Clinical Practice Guidelines for Bipolar Disorder
From the Department of Veterans Affairs

Mark S. Bauer, M.D.; Ann M. Callahan, M.D.; Chowdary Jampala, M.D.; Frederick Petty, Ph.D., M.D.; Martha Sajatovic, M.D.; Vicky Schaefer, R.N.; Byron Wittlin, M.D.; and Barbara J. Powell, Ph.D.

Background: For the last several years, the Department of Veterans Affairs (VA) has been involved in the development of practice guidelines for major medical, surgical, and mental disorders. This article describes the development and content of the VA-Clinical Practice Guidelines for Bipolar Disorder, which are available in their entirety on the Journal Web site (http://www.psychiatrist.com).

Method: A multidisciplinary work group composed of content experts in the field of bipolar disorder and practitioners in general clinical practice was convened by the VA's Office of Performance and Quality and the Mental Health Strategic Health Group. The work group was instructed in algorithm development and methods of evidence evaluation. Draft guidelines were developed over the course of 6 months of meetings and conference calls, and that draft was then sent to nationally prominent content experts for final critique.

Results: The Bipolar Guidelines are part of the family of the VA Clinical Guidelines for Management of Persons with Psychosis and consist of explicit algorithms supplemented by annotations that explain the specific decision points and their basis in the scientific literature. The guidelines are organized into 5 modules: a Core Module for diagnosis and assignment to mood state plus 4 treatment modules (Manic/Hypomanic/Mixed Episode, Bipolar Depressive Episode, Rapid Cycling, and Bipolar Disorder With Psychotic Features). The modules specify particular diagnostic and treatment tasks at each step, including both somatotherapeutic and psychotherapeutic interventions.

Conclusion: The VA Bipolar Guidelines are designed for easy clinical reference in decision making with individual patients, as well as for use as a scholarly reference tool. They also have utility in training activities and quality improvement programs.

(J Clin Psychiatry 1999;60:9–21)

Clinical practice guidelines represent a profound paradigm shift as U.S. health care enters the 21st century. A generation ago, diagnoses and treatment decisions were made according to physician experience, tradition, and training. However, as economic limitations and consumer awareness have increased, better assessment of treatments and outcomes in general clinical practice has become necessary. Practice guidelines represent one type of effort to address this need by articulating parameters for optimal clinical practice based on available scientific evidence and generally accepted clinical opinion.

In medicine and surgery, the need for practice guidelines has been apparent for at least 15 years, when major unexplained variations in the rates of common surgical procedures were reported across neighboring cities. The implementation of standardized guidelines has been one method used to reduce such variability. By contrast, psychiatry has only recently begun to document and examine variability in clinical practice. One of the few studies on this issue was conducted by Fortney et al. in the Department of Veterans Affairs (VA), who demonstrated a 4-fold variation in length of inpatient stay for depression.
across VA medical centers. This variability could not be explained by either case mix or other patient-related factors. Thus, the VA is likely to provide an opportunity to study and standardize general clinical practice for common mental health problems.

The VA also provides an ideal, and important, system in which to develop and study the impact of mental health practice guidelines on general clinical practice. First, VA clinicians responsible for making psychiatric treatment decisions are trained in a broad spectrum of theoretical orientations, thus making it likely that many variations in practice patterns such as the above\(^4\) are based on individual factors.

Second, the VA serves a large number of seriously mentally ill veterans who, as a group, are consumers of large amounts of services, making optimal treatment of this population a high priority for the VA system. For instance, between 405,000 and 630,000 veterans suffer from serious mental illness, and about 326,000 of these veterans use VA services each year.\(^5\) These seriously mentally ill veterans are 5 times more likely to use VA services than veterans in the general population. During fiscal year 1993, the VA provided 4 million days of inpatient care for these individuals at a cost of approximately $1.3 billion, and 4.5 million outpatient visits costing $225 million.\(^6\) Further, the number of veterans treated in outpatient settings has increased by nearly 20% between 1990 and 1995.\(^5\)

Third, the VA system is centralized and hierarchical and maintains an extensive automated data management system. These characteristics make it feasible both to implement systemwide changes effectively in clinical practice and to monitor their results.

The VA has recognized 3 varieties of clinical guidelines as potentially useful: Clinical Practice Guidelines, Clinical Algorithms, and Clinical Pathways.\(^7\) Clinical Practice Guidelines are statements that assist both the practitioner and patient in making the best decisions about appropriate health care in specific circumstances. They take the form of explicit recommendations for the performance or exclusion of specific procedures or services. Clinical Algorithms, incorporated into Clinical Practice Guidelines, are explicit decision tools in the form of flow charts or decision trees. They systematically guide the user through a series of steps that describe key elements of treatment, e.g., diagnosis, therapeutic interventions, time and/or length of treatment. This type of algorithm is the core of the VA Bipolar Guidelines. Clinical Pathways are locally developed management tools that are based on systemwide Clinical Practice Guidelines and Algorithms. They define key processes and events, which are important to the day-to-day management of care in a given environment.

To date, the VA has developed algorithm-based guidelines for several common health problems of veterans, including heart disease, chronic pulmonary disease, and common surgical diagnoses (available through the VA Office of Performance and Quality). The first guideline developed for a major mental illness was for major depressive disorder and was completed in 1996.\(^6\) Several months later, working groups were convened to establish treatment guidelines for the major psychoses.\(^7\) This document was divided into 4 individual sections on organic psychoses, schizophrenia, bipolar disorder, and psychosocial rehabilitation. The VA Bipolar Guidelines from this family of guidelines are the subject of this review.

The purpose of this article is to introduce readers to the Bipolar Guidelines and to describe their empirically based development. The algorithms are presented in their entirety, with an overview outlining the most salient or controversial decision points. The entire text of the Bipolar Guidelines, comprised of over 50 pages of algorithms and annotations, is available on the Journal Web site (http://www.psychiatrist.com). Comparison with other major guidelines for bipolar disorder is found in the Discussion section of this article.

**METHOD**

Overview of the Developmental Process for VA Mental Health Guidelines

The VA Office of Performance and Quality and the Mental Health Strategic Health Care Group coordinated the development of Major Depressive Disorder\(^4\) and Psychoses Guidelines,\(^8\) with the Bipolar Guidelines a subset of the latter. The principles for development of each of the guidelines were identical. With support from the VA’s External Peer Review program, multidisciplinary work groups were created to work on each of the guidelines. Each group consisted of facilitators who were experienced in algorithm development and decision-making processes, content experts, and professionals in general clinical practice in VA, university, and/or private practice venues. The consulting group conducted an extensive literature search using bipolar affective disorder, schizophrenic disorder, and related terms, and recent articles were provided to team members for use in the guideline development. Consumer input was solicited from clients and family members by conducting focus groups at 5 medical centers across the nation.

The working groups first met in November 1996 for a 2-day orientation and education session. All members received instruction in formal algorithm methodology and group decision-making methods (e.g., nominal group process, delphi method). The group was also instructed in the U.S. Agency for Health Care Policy and Research (AHCPR)\(^9\) and American College of Cardiologists and American Heart Association (ACC/AHA)\(^11\) methods for evidence evaluation, as summarized in Table 1. The groups were oriented to the framework for the final product, which was to consist of a set of freestanding algorithms supplemented by a series of text annotations that...
Given the complexity of bipolar disorder, each content expert was given responsibility for each of several key areas, which were to be developed into separate but linked algorithms. In addition to the core diagnostic module, which was developed by the entire group, the 4 key areas designated for individual modules were Manic/Hypomanic/Mixed Episode, Bipolar Depressive Episode, Rapid Cycling, and Bipolar with Psychotic Features (including schizoaffective disorder). The content expert solicited assistance from other members, such as performing literature searches, critiquing, editing, and revising. In addition to the 2 face-to-face meetings, approximately 16 hours of conference calls were devoted to these activities. In addition, group members communicated with each other as needed via e-mail, fax, and personal telephone calls.

The resultant Bipolar Guidelines draft was then sent to 10 content experts (predominantly non-VA), who provided written or verbal critiques. Version 1.0 was released to the field in September 1997 as part of the Clinical Guidelines for Management of Persons with Psychoses, which also included the other 3 guidelines noted above. Minor text and algorithm corrections and clarifications were then incorporated in the subsequent several months, with Version 1.1 (the version summarized in this article) released in early 1998.

The results section of this article serves several functions. First, it provides an overview of the structure and use of the Bipolar Guidelines; these are similar to the other VA guidelines for mental illnesses. Second, the content of the Bipolar Guidelines is summarized. Third, any particularly controversial or important point is noted and briefly reviewed. A more extensive review of these issues can be found in the annotations of the guidelines themselves, located in their entirety on the Journal Web site; reference to specific annotations in the text of this article points the reader to the appropriate section of the appropriate module of the guidelines for further review.

RESULTS

Core Diagnostic Module

The Core Module (Module D) is intended to guide clinicians in assessing a patient’s current mood state and episode history so that individuals with suspected bipolar disorder can be routed into the appropriate algorithm for future assessment and treatment. It is assumed that individuals entering the Core Module have been screened in the base module of the overall Psychoses Guidelines for (1) the presence of a mood disturbance and (2) the absence of secondary medical or substance abuse/dependency that might account for the mood disturbance. On the basis of the current episode, individuals are triaged through a series of specific algorithm steps into 1 of the 4 diagnosis-specific modules. Individuals with

---

**Table 1. Classification of Evidence and Recommendations According to the AHCPR and ACC/AHA Systems**

<table>
<thead>
<tr>
<th>AHCPR Classification of Strength of Evidence</th>
<th>ACC/AHA Classification of Strength of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A: Randomized controlled trials</td>
<td>Class I: Usually indicated, always acceptable, and considered useful and effective</td>
</tr>
<tr>
<td>Class B: Well-designed clinical studies</td>
<td>Class II: Acceptable, of uncertain efficacy, and may be controversial</td>
</tr>
<tr>
<td>Class C: Panel consensus</td>
<td>Class IIa: Weight of evidence in favor of usefulness/efficacy</td>
</tr>
<tr>
<td>Class II: Acceptable, of uncertain efficacy, and may be controversial</td>
<td>Class IIb: Not well established by evidence, can be helpful and probably not harmful</td>
</tr>
<tr>
<td>Class III: Not indicated and may be harmful</td>
<td>Class C: Panel consensus</td>
</tr>
</tbody>
</table>

Abbreviations: AHCPR = U.S. Agency for Health Care Policy and Research, ACC/AHA = American College of Cardiologists and American Heart Association.
Figure 1. Bipolar Disorder Core Module (Module D)

1. Persons with signs, symptoms, or history of mood disorders

2. Evaluate for concurrent substance abuse problem and institute Module C

3. Meets DSM-IV criteria for current or past major depressive episode? [A]
   - Y: Go to Current Bipolar Depressive Episode Module E
   - N: Meets DSM-IV criteria for current manic, hypomanic, or mixed episode? [D]
     - Y: Person with Rapid Cycling? [E]
       - Y: Go to Rapid Cycling Module G
       - N: Go to Rapid Cycling Module G
     - N: Go to Guideline for Major Depressive Disorder

4. Meets DSM-IV criteria for current manic, hypomanic, or mixed episode? [D]
   - Y: Person with Rapid Cycling? [E]
     - Y: Go to Rapid Cycling Module G
     - N: Go to Guideline for Major Depressive Disorder
   - N: Meets DSM-IV criteria for past manic, hypomanic, or mixed episode? [D]

5. Person with Rapid Cycling? [E]
   - Y: Go to Rapid Cycling Module G
   - N: Go to Guideline for Major Depressive Disorder

6. Meets DSM-IV criteria for past manic, hypomanic, or mixed episode? [D]
   - Y: Institute prophylaxis and consider psychosocial rehabilitation [F]
   - N: Go to Guideline for Major Depressive Disorder

7. Treat for cyclothymia [C]

8. Person with Rapid Cycling? [E]
   - Y: Go to Rapid Cycling Module G
   - N: Go to Current Bipolar Depressive Episode Module E

9. Institute prophylaxis and consider psychosocial rehabilitation [F]

10. Meets DSM-IV criteria for cyclothymia? [B]
    - Y: Go to Current Bipolar Depressive Episode Module E
    - N: Meets DSM-IV criteria for current manic, hypomanic, or mixed episode? [D]

11. N: Evaluate for concurrent substance abuse problem and institute Module C

12. Meets DSM-IV criteria for current manic, hypomanic, or mixed episode? [D]
    - Y: Institute prophylaxis and consider psychosocial rehabilitation [F]
    - N: Go to Guideline for Major Depressive Disorder to rule out Dysthymia

13. Meets DSM-IV criteria for current manic, hypomanic, or mixed episode? [D]
    - Y: Institute prophylaxis and consider psychosocial rehabilitation [F]
    - N: Go to Guideline for Major Depressive Disorder

    - Y: Go to Rapid Cycling Module G
    - N: Go to Current Bipolar Depressive Episode Module E

15. Go to Rapid Cycling Module G
suspected bipolar disorder who are found to have major depressive disorder or dysthymia are screened out and referred to the VA Major Depression Guidelines.8

The Core Module algorithm (Figure 1) serves as a prototype for the algorithms for the other 4 modules; thus, it is explained here in somewhat greater detail. The starting place for the algorithm is an oval called the “clinical state box,” which describes the presenting problem. The algorithm then guides the reader through a series of yes/no decision-making steps (hexagons). Steps that require some clinical action for all individuals are denoted as “do boxes” (rectangles). The “go to” circles at the various terminal steps of the algorithms indicate that DSM-IV12-based diagnostic criteria for a particular condition have been met, and the user is then routed to the appropriate diagnosis-specific module. An alphabetical letter appearing within a box indicates that there is an accompanying text annotation, as described in the Method section above.

The Core Module algorithm is sufficiently comprehensive and flexible to meet clinicians’ needs in assessing all individuals with suspected bipolar spectrum conditions. Specifically, it is designed to triage individuals who present for treatment with or without current medications, to evaluate individuals with cyclothymia, and to accommodate individuals with bipolar disorder who present for treatment while not in a major mood episode. With regard to this last group, the relevant annotations (annotations E and F) indicate the necessity of long-term treatment with mood stabilizers for individuals with bipolar disorder. Accordingly, the data for prophylactic efficacy of the available agents are reviewed in detail along with a discussion of the costs and benefits.

The Core Module also presents an overview of psychosocial interventions for bipolar disorder. These include psychoeducation, formal psychotherapy, and psychosocial rehabilitation. The guidelines specify psychoeducation for all individuals and formal psychotherapy or psychosocial rehabilitation for selected individuals, depending on the clinical situation.

Manic, Hypomanic, or Mixed Episode Module

As seen in Figure 2, the clinical state oval indicates that individuals in the Manic, Hypomanic, or Mixed Episode Module (Module E) meet DSM-IV12 criteria for one of these episodes and are free of causative general medical condition, substance intoxication, or substance withdrawal. The clinician must then determine the appropriate setting of care, initiate psychoeducational tasks, evaluate for other psychosocial interventions, and ensure normal thyroid functioning. Subsequent actions involve evaluating the status of current medications, making medication adjustments, and monitoring additional symptoms such as insomnia and anxiety.

The guidelines recommend that if an individual is in a manic, hypomanic, or mixed state and is receiving antidepressants, these medications should be discontinued. If there is a history of response to a previous mood-stabilizing regimen that has been stopped, that regimen should be restarted; if there has been no previous treatment with a mood stabilizer, one should be initiated (annotation J). If, after 3 weeks of treatment, there is no response to the optimal dose of the initial mood stabilizer, or if there is a clear history of nonresponse to the current mood stabilizer, the guidelines recommend starting a different mood stabilizer and tapering off the initial one (annotation K). If there is only a partial response, or if none of the mood stabilizers prove to be efficacious, a combination of different mood stabilizers (preferably lithium plus one of the anticonvulsants) is recommended treatment. In the event that mood stabilizers, either singly or in combination, do not control the acute manic symptoms, other agents with possible antimanic properties (e.g., clozapine, lamotrigine, or gabapentin) should be tried (annotation K). Once the acute manic symptoms are under control, prophylactic treatments and psychoeducation should be initiated, along with psychosocial rehabilitation if indicated (annotation F).

One of the more controversial aspects of the guidelines is their assessment of the relative strength of evidence for the available mood stabilizers—lithium, valproate, and carbamazepine—as antimanic agents. Based on the strength of evidence review of the literature, lithium is recommended as the first-line agent for both acute antimanic and prophylactic use for treating manic and mixed episodes, although some recent evidence indicates that valproate may be more effective than lithium in mixed episodes (annotation J). Also of relevance is the fact that lithium is the only agent to date for which efficacy has been established as a prophylactic agent for management after the acute episode has resolved, adding to the strength of recommendation that lithium should be the first-line antimanic agent.

While there is currently considerable enthusiasm for using the anticonvulsant valproate as a first-line acute treatment, only a relatively small number of controlled trials exist compared with the more extensive data on lithium. Those data that do exist indicate that its overall efficacy is comparable with that of lithium.13,14 Valproate may be particularly useful in treating individuals with mania who fail to respond to lithium14,15 or individuals with mania with concurrent depressive features (mixed manics).13,16 Evidence for the efficacy of carbamazepine in treating acute mania is less extensive than that for lithium. Electroconvulsive therapy (ECT) may also be efficacious as a treatment for acute mania, have a role in the treatment of selected individuals, and be used as a maintenance treatment if there are compelling reasons for not using the mood-stabilizing medications. Clearly, though, additional controlled studies are in progress, and this issue will have to be revisited in later revisions of the guidelines.
Figure 2. Current Manic, Hypomanic, or Mixed Episode (Module E)

1. Person meets DSM-IV criteria for manic, hypomanic, or mixed episode and is free of any general medical condition, intoxication, or withdrawal

2. Determine appropriate setting for care
   - Begin psychoeducational tasks and evaluation for ongoing psychotherapy and/or psychosocial rehabilitation
   - Ensure normal thyroid function

3. Is person taking antidepressants or mania-inducing medication?
   - Y: Reduce/stop antidepressants
   - N: Continue prophylaxis and consider psychosocial rehabilitation

4. Response?
   - Y: Go to Bipolar with Psychotic Features Module H
   - N: Restart previous regimen

5. Response?
   - Y: Initiate and optimize mood stabilizer. Assess in 2–3 weeks
   - N: Taper or discontinue neuroleptic and benzodiazepines (if applicable)

6. Is person experiencing insomnia/agitation, or is anxiety present?
   - Y: Go to Bipolar with Psychotic Features Module H
   - N: Continue prophylaxis and consider psychosocial rehabilitation

7. Consider benzodiazepine treatment
   - Y: Institute prophylaxis and consider psychosocial rehabilitation
   - N: Continue prophylaxis and consider psychosocial rehabilitation

8. Go to Box 19

9. Are psychotic features present?
   - Y: Initiate and optimize mood stabilizer. Assess in 2–3 weeks
   - N: Continue prophylaxis and consider psychosocial rehabilitation

10. Was person previously treated with mood stabilizers?
    - Y: Response to previous mood stabilizer treatment regimen?
    - Y: Initiate and optimize mood stabilizer. Reassess in 2–3 weeks
    - N: Continue prophylaxis and consider psychosocial rehabilitation
    - N: Add/change mood stabilizer until stable or consider alternative therapy

11. Response?
    - Y: Initiate and optimize mood stabilizer. Reassess in 2–3 weeks
    - N: Continue prophylaxis and consider psychosocial rehabilitation

12. Response?
    - Y: Add/change mood stabilizer until stable or consider alternative therapy
    - N: Taper or discontinue neuroleptic and benzodiazepines (if applicable)
Figure 3. Current Bipolar Depressive Episode (Module F)

1. Person meets DSM-IV criteria for bipolar depressive episode free of any general medical condition, intoxication, or withdrawal.

2. Determine appropriate setting for care
   - [A] Begin psychoeducational tasks and evaluation for ongoing psychotherapy and/or psychosocial rehabilitation
   - [B] Ensure normal thyroid function

3. Is person experiencing anxiety, agitation, or insomnia?
   - [D] Consider benzodiazepine treatment
   - [N] Continue symptoms?

4. Go to Bipolar with Psychotic Features Module H

5. Are psychotic features present?
   - [F] Treat the psychosis
   - [N] Initiate/opimize mood stabilizer. Reassess in 2–4 weeks

6. Continued symptoms?
   - [G] Institute prophylaxis and consider psychosocial rehabilitation

7. Initiate lithium or antidepressant treatment. Reassess response in 2–4 weeks

8. Response?
   - [J] Assess need for continued antidepressant treatment

9. Partial response?
   - [L] Augment or combine antidepressants

10. Switch antidepressants
    - [N] Utilize ECT or alternative therapies until response

11. Response?
    - [J] Assess need for continued antidepressant treatment

12. Go to Bipolar with Psychotic Features Module H

13. Continue prophylaxis and consider psychosocial rehabilitation

14. Consider benzodiazepine treatment

15. Go to Bipolar with Psychotic Features Module H

16. Is person experiencing anxiety, agitation, or insomnia?
   - [D] Consider benzodiazepine treatment

17. Go to Bipolar with Psychotic Features Module H

18. Go to Bipolar with Psychotic Features Module H

19. Go to Bipolar with Psychotic Features Module H

20. Go to Bipolar with Psychotic Features Module H
Bipolar Depressive Episode Module

The algorithm for the treatment of individuals with bipolar depressive episode (Module F) is presented in Figure 3. The guidelines recommend that the first step in the treatment of acute bipolar depression is to initiate, or, if the patient is already being treated, to optimize the current mood stabilizer (annotation G). Controlled studies have shown that lithium is the most effective mood stabilizer for the treatment of acute bipolar depression. While less extensive data exist for carbamazepine or valproate prior to the initiation of an antidepressant (annotation I). The combined use of lithium and carbamazepine has been shown to enhance efficacy in bipolar depression. Although possibly helpful, there are fewer data to support the efficacy of lithium and valproate or carbamazepine and valproate.

Antidepressants should be used conservatively when treating patients with bipolar disorder. This recommendation is based on the increased risk of antidepressant-induced mania with which these agents have been associated. It is likely that all antidepressants can induce mania in susceptible patients. Furthermore, antidepressant treatment may have a negative impact on the natural course of bipolar disorder by inducing rapid cycling and mixed states. Although it has been reported that the tricyclic antidepressants (TCAs) have a greater propensity to induce mania than the selective serotonin reuptake inhibitors (SSRIs), this report was derived from post hoc reanalysis of data collected for different purposes. On the other hand, data from a small prospective controlled trial indicated that bupropion is less likely to induce mania than desipramine; some data from open studies also support this finding.

Despite the inherent risks, it is often necessary to administer antidepressants to patients with severe or recurrent bipolar depression. In such cases, the guidelines recommend that antidepressants be administered at the lowest effective dose for the shortest time possible and that a mood stabilizer always be coadministered. In addition, frequent evaluation for the emergence of manic symptoms is required. Should manic symptoms occur, the antidepressant should be reduced or discontinued.

The relative efficacy of the various antidepressants in bipolar depression has not been extensively studied. Treatments for which controlled data exist include ECT, TCAs, monoamine oxidase inhibitors, and bupropion (annotation I). Some investigators have reported that ECT may be the most effective treatment. Tranylcypromine also may be particularly efficacious, especially for patients with hypersomnia and hyperphagia. TCAs appear to be less effective; controlled studies have shown an overall response rate of approximately 55%. While clinical experience suggests that bupropion may have superior efficacy in bipolar depression, controlled data are lacking. Finally, there are no published controlled studies of the SSRIs or other newer antidepressants in bipolar depression. However, clinical experience indicates that both SSRIs and venlafaxine may be useful treatments.

Rapid Cycling Module

The algorithm for the treatment of rapid cycling in individuals with bipolar disorder (Module G) is presented in Figure 4. Rapid cycling is defined by DSM-IV as the occurrence of 4 or more affective episodes of any polarity within a 12-month interval. Evidence indicates that individuals with rapid cycling respond less well to mood stabilizers than do other types of bipolar patients. In addition, certain treatments such as antidepressants may worsen the course of the disorder. Evidence also indicates that individuals with rapid cycling should be closely monitored for hypothyroidism, which may occur in higher frequency in this group compared with those individuals without rapid cycling.

Because of these factors, identification of rapid cycling is critical for the effective management of individuals with bipolar disorder. In recognition of the importance of this phenomenon, the Core Module first addresses rapid cycling and triages affected individuals directly into the Rapid Cycling Module prior to assignment to the Manic/Hypomanic/Mixed or Bipolar Depressive Episode modules.

Three specific aspects of the Rapid Cycling Module deserve particular note. First, a review of the available evidence on the response of individuals with rapid cycling to mood stabilizers revealed relatively few controlled, prospective treatment trials (annotation C). While lack of response to lithium may be one of the hallmarks of rapid cycling, there are few data indicating that rapid cycling responds better to any of the anticonvulsant mood stabilizers than to lithium. Therefore, lithium is recommended as the first-line treatment for individuals with rapid cycling (annotation C). Thus, the guidelines do not necessarily recommend switching from lithium to anticonvulsants, since the clinician first should ensure that the optimum dose of the existing mood stabilizer is being used.

However, this issue should be reevaluated periodically as more data become available on the response of rapid cycling to various newer mood stabilizers. The guidelines propose that the first step in treating all patients with bipolar disorder, including those patients with rapid cycling taking antidepressants alone, is the initiation of mood stabilizers; an acceptable alternative is to discontinue antidepressants, and then if a patient becomes...
Figure 4. Rapid Cycling (Module G)

1. Person meets criteria for rapid cycling

2. Determine appropriate setting for care
   [A] Begin psychoeducation tasks and evaluation for ongoing psychotherapy and/or psychosocial rehabilitation
   [B] Ensure normal thyroid function

3. Mood stabilizes?

4. Institute prophylaxis and consider psychosocial rehabilitation

5. Initiate/maximize current mood stabilizer [C]

6. Mood stabilizes?

7. Is person taking antidepressants? [D]

8. Reduce or stop antidepressants [E]

9. Response? [F]

10. Combine mood stabilizers [G]

11. Continued rapid cycling?

12. Trial of alternative therapies until mood stabilizes [H]

13. Prolonged depression? [I]

14. Careful trial of nontricyclic antidepressants [H]

15. Depression improved?

16. Mania/mixed resumes?

17. In the event of continued rapid cycling [K]

18. Go to Box 10

19. Prolonged mania/mixed?

20. Institute prophylaxis and consider psychosocial rehabilitation [B]

Go to Current Manic/Hypomanic/Mixed Episode Module E

Go to Box 14

Institute prophylaxis. Continue psychosocial rehabilitation [B]

Monitor for emergence of hypomania, agitation

Go to Box 8

Institute prophylaxis.

Go to Box 14
depressed, as usually occurs, enter Module F (Bipolar Depressive Episode) and begin mood stabilizers.

Second, for rapid cycling individuals who present while taking both mood stabilizers and antidepressants, the guidelines suggest that the first intervention is to reduce or discontinue the use of the antidepressant (annotation E). If the mood does not then stabilize, the guidelines recommend either an additional mood stabilizer or a change to a different mood stabilizer. Following this, a careful trial of nontricyclic antidepressants is recommended (annotation J).

Third, a series of “alternative therapies” (e.g., clozapine, lamotrigine, gabapentin, high-dose levothyroxine) are suggested for treating individuals who prove refractory to other interventions. These therapies, summarized in annotation H, are evaluated and graded according to AHCPR evidence standards and may be of particular help to clinicians seeking treatment for individuals with refractory rapid cycling.

**Bipolar Disorder With Psychotic Features Module**

The algorithm for the treatment of individuals with bipolar disorder with psychotic features (Module H) is presented in Figure 5. Although schizoaffective disorder has been conceptualized as having features of both schizophrenia and the mood disorders, it is treated through the Bipolar Guidelines because individuals with this disorder may be helped by mood stabilizers and antidepressants. These agents may be neglected if schizoaffective disorder were conceptualized as a variant of schizophrenia. The major difference in treating individuals with schizoaffective disorder and those with bipolar disorder with psychotic features is that the former may require chronic neuroleptic treatment while the latter may need neuroleptics only on an episodic basis (annotation C).

DSM-IV defines psychosis by the presence of either delusions or hallucinations, and may also include bizarre behavior or thought disorganization. Individuals with manic, mixed, or depressive states may have psychotic symptoms that are mood-congruent, or, more rarely, mood-incongruent. Psychosis in bipolar disorder should be carefully addressed, as it may be associated with worse functional outcome, greater risk of violence, and increased risk of illness relapse.

The guidelines highlight 3 important aspects in treating psychosis in bipolar disorder. First, because mood stabilizers often require several weeks of administration for a maximal response, adjunctive antipsychotic medication may be needed for individuals with bipolar disorder and psychosis or severe agitation. This recommendation is based on evidence that shows the effectiveness of antipsychotic medication in the management of acute manic psychosis.

Second, for individuals with bipolar (though not necessarily schizoaffective) disorder, the guidelines recommend tapering and eventually discontinuing antipsychotic agents when the acute psychotic episode resolves. Few data support routine use of neuroleptics alone as maintenance treatment for bipolar disorder. Moreover, neuroleptics may exacerbate postmanic depressive episodes or induce rapid cycling in some individuals with bipolar disorder. In addition, individuals with primary mood disorders may be particularly vulnerable to the development of neuroleptic-induced tardive dyskinesia. Even so, it is important to recognize that long-term use of neuroleptics may be required for individuals who have a poor response to mood-stabilizing agents, or for those whose symptoms or functional status worsens upon discontinuation of neuroleptics.

Finally, clinicians should remember that schizoaffective disorder is a complex and poorly understood entity for which clinical diagnostic criteria were not adopted un-
Clinical Practice Guideline Controversies

Purpose. The 2 major misunderstandings regarding the purpose of guidelines are that they will set legal precedents and open practitioners for malpractice suits if they are not followed and that the guidelines are cost-containment or treatment-limiting tools. Each of these misconceptions, along with other beliefs, has made some practitioners hesitant to accept and utilize guidelines—and cost issues have made some administrators overly enthusiastic in their embrace. With regard to the first misunderstanding, it must be recalled that guidelines are a series of recommendations for the performance or exclusion of procedures or services. Because they are recommendations and need to be applied within the context of clinical judgment, they can best be considered streamlined or distilled textbooks containing useful information to assist practitioners, rather than mandates. With regard to the latter misbelief, we know of no data indicating that guidelines actually save money. In fact, those guidelines that mandate screening for certain diseases may actually increase costs to a health care system. We actually anticipate that this will be the case if the VA Major Depression Guidelines are fully implemented, since screening and treatment of uncomplicated depression in primary care will provide needed access to treatment for a segment of the population that either was not identified as depressed or was so identified but refused to be treated in the mental health sector. On the other hand, it must be pointed out that many guidelines designate a series of first-line treatments to be followed by second-line treatments of less favorable or uncertain efficacy or side effects. This method can best be considered as sequencing, rather than limiting, treatment. Where those second-line treatments are more expensive, it is possible that following guidelines could guide practitioners to the less expensive treatment first, thereby reducing expenditures somewhat.

Construction. There is little unanimity on the structure or content of guidelines in general. At present there are almost as many formats for guidelines as there are guidelines themselves. In an integrated and hierarchical system like the VA, the form of guidelines has been mandated (see the Method section) so that guidelines for major depression share the same form as those for psychosis and those for heart disease. As outlined below, however, bipolar guidelines from different sources differ substantially among themselves, making relative comparison difficult.

Moreover, there is little agreement regarding the most useful content of guidelines. Some are based on a broad review of scientific evidence; others reflect best practice of a group of clinicians. It should be noted that among those guidelines that utilized scientific evidence, Class A evidence (defined by AHCPR standards) is exhausted quite early in most mental health guidelines, leaving the bulk of the steps based on panel consensus or expert opinion. Guideline developers currently walk a fine line between making the format and content of guidelines so voluminous and scholarly as to be unusable in everyday practice versus so commonsensical that they add little to everyday practice. Similarly, guideline developers must balance being so specific in their sequence of recommendations that they are relevant only to a highly selected sample of patients versus being so general as to be platitudinous.

Implementation. Finally, guidelines that are not linked to implementation and education efforts are likely to gather dust on the shelf (or in cyberspace) rather than to be used actively in practice. As outlined below, the VA has endeavored to structure such efforts. However, the specifics of how to measure compliance and implementation in a nonresearch general clinical practice setting are by no means straightforward. It is likely that the efforts of the VA Office of Performance and Quality in this regard will both be illustrative of the difficulties in this endeavor and also be an example of a state-of-the-art measurement program. Sobering, however, is the research evidence that guidelines may not be followed effectively and accurately by practitioners, even if the practitioners believe that they are doing so (e.g., Lomas et al.).

Comparison With Other Bipolar Guidelines

These VA Bipolar Guidelines join 2 other recently developed guidelines on bipolar disorder, the American Psychiatric Association (APA) Practice Guidelines and the Expert Consensus Guidelines. There are several similarities among these guidelines. First, each employed the best available empirical data to fashion their recommendations, using predetermined standards for evidence evalua-
tion. In the case of the APA and VA guidelines, AHCPR standards were used for evaluation of evidence, while the Expert Consensus Guidelines utilized statistical methods for characterizing experts’ opinions. It is notable that the VA guidelines also rated the strength of each of their recommendations, in order to reflect relative level of confidence in the conclusions, using ACC/AHA standards. Second, each of the guidelines made the most of expert opinion, both published and oral. Third, each employed methods of integrating disparate opinions, either through recommendations that were based on consensus among participants (APA and VA guidelines) or through statistical reduction of survey data (Expert Consensus Guidelines).

Before comparing the VA guidelines to other guidelines for bipolar disorder, it is important to note the limitations of the VA guidelines themselves. The VA work group was smaller than those for the other 2 guidelines, and the physicians were drawn primarily from VA practitioners. This was balanced by a non-VA review body of content experts that gave a helpful critique to the first substantive draft. The main focus of the guidelines was to serve the needs of VA patients. However, the content experts all had university appointments and gathered their review to the population of bipolar patients in general clinical practice. Finally, the guidelines were constructed under a relatively short time frame for a scholarly project of this magnitude. While these time pressures were met with vigorous efforts by a scholarly (and obsessive) work group, it is likely that there are some omissions or formatting errors. Some of these have been corrected in subsequent revisions of Version 1; the authors would be pleased to find out from users of the Bipolar Guidelines if other errors have been missed.

There are also several features that differentiate the VA Bipolar Guidelines from these earlier efforts. First, the VA guidelines from the outset used a broad base of participants, by design including practitioners from multiple clinical disciplines and including both content experts and those in general clinical practice. This strategy was designed to support the general clinical applicability as well as the scholarly basis of the ultimate product.

Second, the VA guidelines were constructed as part of a federal, public domain effort whose motivation and support were derived from a government agency charged with caring for individuals with the disorder in question. The stimulus for development of these guidelines stemmed primarily from agency needs and via agency support. Therefore, there was no financial or other support from either industry or professional guild interests in the development of these guidelines.

Third, and perhaps most evident from even a cursory glance at these guidelines, their centerpiece is a set of highly structured algorithms that are supported by extensive scholarly annotations. This algorithm-based format was chosen to facilitate use of the guidelines by clinicians in making individual treatment decisions. These explicit step-by-step algorithms are not lock-step determinants of treatment, but rather structure the decision-making processes as the clinician walks individual cases through the various assessment and treatment decisions. Moreover, the in-depth annotation format allows both clinicians and researchers to review the scientific and clinical data—or lack thereof—that serve as the basis for each recommendation.

Uses of the Guidelines

While the primary impetus behind the development of the VA Bipolar Guidelines was to assist clinicians in making appropriate clinical decisions in the assessment and treatment of bipolar disorder, the guidelines also serve several other purposes. As noted above, the annotations provide an extensive scholarly review of the currently available literature on bipolar disorder. As such, they should be of use to researchers and other scholars as well as practitioners.

In addition, the guidelines are structured to serve educational purposes. Their step-by-step algorithm format can be helpful in teaching students and advanced clinical trainees about how to structure diagnostic reasoning and sequence subsequent treatment decisions. The guidelines’ structure implies that treatment decisions are critically dependent upon accurate assessment of mood state, a point often underappreciated by trainees in the early stages of their clinical work.

Finally, the guidelines can also provide a rational and scientific basis for quality improvement and utilization management efforts. As an example, in recognition of the variability of management of major depressive disorder in the VA, the Undersecretary for Health has designated that the Major Depressive Disorder Guidelines be implemented and monitored throughout the VA as part of the VA network directors’ performance plans for fiscal year 1998, and the network directors have in turn incorporated this expectation into the performance plans of chief executive officers of individual medical centers as well. The Bipolar Guidelines and other sections of the Psychosis Guidelines have been similarly designated for implementation during the 1999 fiscal year.

In conclusion, the VA Bipolar Guidelines and the other VA practice guidelines for mental health reflect the VA’s continuing commitment to applying state-of-the-art knowledge to improve the lives of veterans with major mental illnesses. They are structured to be useful both as a day-to-day reference tool for general clinical practice and as a scholarly reference tool. VA and non-VA practitioners should also find them helpful as educational and quality improvement resources. It will be of interest to the field to see whether a system as diverse yet so hierarchical as the VA can change clinical practice by investing in the development and implementation of such guidelines.
Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clozapine (Clozaril), desipramine (Norpramin and others), gabapentin (Neurontin), lamotrigine (Lamictal), levothyroxine (Levothroid, Synthroid), tranylcypromine (Parnate), venlafaxine (Effexor).

REFERENCES

20. Kramlinger KG, Post RM. The addition of lithium to carbamazepine: antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatry 1989;46:794–801
21. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144:1403–1411
30. Bauer M, Whybrow P. Validity of rapid cycling as a modifier for bipolar disorder in DSM-IV. Depression 1993;1:11–19
35. Westermeyer J, Harrow M, Marengo J. Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. J Nerv Ment Dis 1991;179:259–266
36. Tohen M, Wateroux CM, Tsuang MT. Outcome in mania: a four year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111