panel.

General Principles

- The goals of treatment are (1) symptomatic remission, (2) full return of psychosocial functioning, and (3) prevention of relapses and recurrences.
- The algorithm development process was guided by the need to balance evidence for efficacy, tolerability, and safety. These core principles are also expected to apply to clinical decisions for individuals as well.
- The treatment options recommended at the various points in the algorithms are based on available data from controlled clinical trials, open trials and retrospective data analyses, case reports and expert clinical consensus, as well as expert opinion, consumer input, and safety and tolerability issues. The later stages in the algorithm involve more complicated regimens, while the earlier stages involve simpler treatments in terms of safety, tolerability, ease of use, side effect profiles, etc. The

treatment algorithms will be revised periodically as more controlled scientific studies (level A), the weight of open trials (level B), or new information about a given medication argues for adjustment.

Choice of Treatment

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

Patient/Clinician Relationship

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

Visit Frequency

- At the beginning of entry into an algorithm, relatively frequent (e.g., every 2 weeks) patient follow-up appointments for further evaluation and assessment should be scheduled in order to optimize treatment outcomes by (1) encouraging patient adherence with treatment, (2) making medication dose changes in a timely manner, and (3) rapidly identifying and correcting potential problems or adverse events associated with treatment.

Clinical Management

- All patients with bipolar disorder who achieve a satisfactory clinical response (and preferably symptom remission) should receive continuation phase treatment.
- Adequate documentation should be completed for each algorithm stage and treatment choice (i.e., critical decision points). If algorithm stages are skipped or if treatment is different from the algorithm(s), the rationale should be adequately documented.
- At baseline and throughout treatment, the patient should be evaluated for possible psychosocial interventions, including psychotherapy.
- Use of the algorithms for treatment of patients with bipolar disorder assumes that a thorough evaluation and diagnosis has been made and that selection of these treatments is appropriate for a given patient. If a patient completes trials of 2 stages of the algorithm without observable positive outcomes, it may be helpful to revisit the diagnosis and perform another evaluation, as well as consider mitigating factors such as substance abuse.
- When there is a choice between brands, generic, or different forms (i.e., slow-release) of a recommended medication, always initiate treatment with the form that is most likely to be tolerated.

ALGORITHMS

Due to the complexity of bipolar illness, the consensus panel first drafted the "ideal" algorithms for treatment of patients with bipolar disorder, which resulted in 7 distinct algorithms. The 7 algorithms varied in the level of supporting data, with some relying almost exclusively on expert consensus. For this reason, and to increase utility and feasibility of large-scale implementation, a subset of panel participants convened a meeting to condense these 7 algorithms into a form that could be implemented within the limited resources of public mental health clinics. The condensed product was then circulated among panel participants, and after several drafts, consensus was reached. The final product consists of an algorithm for mania/hypomania, which includes 3 pathways for the treatment of euphoric mania/hypomania, mixed or dysphoric mania/hypomania, and psychotic mania. A second algorithm for treatment of a major depressive episode is used in conjunction with the primary algorithm, if a patient develops persistent or severe depressive symptoms. Algorithms for treatment of rapid cycling and bipolar II disorder were eliminated due to the need to simplify for implementation

and the limited controlled evidence regarding best treatments for rapid cycling or bipolar II disorder. Therefore, the final product is intended for treatment of patients with a diagnosis of bipolar I disorder.

All patients will receive treatment with the core algorithm for mania/hypomania, with the intermittent use of the depression treatment algorithm as needed in addition to the algorithm for hypomania/mania. The panel clearly recommended that all patients with bipolar I disorder receive continuing treatment with an antimanic agent from among those included in the core algorithm for mania/hypomania. These algorithms are intended for both outpatients and inpatients. Early stages include monotherapy with widely utilized medications; later stages quickly move to more complex medication combinations that may involve greater risk of side effects and require closer monitoring and attention by the clinician. Patients progress through the stages if there is inadequate response to treatment or intolerance to medication side effects. The stages, along with critical research citations, consensus opinion, and issues regarding discussion of safety and tolerability for that treatment strategy, will be presented in turn. Continuation and maintenance phase treatment issues will be addressed after presentation of the algorithms for acute phase treatment.

Clinicians should take into consideration the following clinical caveats: (1) Severely ill patients should be seen more often (i.e., weekly) than patients who are less ill. Less ill but still symptomatic patients should be seen more often (every 2 weeks is recommended) than patients whose symptoms have remitted. (2) A single week of improvement may not represent a stable effect. Since the recommendation to go to continuation phase assumes a stable response, patients should be evaluated for at least 2 weeks following the first week of "response" to ensure stability of improvement before progressing to the continuation phase of treatment. (3) In the continuation phase for mania/hypomania, patients should be seen at least monthly for the first 3 months, then every 2 to 3 months thereafter.

The aim of treatment is symptom remission and normalization of function rather than just symptom improvement. Although not all patients obtain a remission, every effort should be made to ensure the greatest maximal benefit for each patient. Therefore, once a response is seen, further tactical (e.g., dosage adjustment or augmentation) or strategic options (e.g., addition of medication, psychotherapy, or rehabilitative services) should be considered before accepting a response that is short of remission.

Within a stage, all medication decisions are based on clinician choice and patient preference. Throughout the algorithm, the 3 elements for making medication choices are efficacy or treatment response (change in symptoms), tolerability (side effects), and serum drug levels (when applicable). The considerations of treatment response and tolerability are both evident. Measurement of serum drug levels is recommended when applicable to ensure adequate dosing is achieved prior to trying medication alternatives and to provide a guide to when there may be room to decrease the dose in a patient with good response but some degree of intolerance. Serum levels may also be useful in assisting with dosage adjustments necessary because of potential drug interactions. Serum levels should be obtained and available for applicable medications prior to each decision point.

Algorithm for Mania/Hypomania

The algorithm for mania/hypomania (Figure 1) begins with the assumption that the patient has received a thorough evaluation and has received a diagnosis of bipolar I disorder. Additionally, symptoms are severe enough to warrant medication treatment. Medications that were deemed appropriate for treatment of hypomania and mania at the time of algorithm development (spring 2001) are included; omissions are intentional. For example, benzodiazepines are not included in the guideline for treatment of mania/hypomania because the algorithm is focused on treatments for the core symptoms of the disorder, although the clinician may use them for treatment of adjunctive symptoms.

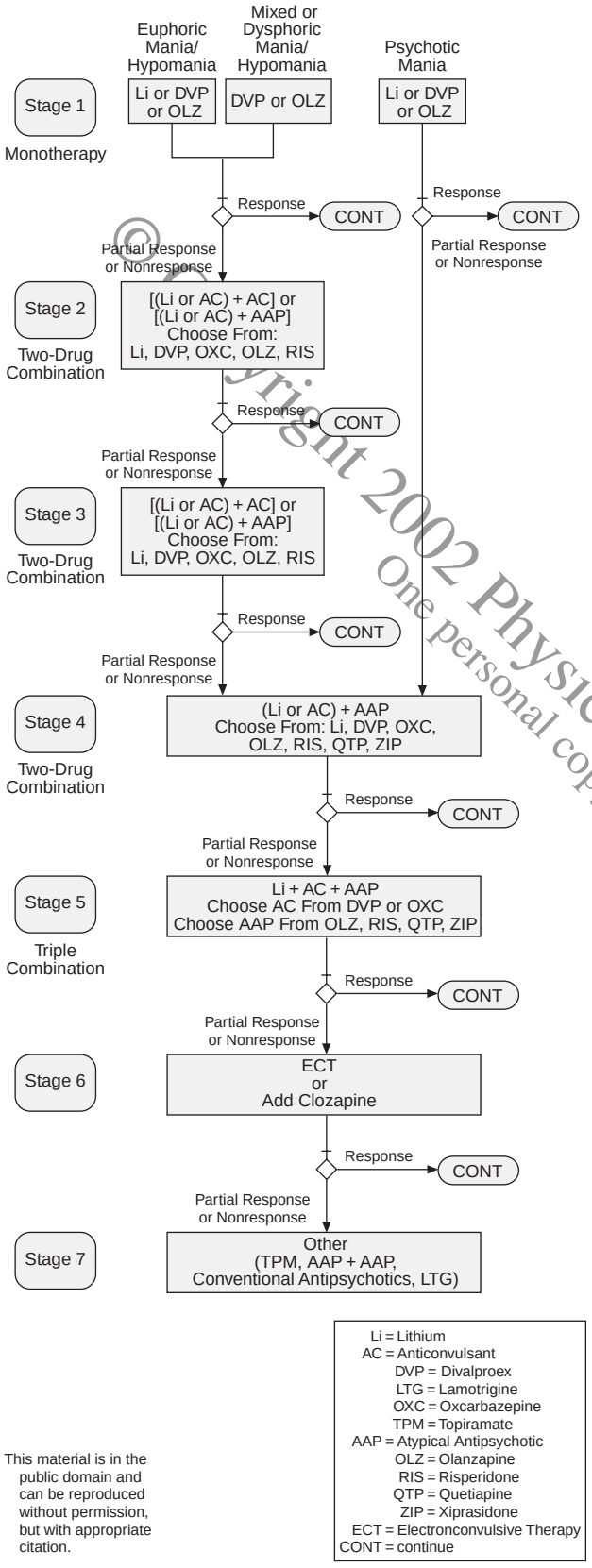
Stage 1. The options for Stage 1 include monotherapy with lithium, divalproex sodium, or olanzapine. These agents will be discussed in turn. For patients presenting with euphoric mania/hypomania or psychotic mania, choice is from any of the 3 agents. For mixed or dysphoric mania, the recommendation is to choose between divalproex and olanzapine.

The efficacy of lithium as an antimanic agent has been well established. However, there are data suggesting that the presence of dysphoric mania predicts poorer treatment response to lithium.[9–11] Therefore, lithium is not recommended as monotherapy for that pathway. Divalproex is recommended as a monotherapy option for any presentation of mania/hypomania.[12,13] Divalproex is specifically recommended, rather than valproic acid, due to its more favorable side effect profile and tolerability.[14]

Olanzapine monotherapy for symptoms of mania/hypomania was added, based on placebo-controlled double-blind trials leading to recent U.S. Food and Drug Administration approval of olanzapine for acute mania.[15–17] A minority opinion of the Consensus Panel expressed concern at putting olanzapine as a first-line monotherapy because of relatively limited safety data on longer-term use of this drug and recent data suggesting a higher risk for development of diabetes.[18–21]

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

Figure 1. Algorithm for Treatment of Mania/Hypomania in Patients With Bipolar I Disorder



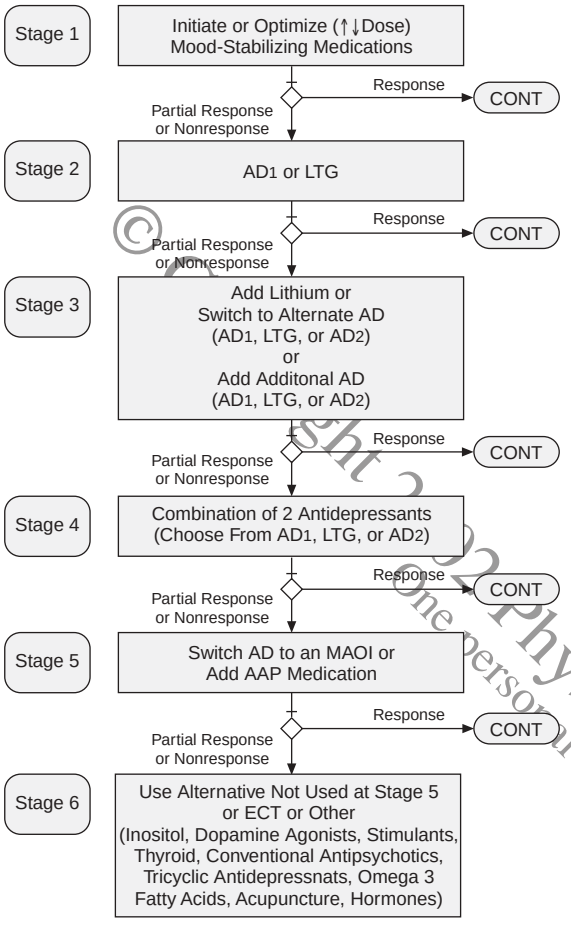
Stage 2. Use of combination therapy essentially has become standard care in the treatment of the majority of patients with bipolar disorder,[22–24] as recognized through clinical consensus and expert opinion versus controlled data. Similar to other recently published algorithms for treatment of bipolar disorder,[25–27] Stage 2 treatment includes combination treatment with 2 agents. Clinicians may choose from the following: lithium, divalproex, oxcarbazepine, olanzapine, or risperidone. Therefore, the combination is either lithium or an anticonvulsant plus an anticonvulsant, or lithium or an anticonvulsant plus an atypical antipsychotic [(Li or AC) + AC, or (Li or AC) + AAP]. Oxcarbazepine and risperidone are added as options here. While there are no double-blind, placebo-controlled trials supporting risperidone monotherapy, there is 1 small double-blind, randomized, single-site trial,[28] an add-on trial,[29] and open reports that support its use in combination.[30–33] Oxcarbazepine is structurally similar to carbamazepine, but does not produce the epoxide metabolite, which is thought to be associated with much of the toxicity and intolerance associated with carbamazepine. Oxcarbazepine has been shown to have comparable efficacy in studies of epilepsy and preliminary work in bipolar patients. It is associated with increased tolerability and fewer drug interactions and does not require serum level monitoring.[34–44] Therefore, consistent with the general principle to use forms of medications associated with greatest tolerability, oxcarbazepine is recommended. While carbamazepine is not included as a monotherapy option, it is recommended in combination with other antimanic drugs.[45–50] A minority opinion within the panel was that further efficacy data in bipolar patients were needed before including oxcarbazepine in the algorithm.

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

Stage 4. This stage also includes combination therapy, but at this point, the clinician is prompted directly to use an atypical antipsychotic agent in combination with lithium, divalproex, or oxcarbazepine (i.e., [Li or AC] + AAP). For patients with psychotic mania, the recommendation is to progress immediately to this combination if Stage 1 monotherapy with lithium, divalproex, or olanzapine is ineffective or only partially effective. Quetiapine and ziprasidone are added as additional choices here. Quetiapine has a number of open and double-blind trials supporting its utility in combination with other medications for bipolar disorder.[51–56] Ziprasidone has one completed double-blind, placebo-controlled, multicenter trial of monotherapy in 210 inpatients with mania, which supports its antimanic properties.[57]

Stage 5. Stage 5 includes "triple therapy," with lithium, an anticonvulsant (choose from divalproex or oxcarbaze-

Figure 2. Algorithm for the Treatment of Depression in Bipolar I Disorder (to be used in conjunction with the primary treatment algorithm for mania/hypomania)



AAP = Atypical Antipsychotic
AD = Antidepressant
ECT = Electronconvulsive Therapy
MAOI = Monoamine Oxidase Inhibitor
AD1 = Bupropion Sustained Release or Selective Serotonin Reuptake Inhibitor
AD2 = Venlafaxine or Nefazodone
LTG = Lamotrigine
CONT = continued

pine), and an atypical antipsychotic medication (choose from olanzapine, risperidone, quetiapine, or ziprasidone).

Stage 6. Electroconvulsive therapy (ECT) is an effective treatment for acute mania,[58,59] but safety, tolerability, and patient acceptance issues led to its placement further down in the algorithm at Stage 6. Many manic patients will experience a relatively rapid response to ECT. Recommended frequency is 3 treatments per week, and ECT should be terminated when patients are in full remission or fail to sustain response over 3 to 6 treatments. At least 6 to 10 ECT treatments should be attempted before declaring a patient resistant to treatment.

Alternatively, clozapine could be added to other medications as a treatment option here.[60–63] This is consistent with clinical recommendations to attempt treatment with other atypical antipsychotic medications before initiating clozapine treatment due to potential tolerability difficulties and the medical monitoring required.

Stage 7. This stage includes other options that may be used as adjuncts to partially effective medication combinations and medications with more limited data. It includes topiramate,[64–69] a combination of medications that includes 2 atypical antipsychotic medications, conventional antipsychotics, and lamotrigine.[70–74]

Strategies to Treat Depression in Bipolar Disorder

The majority of the algorithm of strategies to treat depression in bipolar I disorder (Figure 2) is based on expert consensus, given the limited evidence for treatment of depression in patients with bipolar disorder. Several treatments that do have evidence supporting their effectiveness are listed at advanced stages due to issues regarding safety and tolerability (monoamine oxidase inhibitor [MAOI] medications, electroconvulsive therapy [ECT]). Within some stages (e.g., Stage 3), several options are provided because the evidence does not support a more specific order of those treatment strategies. It is assumed that this algorithm will be utilized in conjunction with the primary treatment algorithm for mania/hypomania. If a patient reports symptoms of depression significant enough to warrant intervention, the clinician is directed to utilize this algorithm as a concomitant treatment strategy in addition to any stage of treatment within the mania/hypomania algorithm. As with any algorithm, if insufficient response in depressive symptoms is achieved, the clinician should continue through the algorithm until satisfactory symptom reduction is achieved.

It is important to carefully consider the addition of an antidepressant to the medication regimen of patients with bipolar disorder. The decision is simplified when the patient has a distinct major depressive episode, without mood lability or hypomania, and the degree of suffering justifies initiating an antidepressant. However, many patients will have significant depressive symptoms, but also periods of dysphoric hypomania, mood lability, irritability, and other more complicated states.[75–79] The balance of optimizing mood stabilizers, possibly adding lithium, or adding an antidepressant must be done on a case-by-case basis. Regardless, the consensus panel maintains that all bipolar depressed patients should have mood-stabilizer treatment optimized.[80]

The algorithm to treat depression in bipolar disorder assumes antidepressants will be used only in conjunction with a mood-stabilizing medication, because of the risk of inducing manic symptoms.[81–83] If a patient develops hypomanic, manic, or mixed symptoms after initiation of an antidepressant agent, the agent should be stopped and those symptoms treated. It may be necessary to adjust the mood stabilizer during treatment (i.e., increase dose with devel-

opment of irritability or mood lability). In some cases, it may be clinically indicated to switch or combine mood stabilizers (i.e., an effective antidepressant is found and continued need for an antidepressant is clear, but this tactic is associated with mild mood lability). It is expected that the clinician will continue to utilize recommendations of the mania/hypomania algorithm even when prescribing antidepressant treatment.

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

Stage 1. The first stage includes initiating and/or optimizing mood-stabilizing medications.[84] The recommendation is that all patients diagnosed with bipolar I disorder be prescribed antimanic medications, using the algorithm for treatment of mania/hypomania. The committee made explicit the recommendation that optimizing mood-stabilizing medications might mean either an increase or decrease in dosing, although no formal studies are available to clearly direct tactics on this issue. In one trial, a second mood stabilizer versus paroxetine was blindly added to the regimen of 27 patients taking either divalproex or lithium and experiencing a depressive episode.[80] While clinical outcomes were similar in the 2 groups, there was a higher number of noncompleters in the group treated with 2 mood stabilizers, which was attributed to intolerance of the combination of 2 mood stabilizers.

Stage 2. Patients entering Stage 2 of the algorithm should have a major depressive episode of sufficient severity to merit medication treatment. Stage 2 includes the addition of a selective serotonin reuptake inhibitor (SSRI), bupropion sustained release (SR), or lamotrigine to existing medications. The SSRI options are open and include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram.[85,86] Randomized controlled trials for unipolar major depression have consistently demonstrated similar efficacy among this class of commercially available antidepressants. Bupropion is an additional option,[87] and the committee recommended the sustained-release version of bupropion due to improved tolerability. On the basis of an accumulating body of the best evidence to date, including placebo-controlled blinded studies (level A evidence) supporting the efficacy of lamotrigine for treatment of bipolar depression, the consensus was to introduce lamotrigine as a Stage 2 option.[72,88–90]

Each of the Stage 2 antidepressants has specific advantages and disadvantages. Particular advantages associated with SSRIs include widespread clinical experience and single daily administration (potentially enhancing compliance). Particular advantages for bupropion SR include (1) little impact on sexual functioning, (2) relatively few drug interactions, and (3) reasonably good tolerability. Lamotrigine has a rare, potential side effect of medically serious rashes (Stevens-Johnson syndrome or toxic epidermal necrolysis). The risk of rash is strongly associated with rate of initial titration; thus, following the recommended medication-dosing schedule is critical. Otherwise, lamotrigine is a generally well-tolerated drug, including single daily administration and little impact on sexual functioning or body habitus.

Stage 3. At this point, the algorithm begins to rely more heavily on clinical consensus and expert opinion, as only limited data on treatment of bipolar depression are available following failure in Stage 2. The algorithm development philosophy is that when there are several options available, with little or no empirically derived reason to rank them, offer choices so that the clinician and patient may discuss and choose among them. Stage 3 offers the clinician and patient several options, including addition of lithium,[91–95] switching to an alternative antidepressant medication (adding venlafaxine or nefazodone as additional options), or adding a second agent from the Stage 2 options (e.g., an antidepressant or lamotrigine).

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

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

Stage 5. Stage 5 includes changing the antidepressant medication to an MAOI or adding an atypical antipsychotic medication.[96] Studies on the use of MAOIs (tranylcypromine) support their effectiveness for bipolar patients in a major depressive episode.[97–99] Because of potential health risks and the need to follow special dietary restrictions and avoid certain medications, MAOIs are located in Stage 5, after medications and medication combinations with fewer level A and B data. Diet restriction guidelines should be provided to all patients receiving MAOI medications.

Stage 6. Recommendations at this stage include using the alternative not used in Stage 5, ECT, or Other. The "Other" list includes options that are exploratory, including inositol, dopamine agonists, stimulant medications, thyroid, conventional antipsychotics, tricyclic antidepressants,

omega-3 fatty acids,[100] acupuncture,[101] and hormones. Despite evidence supporting a partial degree of efficacy in bipolar depression,[85–87,97] tricyclic antidepressants (TCAs) are included in Stage 6 "Other" due to (1) their relatively less favorable side effect profile, (2) their narrow safety margin, and (3) evidence suggesting increased switches into mania relative to newer antidepressants (e.g., bupropion or SSRIs).[84,102,103] However, TCAs are considered an acceptable treatment strategy, especially if the patient has a prior history of good response with no ill effects.

Additional Treatment Interventions

The physician manual that supports implementation of these guidelines includes recommendations for adjunctive treatments, including interventions for insomnia, agitation, and other associated symptoms. Additionally, the manual includes recommendations for side effect management and modifications that may be required for inpatient use of the algorithms.

Recommendations for Continuation Phase Treatment

Algorithm for mania/hypomania. After response (or preferably remission), the medication(s) should be continued for at least 3 months at the dose effective during the acute phase. Patients should be evaluated at least every 3 months during continuation treatment (if possible, every 1–2 months). Frequent contact is critical to increase patient medication adherence and to detect early symptoms of relapse. Importantly, once the medication regimen is stabilized during the latter portion of continuation phase, it is recommended that efforts be made to simplify it. When one of the ongoing medications is discontinued, the dosage should be tapered no more rapidly than 25% per week and not before 3 months of full remission has occurred.[104–106] Tapering and discontinuation usually can be completed over a 1- to 2-month period. Patients should be educated concerning the signs and symptoms of recurrence of an acute manic/hypomanic or depressive episode. While little is scientifically known about the relative need for combined mood stabilizers long term, the expectation is that many, if not most, patients will need combination treatment long term. Related to this is the relatively unstudied area of whether using combination treatment will allow somewhat lower doses while maintaining mood stability. Once the patient is stabilized, consideration of tapering a medication associated with either side effects or limited partial response, while continuing other medications, is reasonable.

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

If the patient received ECT during the acute phase, continuation phase treatment with antimanic medication(s) is recommended after the initial treatment phase of ECT is completed. Selecting an antimanic medication(s) that the patient has not previously received or one that the patient has responded to during a previous episode is generally recommended. However, if necessary, a previously partially effective antimanic medication may be used alone or in combination with other medications. Dosing, duration of treatment, monitoring, and medication tapering are as described above. If a patient relapses during continuation phase treatment, continuation ECT should be considered.

Algorithm for treatment of depression in bipolar disorder. After full response (or preferably remission), the antidepressant medication(s) should be continued for 1 to 3 months at the dose effective during the acute phase. Patients should be evaluated at least every 3 months during continuation treatment (if possible, every 1–2 months). Once again, frequent contact is critical to increase patient medication adherence and to detect early symptoms of relapse.

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

The risks and/or benefits of prolonged use of antidepressant medications in this population are under debate, and this decision should be made by the patient and physician after weighing past history of depressive episodes and clinical response to the medication. When discontinuing the antidepressant, the dosage should be tapered no more rapidly than 25% per week and not before 1 to 3 months of full remission have occurred. Tapering and discontinuation usually can be completed over a 1- to 2-month period. In major depressive disorder (unipolar), a new depressive episode is most likely to occur within the first 8 months of medication discontinuation; therefore, patients should be evaluated every 2 to 4 months during that period. Patients should be educated concerning the signs and symptoms of recurrence of depressive symptoms.

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

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

treatment, monitoring, and medication tapering are as described above. If a patient relapses during continuation phase treatment with an antidepressant, continuation ECT should be considered.

Recommendations for Maintenance Phase Treatment

Guidelines are limited due to relatively few scientific studies on the long-term management of bipolar patients. In practice, essentially all patients will need antimanic medication(s) to prevent return of symptoms. The lowest possible dose is recommended, while maintaining the medication at therapeutic levels. General practice at this time is lifetime medication following 2 manic episodes, or 1 episode if it was a severe episode and/or significant family history of bipolar or major depressive disorder is present. For a first episode of bipolar mania with no family history of bipolar or major depressive disorders, medication tapering and discontinuation may be considered after the continuation period is completed (usually 6 months in remission), depending on the severity of the first episode, surrounding factors, and prodromal history. Patients should be educated to detect emergent mood symptoms and monitored periodically.

For patients who received antidepressant medications, it is likely that some will need antidepressants long term to prevent return of symptoms. The lowest possible effective dose is recommended, while maintaining treatment with an antimanic agent(s).

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 pharmacologic management of bipolar disorder. The patient's risk factors for recurrence should be considered in the decision process.

CONCLUSION

The algorithms reflect current recommendations for treatment of bipolar I disorder from a panel of experts, informed by TDMHMR physicians, advocates, and consumers. The intention is that clinicians will use these guidelines, with the accompanying manual (see http://www.mhmr.state.tx.us/CentralOffice/MedicalDirector/TIMA), to begin treatment with the often severely and persistently ill patients with bipolar I disorder seen in most public mental health settings.

The priority when developing the sequential algorithm recommendations was to provide clinicians with a useful tool to make evidence-based treatment decisions in the often resource-poor environment of a public mental health setting. The consensus panel was broad in scope and content of discussion, and 7 distinct algorithms were originally developed for varying presentations of bipolar disorder. The limits of the expert consensus approach and evidence-based treatment of bipolar disorder are reflected in the inclusion of multiple choices within many algorithm stages. When available data, safety, and expert consensus judged options as relatively equivalent, they were included as options within a stage. Similarly, in those areas where almost no controlled data existed, and for which experts were unable to provide evidence-based, ranked options, we chose not to provide specific recommendations (e.g., rapid cycling and bipolar II).

Importantly, throughout the consensus process, recognition and use of available evidence was a priority. It is encouraging to see active research programs underway to expand our knowledge base on best treatment practices for patients with bipolar I disorder. These algorithms provide a beginning to a sequential approach of medication management for patients with bipolar I disorder. The recently completed TMAP Phase 3 study found that patients using the algorithm package (enriched treatment plus patient and family education) showed significant improvement relative to patients receiving treatment as usual in a matched clinic.[107] Whether the use of treatment algorithms alone will translate to better outcomes when disseminated throughout the Texas public mental health system is not known.

Guidelines must, of necessity, be revised and updated on a regular basis. The versions presented here are being disseminated throughout the Texas public mental health system and will be reviewed and updated as needed in 2002. The algorithms and a manual supporting implementation are available on the TDMHMR Web site at http://www.mhmr.state.tx.us/centraloffice/medicaldirector/TIMA.html.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), citalopram (Celexa), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), inositol (Amino-Cerv and others), lamotrigine (Lamictal), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), tranylcypromine (Parnate), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon).

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