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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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
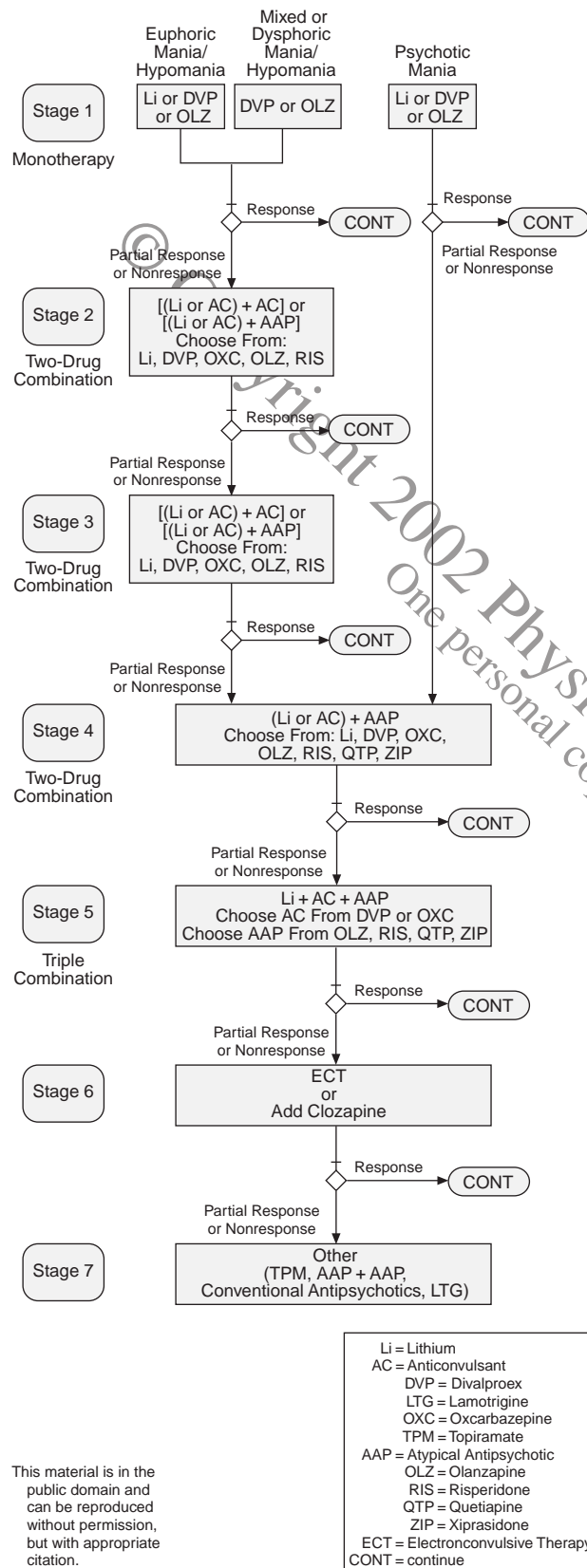
Stage 2. Use of combination therapy essentially has become standard care in the treatment of the majority of patients with bipolar disorder,[22–24] as recognized through clinical consensus and expert opinion versus controlled data. Similar to other recently published algorithms for treatment of bipolar 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-

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