Implementing Evidence-Based Treatment of Manic and Mixed Episodes

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Manic and mixed episodes can be challenging to treat despite published guidelines and algorithms. An alternative iterative approach that offers evidence-based treatment options at critical decision points may help to individualize care. Implementing such an approach begins with making a diagnosis and recognizing individual patient factors, weighing treatment options, and developing a menu of reasonable treatment choices based on the best available evidence. A critical review of the evidence is needed to ensure that interventions with the highest quality evidence are offered preferentially and that relevant individual factors are considered. Educating patients, negotiating treatment options, and selecting a pathway of care with the patient are important steps before initiating an intervention. After initiating an intervention, follow-up proceeds by measuring efficacy and adverse events with the aim of determining whether or not the patient is benefiting from treatment. Based on this knowledge, new individual factors are known and new evidence can be reviewed, so the cycle begins again. Using this iterative approach to treat patients with bipolar disorder in manic and mixed episodes promotes personalized care and relies on understanding the quality of evidence for the treatments commonly used to treat these phases of bipolar disorder. *(J Clin Psychiatry 2006;67[suppl 11]:12–17)*

Bipolar mood disorder is a common, chronic, and often severe mental illness. The complexity of the condition and the lack of a standard intervention model make treating patients with manic and mixed episodes among the greatest challenges facing psychiatrists. Psychiatrists want to treat patients based on the evidence, but each patient presents with unique characteristics, histories, comorbidities, and responses to treatment. By using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) disease management model as a guide, physicians can customize evidence-based treatment strategies in an alternative treatment pathway that individualizes care and reduces the risk of adverse events. STEP-BD is a multicenter, National Institute of Mental Health–supported study designed to assess optimal treatment strategies for patients with bipolar disorder, through both naturalistic and randomized controlled trials.[1]

ITERATIVE APPROACH

At the core of individualizing treatment is recognizing that we clinicians do not know what will work best for an individual patient. By using an iterative approach, a critical decision point can be defined and an intervention initiated at that point (Figure 1). The iterative approach integrates measurement into the management of patients so that benefit to the patient can be assessed and the decision to continue or alter the treatment approach can be made based on the evidence. The iterative approach promotes the best use of physician knowledge and patient participation in managing treatment options.

In order to use this approach, 2 kinds of information are required. One fund of knowledge includes the evidence supporting interventions pertinent to the critical decision point. The vast amount of information that flows across our desks and computer screens often adds confusion rather than clarity to the knowledge we need to make treatment decisions for our patients. The task of weighing the evidence can be simplified by defining categories of evidence and then considering interventions for which the highest level of evidence is available. Studies with sufficiently rigorous methodology to permit valid statistical causal inference merit top ranking and are referred to here as Category A evidence. For example, data from double-blind, placebo-controlled studies having an adequate sample size. Data from this category allow clinicians to make valid causal inferences. Other categories that could help organize the evidence are shown in Table 1. The other fund of knowledge needed to use the proposed iterative schema relates to individual factors. This knowledge base includes both what is already known about this individual patient's response to prior treatment or tolerance to adverse effects. By reviewing the evidence alongside known

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This article is derived from a series of planning teleconferences held in July and August 2005 and supported by an educational grant from GlaxoSmithKline.

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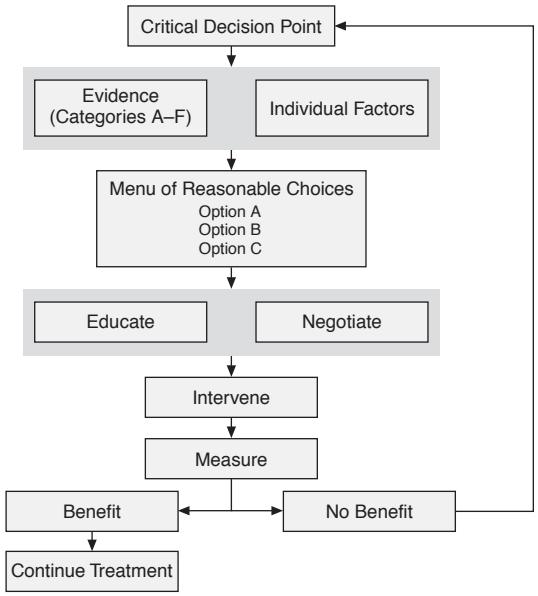
Figure 1. An Iterative Approach to Treating Patients



individual factors, a menu of reasonable treatment options for each individual patient can be generated.

The next steps involve educating the patient about the options, negotiating with the patient which intervention he or she will accept, and then initiating a treatment plan (see Figure 1). Once the intervention has been implemented, its effectiveness must be measured. If the patient is benefiting from treatment, the treatment plan can be continued. If the patient is not benefiting from treatment, the next critical decision point involves determining whether to alter the intervention. Since knowing that the patient is or is not benefiting from treatment adds new information about the individual, proceeding through this decision loop does not mean returning to the same starting point. As the process cycles around this iterative pathway, a new menu of reasonable treatment options that are specific to the individual can be offered based on what is known about the patient and the evidence.

ITERATIVE APPROACH APPLIED TO TREATING MANIC AND MIXED EPISODES

Identifying Clinical Mood States

Applying an iterative approach to treating patients with bipolar disorder in manic and mixed episodes begins with identifying those mood states. A systematic evaluation must be performed initially and at every follow-up visit to determine current clinical state. Seven of the 8 clinical mood disorder states used in STEP-BD are based on the mood state definitions in the DSM-IV: (1) depression; (2) mania; (3) mixed; (4) hypomania; (5) full remission (8 consecutive weeks well), which is known as "recovered"

Table 1. Categories of Evidence[a]

A. More than 1 double-blind, placebo-controlled trial with adequate sample[b]
B. Double-blind comparison trials with adequate sample[b]
C. Open comparison trials with adequate sample[b]
D. Uncontrolled observation or controlled study with ambiguous result
E. No published evidence (± class effect)
F. Available evidence negative

[a]Data from Silverstone and Silverstone.[34]
[b]Adequate sample = statistical power ≥ 0.8 to detect meaningful differences at $p < .05$.

in STEP-BD; and partial remission, which has 2 definitions in DSM-IV that are 2 separate items in STEP-BD as follows: (6) "continued symptomatic," wherein some symptoms are still present but full criteria are no longer met and (7) "recovering," wherein there are no longer any significant symptoms but the period of remission has been less than 8 consecutive weeks. STEP-BD uses the term *roughening*, which is not found in DSM-IV, to indicate the occurrence of a subsyndromal state after the patient has "recovered." Using this systematic evaluation, the clinician can assign one of these clinical states to the patient at every visit.

Analyzing Evidence

The relatively limited number of positive studies pertaining to the treatment of acute manic and mixed episodes that were placebo-controlled and had an adequate sample size include trials of lithium and divalproex,[2] aripiprazole,[3] carbamazepine,[4–6] olanzapine,[7,8] quetiapine,[9–11,21] risperidone,[12–16] and ziprasidone.[17] Negative or failed trials have been published for lamotrigine,[18] gabapentin,[19] and topiramate.[20]

On the positive side, in 1994 in the first double-blind, parallel-group study of divalproex with a lithium arm and a placebo control for patients with acute mania, Bowden et al.[2] reported that both divalproex and lithium were superior to placebo. This was welcome news at the time because it supported the use of valproic acid as an alternative to lithium and increased the number of proven treatments by 100%. However, at the end of this 3-week trial, patients treated with divalproex or lithium still had sufficient symptoms to enter the trial anew. The average score on the mania rating scale portion of the Schedule for Affective Disorders and Schizophrenia after 3 weeks was 16, while the score required to enter the study was a score of at least 14. More trials of other treatments were needed.

Since then, 5 dopamine-blocking agents have been shown to be effective in placebo-controlled monotherapy trials with adequate sample size: aripiprazole,[3] olanzapine,[7,8] quetiapine,[9–11,21] risperidone,[12–16] and ziprasidone.[17] As an example of what can be learned from reviewing the evidence, the following is a comparison of data from 2 double-blind, placebo-controlled monotherapy trials of risperidone.[13,14] Patients in both studies were diagnosed

with DSM-IV bipolar I disorder in either a current acute manic episode or mixed episode. Both studies were conducted at multiple sites, lasted 3 weeks, and the primary efficacy measure was the mean change in score from baseline to endpoint on the Young Mania Rating Scale (YMRS). One study was conducted in the United States,[14] the other in India,[13] and both found a robust benefit for risperidone. A greater separation from baseline scores occurred in the patients who were treated in India than those treated in the United States. One reason is that patients in India began the study more severely ill; they had higher baseline scores on the YMRS than the patients in the United States. Patients in India were also dosed more aggressively. One lesson, then, is that dosing matters. Interestingly, although there was a greater change from baseline scores in the India study, the final scores in both studies were nearly identical.

Another category of evidence might be placebo-controlled combination trials with adequate sample size. Findings in this category might include positive studies for lithium, valproate,[22] olanzapine,[23,24] risperidone,[25,26] haloperidol,[22,27] and quetiapine.[28] Negative or failed combination trials exist for gabapentin[19] and lamotrigine.[18] Muller-Oerlinghausen and colleagues,[22] for example, conducted a 21-day, randomized, double-blind, parallel-group, placebo-controlled trial of valproate sodium administered as an adjunct to antipsychotic medication to patients with acute mania. Of the 136 inpatients enrolled in the study, 69 were assigned to valproate and 67 were assigned to placebo. Most patients in both the valproate and placebo groups also received haloperidol and/or perazine; others received another dopamine-blocking agent of the treating psychiatrist's choice. The findings indicated that adjunctive valproate plus a conventional antipsychotic provided greater symptom reduction than the antipsychotic with placebo, and a lower mean dose of the antipsychotic agent was needed when valproate was added.

Most combination therapy studies allow the clinician to choose the mood stabilizer and add either placebo or an antipsychotic. One study,[27] for instance, allowed the addition of placebo, haloperidol, or risperidone to a mood stabilizer for patients in an acute manic or mixed episode. Similar to the results obtained by Muller-Oerlinghausen et al.,[22] ratings of "much improved" or "very much improved" on the Clinical Global Impressions change scale were reported by 30% of patients (14 of 47) who received a mood stabilizer plus placebo, 50% of patients (25 of 50) who received a mood stabilizer plus haloperidol, and 53% of patients (27 of 51) who received a mood stabilizer plus risperidone. Overall, the combination of an antipsychotic with a mood stabilizer has been shown to be superior to a mood stabilizer alone or an antipsychotic alone for the rapid reduction of manic symptoms. Based on the evidence, some antimanic agents used as monotherapy are effective in reducing manic symptoms, but combinations of a dopamine-blocking antimanic agent and a non–dopamine-blocking antimanic agent are more likely to achieve a higher success rate when used in combination than treatment with a single agent. Carbamazepine appears to be an exception to this generalization,[4-6] probably owing to its induction of enzymes involved in metabolism of antipsychotic drugs.

Some available evidence may be negative, and it is important to create a category for that information as well. Evidence on topiramate monotherapy, for example, has been negative for treating mania or mixed episodes. Data[20] across 4 double-blind, placebo-controlled trials did not support the efficacy of topiramate as monotherapy in acute mania or mixed episodes.

Creating a Menu of Reasonable Options

After reviewing the evidence and considering all that is known about the patient, constructing the menu of reasonable options begins with determining the most appropriate strategy for the patient's circumstances. The sequential care strategy is selected when the priority is tolerability, and the urgent care strategy is selected when the immediate efficacy is the priority. For example, if a patient has mildly elevated blood pressure, sequential care may progress from diet and exercise to a diuretic, and then perhaps to a β-blocker. Conversely, if the patient has malignant hypertension, urgent care, such as admission to the hospital and perhaps an intravenous antihypertensive, would be offered. An urgent care approach would maximize the effectiveness of treatment and perhaps save a life.

Similarly, a higher perceived risk may be seen in patients in acute manic and mixed episodes—an agitated, psychotic, or violent patient. For these patients, an urgent care approach that involves a combination of effective treatments or aggressive titration to the effective dose range may be required. The 8 critical decision points in the acute mania pathway (urgent care) are shown in Tables 2 and 3. On the other hand, a mildly ill patient would likely benefit from sequential care that begins with monotherapy at a low dose that gradually escalates over time to an effective dose range (with scheduled follow-up to monitor response to treatment and maximize tolerability).

Educating and Negotiating

The treatment factors that are important to consider in managing illness include: (1) what the intervention is, (2) how well it is likely to work (i.e., efficacy, tolerability, and safety), (3) how agreeable the patient is to the assessment and treatment plan, (4) how able the patient is to adhere to the treatment plan, and (5) what environmental factors may influence outcomes (e.g., family support or burden tolerance, the possible stigma associated with treatment). Clinicians must educate their patients and negotiate in a nonadversarial, collaborative manner that aims to achieve concordance over time rather than simply compliance based on persuasion.

Table 2. Initial Management Recommendations in the Acute Mania Pathway[a]

Step	Decision Point	Recommendation
1	Abnormal state with elevated mood warranting treatment	Assess symptom acuity to determine target symptoms Review diagnostic criteria, current clinical status, and individual history
2	Ensure safety	Choose appropriate treatment venue (ie, acutely manic patients typically require hospitalization) Initiate medical workup as clinically necessary to rule out life-threatening conditions and common causal factors Taper and eliminate use of substances with known mood-elevating or psychotomimetic effects (eg, antidepressants, stimulants, steroids, substances of abuse), if possible
3	Determine treatment priority: tolerability versus immediate efficacy	Review indications for sequential care and urgent care and capacity to maintain acceptable behavioral control within the resources available in the therapeutic venue

[a]Adapted from Sachs.[35]

Table 3. Sequential Care Versus Urgent Care in the Acute Mania Pathway[a]

Step	Decision Point	Sequential Care	Urgent Care
4	Initiate/optimize specific antimanic medications	Choose lithium, valproate, carbamazepine, or atypical antipsychotic with proven antimanic efficacy	For combination treatment, select agents with known antimanic efficacy appropriate for aggressive dose titration Include 1 dopamine-blocking agent and 1 non–dopamine-blocking agent Valproate and atypical antipsychotics are recommended for use in urgent care Consider conventional antipsychotic agents
5	Determine need for antipsychotic medication	Review indications for antipsychotic medication	Consider conventional antipsychotic agents
6	Determine need for additional antimanic treatment	Add sequentially as warranted by clinical response to an adequate course beginning with most tolerable agent not already in use Consider agents with proven antimanic efficacy and/or agents with nonspecific efficacy for targeted problem symptoms (eg, sedatives, hypnotics, anxiolytics)	Add most efficacious agent not already in use when maximal tolerated doses of current therapeutic regimen have produced no benefit or insufficient benefit within the period required for onset of action Consider agents with proven antimanic efficacy and/or agents with nonspecific efficacy for targeted problem symptoms (eg, sedatives, hypnotics, anxiolytics)
7	Consider indication for nonstandard interventions	Review treatment options with putative antimanic efficacy	Review treatment options with putative antimanic efficacy
8	Determine indication for electroconvulsive therapy (ECT)	Offer as an option at any time or when 2 or more adequate trials with agents of known efficacy have proven ineffective or when patient is unable to tolerate adequate pharmacologic treatment	Offer as an option at any time or when combination treatment at maximal tolerable doses has produced no benefit over a period of 2 weeks or more or when patient is unable to tolerate adequate pharmacologic treatment

[a]Adapted from Sachs.[35]

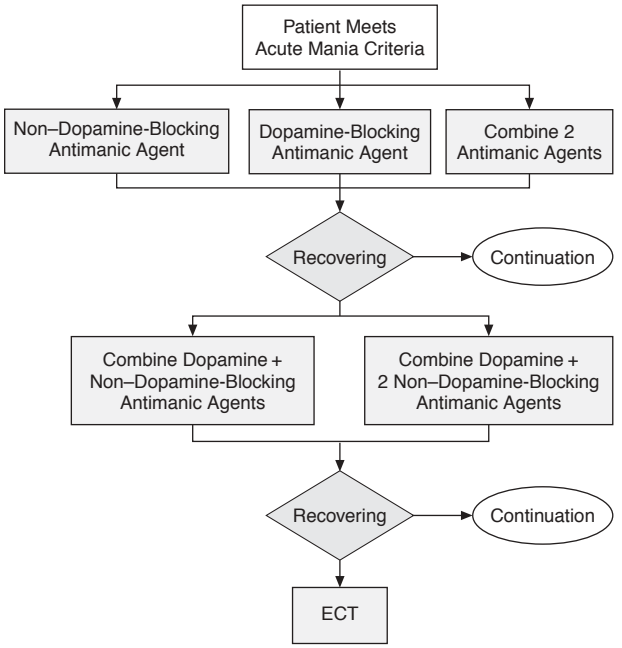
Intervening

Following the acute mania pathway (Figure 2), 3 treatment options could be considered: (1) a non–dopamine-blocking antimanic agent, (2) a dopamine-blocking agent, or (3) a combination of dopamine- and non–dopamine-blocking agents that have been proven to be efficacious for mania. If the patient recovers with one of these treatment options, then treatment will move into the continuation phase and, finally, maintenance treatment. If the patient does not do well with one of these treatment options, then treatment will move into combination therapy, which may include combining a dopamine blocker with 2 of the non–dopamine-blocking antimanic agents. At this level, if the patient does well, treatment moves into the continuation phase and maintenance treatment. If the patient does not do well, the patient would be considered a candidate for electroconvulsive therapy (ECT).

The pathway for treating patients in a mixed episode (Figure 3) begins with the same 3 treatment options that are offered to patients for mania. The difference depends on the response to those first treatments. Again, if the patient is doing well, treatment will move into a continuation phase and maintenance treatment. If the patient is not responding, however, and moves into a pure manic or mixed episode, the acute manic pathway is followed. If the patient moves into a depressive episode, treatment is based on what is known about the specific patient. If the depression has been present for less than 3 weeks, a bimodal agent—an agent that has evidence of acute or prophylactic efficacy for depression as well as mania—would be offered. Bimodal agents might include lamotrigine, lithium, olanzapine, quetiapine, and valproate. If the depression has been present longer than 3 weeks, a bimodal agent would be offered and a standard antidepressant medication would be considered. If the patient is not benefiting from these interventions, then ECT would be offered.

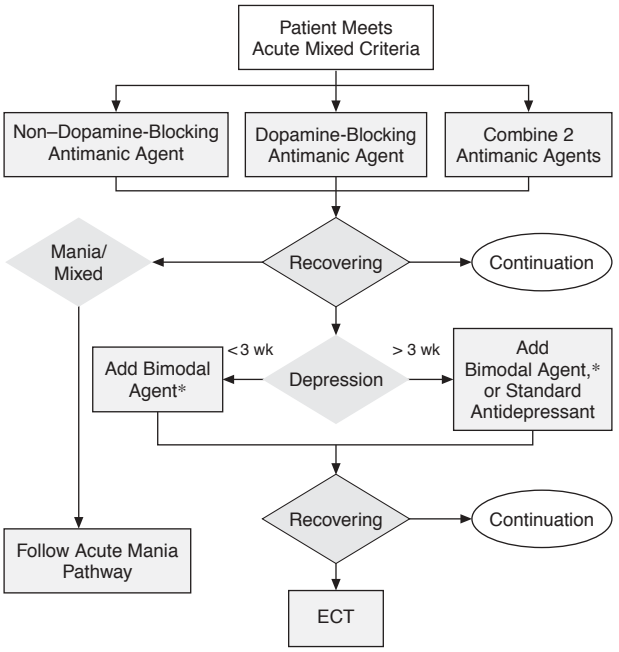
Outpatients usually fit into the sequential care approach, in which patient preference is a primary driver of treatment decisions, and very ill inpatients often need the urgent care approach, in which treatment decisions are more driven by the clinician's medical legal obligation. The urgent care approach uses much more aggressive dosing. The idea is to

Figure 2. STEP-BD Acute Mania Pathway



Abbreviations: ECT = electroconvulsive therapy, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Figure 3. STEP-BD Acute Mixed Pathway



*Agents with acute or prophylactic efficacy for depression and mania.
Abbreviations: ECT = electroconvulsive therapy, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

determine the dosing strategy for each patient and then follow that strategy to achieve either the tolerability or the immediate efficacy that meets the patient's need.

These strategies for individualizing care are based on knowing the level of evidence for various treatments that are available, knowing individual factors for the patient, generating a menu of reasonable choices, and then implementing treatment. By staying abreast of new data and interventions as they become available, clinicians will maintain a heightened awareness of how to best manage their patients. The next step in managing patients is to integrate measurement of outcomes into follow-up.

Measuring

As clinicians, we are responsible for the adverse effects of the treatments we prescribe. Discussing with the patient whether the benefit of treatment is worth the cost in terms of side effects and expense is important. In addition to efficacy, adverse effects must be routinely measured and discussed with patients to gauge the overall effectiveness of each intervention based on individual outcome. Part of patient education includes reviewing specific testing that will be performed to reduce the risk of adverse events, such as monitoring thyroid blood counts for patients taking lithium or liver function tests for patients taking anticonvulsants. Clinicians need to remember the parameters that define metabolic syndrome for patients who are taking second-generation antipsychotics. Evidence regarding metabolic syndrome and the risk of diabetes has led to guidelines[29] from the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity that suggest that, in addition to baseline measurements of blood pressure and weight, clinicians ought to be measuring waist circumference, fasting plasma glucose levels, and lipid profiles over time, as well as reviewing family history for hyperlipidemia and cardiac risk factors.

Certain treatments appear to be less problematic than others. By evaluating individuals, clinicians may be able to reduce some of the risks associated with particular antipsychotics, such as olanzapine or risperidone, by adding valproate.[30] It has been shown,[31] for instance, that total cholesterol levels for patients taking olanzapine and risperidone increase from baseline, but the addition of valproate decreases those elevations.

Other risk factors, however, may not be immediately evident. Joffe et al.[32] confirmed observations from Isojarvi et al.,[33] for instance, that valproate was associated with polycystic ovarian syndrome (PCOS). Joffe et al. reported that, of 86 women treated with valproate for bipolar disorder, 9 (10.5%) had treatment-emergent PCOS compared with 142 non–valproate users, of whom only 2 (1.4%) had treatment-emergent PCOS ($p = .003$). Interestingly, the onset of PCOS in all of these cases was within the first

year of treatment. This risk factor should be reviewed with women along with the need to monitor regularity of menstruation and weight change. This example highlights the need for monitoring and individualizing treatment.

CONCLUSION

Applying a systematic iterative approach to treating patients allows for a great deal of personalization of guidelines based on patient response and history. Clinicians can define the critical decision points based on their own knowledge and experience. Using this approach requires knowledge of the concise schema that make up the pathways and a critical awareness of the evidence with the caveat that the evidence is subject to revision as new data and interventions become available.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, lithium is not approved by the U.S. Food and Drug Administration for the treatment of mixed episodes.

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