# Synopsis of the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder

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## Abstract

**Objective:** The US Department of Veterans Affairs (VA) and Department of Defense (DOD) Work Group revised the 2013 VA/DOD Clinical Practice Guideline (CPG) for the Management of Bipolar Disorder (BD). This paper reviews the 2023 CPG and its development process, including how recommendations were made for evidence-based treatment in BD.

**Methods:** Subject experts and key stakeholders developed 20 key questions and reviewed the published literature after a systematic search using the PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) method. The evidence was then evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. Recommendations were based on quality and strength of evidence and informed by other factors, including feasibility, patient perspectives, and the unique needs of people with BD. Peer review by an external group of experts then resulted in completion of the CPG.

**Recommendations:** While the scope of the CPG is broad, this synopsis focuses on clinically relevant recommendations related to the identification and management of BD, including the acute and maintenance phases of illness.

*J Clin Psychiatry 2025;86(1):24cs15546*

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Bipolar disorder (BD), including bipolar disorder type 1 (BD 1) and bipolar disorder type 2 (BD 2), is a serious mental health condition affecting more than 40 million people worldwide.[1] Symptoms of BD include fluctuations in mood, thought, energy, behavior, and social functioning. It is the 16th leading cause of years lost to disability (YLD) across age groups and ranks 6th globally among younger samples (ages 10–24 years). Nearly ten million person-years are lost because of BD, representing 1.3% of global estimates of YLD. A diagnosis of BD is associated, on average, with about ten years of reduced life expectancy.[2] The costs of BD extend far beyond measures of individual disability and contribute to substantial total direct costs to health care systems (ie, over $200 billion in 2015) and high emotional and financial costs to families and social support systems that help people in managing this chronic mental health condition.[3,4]

Bipolar disorder presents significant challenges within the patient populations of the US Department of Defense (DOD) active-duty personnel and US Department of Veterans Affairs (VA) veterans. In DOD settings, BD is associated with a substantial portion of mental health hospitalizations,[5] and BD 1 is considered incompatible with retention in service. In 2021, VA clinicians cared for over 130,000 veterans with BD.[6] This group of VA-treated veterans is associated with extensive mental health and medical comorbidities, as well as high rates of health care utilization (including emergency and inpatient services). A diagnosis of BD among active-duty personnel and military veterans is associated with substantially increased risk of suicide,[7] underscoring the

## Clinical Points

- This is a rigorous, evidence-based review of the management of bipolar disorder, with a 10-year update from the previous US Department of Veterans Affairs and Department of Defense Clinical Practice Guidelines.
- As bipolar disorder is a lifelong illness, clinicians should choose acute treatments with maintenance efficacy in mind.
- Past treatments should be reviewed to assure that the treatments with the most evidence have been offered to the patient.

urgent need to provide effective care within DOD and VA settings.

## GUIDELINE DEVELOPMENT PROCESS

The development of all VA/DOD guidelines is directed by the Evidence-Based Practice Guideline Work Group and adheres to the standards for trustworthy guidelines that were set by the National Academy of Medicine.[8] Senior leaders within the VA and DOD selected a multidisciplinary Work Group of practicing clinician stakeholders and clinical researchers to update this guideline. The Work Group included internal medicine, neuropsychiatry, pharmacy, psychiatry, psychology, and social work. The Work Group was required to disclose any conflicts of interest throughout the process and did not identify any financial conflicts of interest. Several Work Group members had intellectual conflicts related to their research interests; these conflicts were mitigated by recusal from evidence discussions related to those areas. In addition, a patient focus group was convened to assess important aspects of treatment for patients and to gain information about patient values and preferences. The Lewin Group, a contracted third party with expertise in guideline development, facilitated meetings and the development of key questions using the PICOTS (population, intervention, comparison, outcome, timing, and setting) format. A consensus process was used to develop 20 key questions, which guided the evidence review and the subsequent recommendation development. Consensus was achieved within the Work Group through an iterative process involving discussions on conference calls. An independent third party, ECRI, conducted the systematic evidence review, which the guideline Work Group then used to develop recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[9–11] The GRADE approach incorporates 4 components to evaluate evidence and develop recommendations: confidence in the quality of the evidence; balance of desirable and undesirable consequences; patient values and preferences; and other considerations, such as feasibility, equity, and subgroup-specific needs. This approach requires that the recommendations are based on evidence and do not rely on unsystematic clinical observations. The search methods and results are detailed in the full guideline (available at www.healthquality.va.gov).

The GRADE approach allowed the Clinical Practice Guideline (CPG) to make recommendations based on the strength of evidence from Weak to Strong, for both recommendations for a treatment or approach or against it, in the context of evaluating the evidence quality as High, Moderate, Low, and Very Low. The evidence quality for a given question is based on the lowest quality evidence included in the review, even if some evidence is considered strong. The recommendation language arises from this, with "recommend" corresponding to a strong recommendation, "suggest" for a weak recommendation, and "neither for nor against" where the evidence cannot be judged to clearly recommend for or against a treatment or action. Because of strict adherence to this process, we did not include "expert opinion" as a level of evidence that would guide treatment, in general, except to the extent that our recommendations ask that decisions be made about all treatments for BD in the context of its being a lifelong condition in most patients.

The resulting recommendations can be found in Table 1. The sections that follow summarize a subset of recommendations in several major domains considered by the Work Group, including Screening, Assessment, and Diagnosis; Pharmacologic Recommendations; Other Somatic Therapies; Nonpharmacologic Recommendations (with an emphasis on psychotherapies); Telehealth and Apps; and Supportive Services and Models of Care Delivery. Other research questions are covered in the full text of the CPG itself (available at www.healthquality.va.gov).

## SCREENING/ASSESSMENT/DIAGNOSIS

BD 1 has a lifetime prevalence of around 1% in adults in the US with rates varying according to study sampling and geographical location.[12] Clinical estimates for bipolar spectrum disorders range as high as 2.4% globally, according to large cross-sectional survey methods across 11 countries.[13]

General populations differ relative to populations accessing primary care, and the evidence base examined by the Work Group included study samples from both primary care and the general population. Evidence from numerous studies suggests that performing routine screening for BD in primary care or general populations will lead to high rates of false positive results.[14–16] Although different patient factors are associated with populations accessing primary care, the Work Group recommended against routine screening in primary care.

**Table 1.**

## Evidence-Based Clinical Practice Recommendations With Strength and Category[a]

| Topic | Subtopic | No. | Recommendation | Strength[b] |
|---|---|---|---|---|
| **Screening and evaluation** | | 1. | We suggest against routine screening for bipolar disorder in a general medical population. | Weak against |
| | | 2. | In specialty mental health care, when there is suspicion for bipolar disorder from a clinical interaction, we suggest using a validated instrument (eg, Bipolar Spectrum Diagnostic Scale, Hypomania Checklist, and Mood Disorder Questionnaire) to support decision-making about the diagnosis. | Weak for |
| | | 3. | For individuals with major depressive disorder being treated with antidepressants, when there is suspicion for mania/hypomania from a clinical interaction, we suggest using a validated instrument (eg, Hypomania Checklist and Mood Disorder Questionnaire) as part of the evaluation for mania/hypomania. | Weak for |
| | | 4. | For individuals with bipolar disorder, there is insufficient evidence to recommend for or against any specific treatment outcome measures to guide measurement-based care. | Neither for nor against |
| **Pharmacotherapy** | Acute mania | 5. | We suggest lithium or quetiapine as monotherapy for acute mania. | Weak for |
| | | 6. | If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania. | Weak for |
| | | 7. | If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preference and characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania. | Weak for |
| | | 8. | We suggest lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone for acute mania symptoms in individuals who had an unsatisfactory response or a breakthrough episode on monotherapy. | Weak for |
| | | 9. | We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania. | Weak against |
| | | 10. | We suggest against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy for acute mania. | Weak against |
| | | 11. | There is insufficient evidence to recommend for or against other first-generation antipsychotics or second-generation antipsychotics, gabapentin, oxcarbazepine, or benzodiazepines as monotherapy or in combination for acute mania. | Neither for nor against |
| | Acute bipolar depression | 12. | We recommend quetiapine as monotherapy for acute bipolar depression. | Strong for |
| | | 13. | If quetiapine is not selected based on patient preference and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression. | Weak for |
| | | 14. | There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression. | Neither for nor against |
| | | 15. | We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression. | Weak for |
| | | 16. | There is insufficient evidence to recommend for or against ketamine or esketamine as either a monotherapy or an adjunctive therapy for acute bipolar depression. | Neither for nor against |
| | | 17. | There is insufficient evidence to recommend for or against antidepressants to augment treatment with second-generation antipsychotics or mood stabilizers for acute bipolar depression. | Neither for nor against |
| | Prevention of recurrence of mania | 18. | We recommend lithium or quetiapine for the prevention of recurrence of mania. | Strong for |
| | | 19. | If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest oral olanzapine, oral paliperidone, or risperidone long-acting injectable for the prevention of recurrence of mania. | Weak for |

*(continued)*

**Table 1 (continued).**

| Topic | Subtopic | No. | Recommendation | Strength[b] |
|---|---|---|---|---|
| **Pharmacotherapy (cont.)** | Prevention of recurrence of mania (cont.) | 20. | There is insufficient evidence to recommend for or against other first-generation antipsychotics, second-generation antipsychotics, and anticonvulsants (including valproate) for the prevention of recurrence of mania. (See Recommendations 18, 19, and 30). | Neither for nor against |
| | | 21. | We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania. | Weak against |
| | | 22. | We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania. | Weak for |
| | Prevention of recurrence of bipolar depression | 23. | We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes. | Strong for |
| | | 24. | We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes. | Weak for |
| | | 25. | If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes. | Weak for |
| | | 26. | We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes. | Weak for |
| | | 27. | There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants (including valproate) as monotherapies for the prevention of recurrence of bipolar depressive episodes. | Neither for nor against |
| | | 28. | There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants in combination with a mood stabilizer for the prevention of recurrence of bipolar depressive episodes. | Neither for nor against |
| | Pregnancy/childbearing potential | 29. | For individuals with bipolar disorder who are or might become pregnant and are stabilized on lithium, we suggest continued treatment with lithium at the lowest effective dose in a framework that includes psychoeducation and shared decision-making. | Weak for |
| | | 30. | We recommend against valproate, carbamazepine, or topiramate in the treatment of bipolar disorder in individuals of childbearing potential. | Strong against |
| **Other somatic therapies** | | 31. | For individuals with bipolar 1 disorder with acute severe manic symptoms, we suggest electroconvulsive therapy in combination with pharmacotherapy when there is a need for rapid control of symptoms. | Weak for |
| | | 32. | In individuals with bipolar 1 or bipolar 2 disorder, we suggest offering short-term light therapy as augmentation to pharmacotherapy for treatment of bipolar depression. | Weak for |
| | | 33. | For individuals with bipolar disorder who have demonstrated partial or no response to pharmacologic treatment for depressive symptoms, we suggest offering repetitive transcranial magnetic stimulation as an adjunctive treatment. | Weak for |
| **Psychosocial and recovery-oriented therapy** | Psychotherapy | 34. | For individuals with bipolar 1 or bipolar 2 disorder who are not acutely manic, we suggest offering psychotherapy as an adjunct to pharmacotherapy, including cognitive behavioral therapy, family or conjoint therapy, interpersonal and social rhythm therapy, and nonbrief psychoeducation (not ranked). | Weak for |
| | | 35. | For individuals with bipolar 1 or bipolar 2 disorder, there is insufficient evidence to recommend for or against any one specific psychotherapy among cognitive behavioral therapy, family or conjoint therapy, interpersonal and social rhythm therapy, and nonbrief psychoeducation. | Neither for nor against |
| | Complementary and integrative health and supplements | 36. | For individuals with bipolar 2 disorder, there is insufficient evidence to recommend for or against meditation as an adjunct to other effective treatments for depressive episodes or symptoms. | Neither for nor against |
| | | 37. | In individuals with bipolar disorder, there is insufficient evidence to recommend for or against augmenting with nutritional supplements, including nutraceuticals, probiotics, and vitamins, for reduction of depressive or manic symptoms. | Neither for nor against |

*(continued)*

**Table 1 (continued).**

| Topic | Subtopic | No. | Recommendation | Strength[b] |
|---|---|---|---|---|
| **Psychosocial and recovery-oriented therapy (cont.)** | Technology-based care | 38. | For individuals with bipolar disorder, there is insufficient evidence to recommend for or against any particular phone application or computer- or web-based intervention. | Neither for nor against |
| **Supportive care/models of care** | Supportive care | 39. | There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with bipolar disorder experiencing housing insecurity. | Neither for nor against |
| | | 40. | For individuals with bipolar disorder who require vocational or educational support, we suggest Individual Placement and Support or Individual Placement and Support Enhanced. | Weak for |
| | Models of care/care delivery | 41. | For individuals with bipolar disorder, we suggest caregiver support programs to improve mental health outcomes. | Weak for |
| | | 42. | For individuals with bipolar disorder, we suggest that clinical management should be based on the collaborative care model. | Weak for |
| **Co-occurring conditions** | | 43. | For individuals with bipolar 1 or bipolar 2 disorder and tobacco use disorder, we suggest offering varenicline for tobacco cessation, with monitoring for increased depression and suicidal behavior. | Weak for |
| | | 44. | For individuals with bipolar 1 or bipolar 2 disorder and co-occurring substance use disorder, there is insufficient evidence to recommend for or against any specific pharmacotherapy or psychotherapy intervention. See VA/DOD Clinical Practice Guideline for the Management of Substance Use Disorder. | Neither for nor against |
| | | 45. | For individuals with fully or partially remitted bipolar disorder and with residual anxiety symptoms, we suggest cognitive behavioral therapy. | Weak for |

[a]Reprinted from the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder.
[b]Strength of each recommendation is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[9–11]

Algorithms for specialty care evaluation, acute mania, and acute depression are included in Figures 1–3 and refer to sidebars, found in Figure 4. The algorithms are based on the evidence review but are written in the context of how treatment decisions might be made in the clinic. We expect clinicians to use the algorithms as guides that require referencing the recommendations in the CPG, and they are not a substitute for doing so.

Despite the recommendation against routine, broad-based screening for BD in primary care, there are key elements of a patient's history that might elevate their risk of a BD diagnosis and thus merit additional evaluation. For example, it is important to assess for BD when patients have a first-degree family member with BD, express symptoms consistent with mania or hypomania, or have irritability or agitation following treatment for depression. In the presence of these factors or other suspicion for BD from a clinical interaction, the Work Group suggested that decision-making about the diagnosis be supported using a validated instrument (eg, Bipolar Spectrum Diagnostic Scale, Hypomania Checklist, or Mood Disorder Questionnaire).[15,17] The Work Group chose to eschew the term "screening" for this recommendation in part because of the heterogeneity of included studies, as there may be subtle differences between screening (across a population) and clinically indicated use of a brief assessment tool (for a subset of patients for whom BD may be suspected).

Importantly, there was insufficient evidence to recommend for or against any specific quantitative treatment outcome measure to guide measurement-based care due to a paucity of data in the systematic evidence review. The Work Group encourages measurement-based care; however, it does not recommend any specific measures over others.[18]

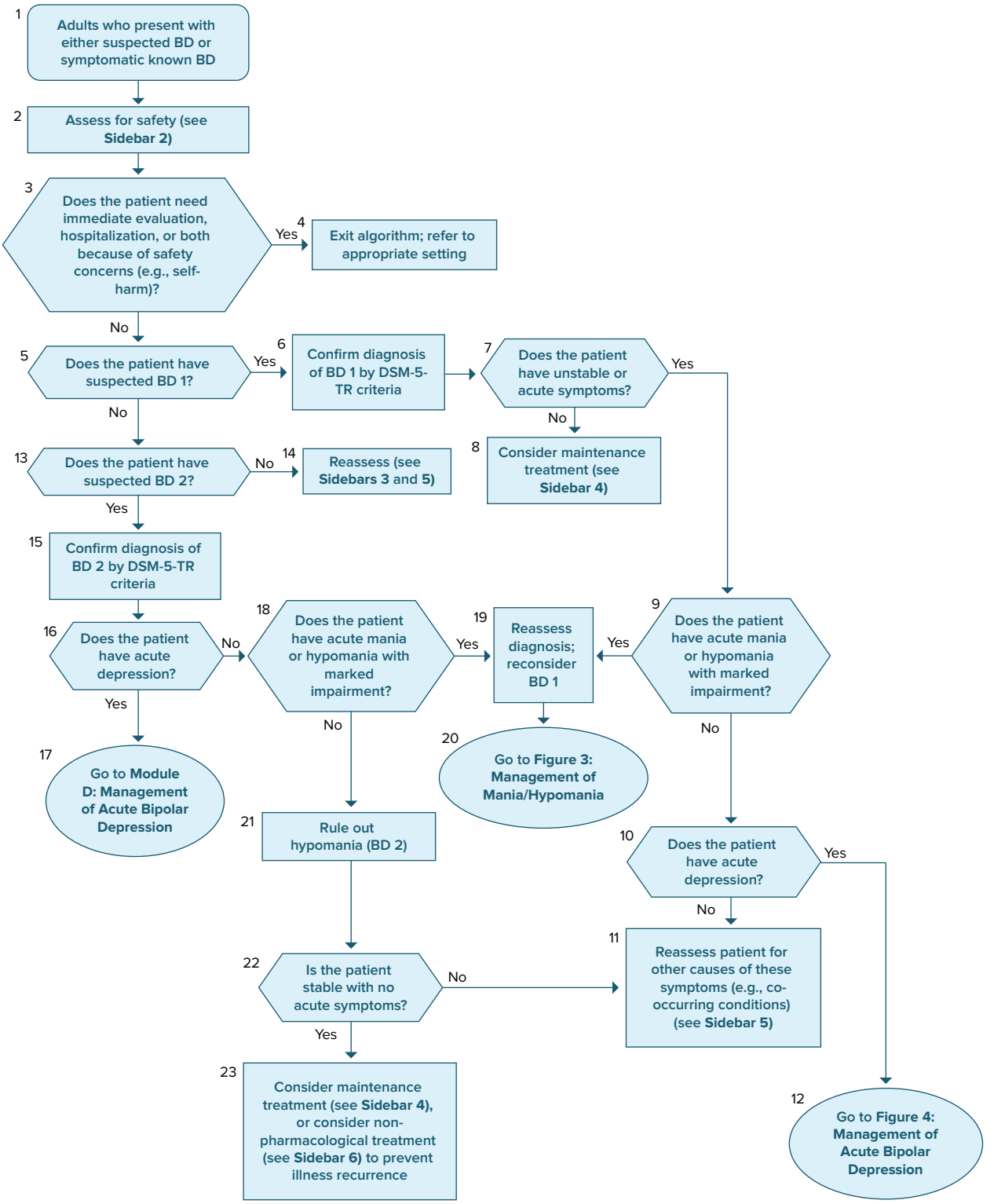
## PHARMACOLOGIC RECOMMENDATIONS

The psychopharmacology section of the CPG emphasizes a 3-phase approach to pharmacologic management: treatment for acute mania, treatment for acute depression, and maintenance to prevent recurrence of both. Traditional practice often focuses on treating acute episodes with effective medications and continuing them in the maintenance phase without considering long-term outcomes. This approach, predominant in BD treatment, risks relapse and polypharmacy, especially if additional medications are introduced during recurrences.

Recognizing BD as typically requiring lifelong treatment, the Work Group advocates for a comprehensive treatment strategy from the outset. This involves assessing the effectiveness of medications not only for acute episodes but also for maintenance (while also taking side effects into consideration), thereby improving long-term outcomes. The Group's evaluation led to recommendations for monotherapies that are effective in both acute and maintenance phases.

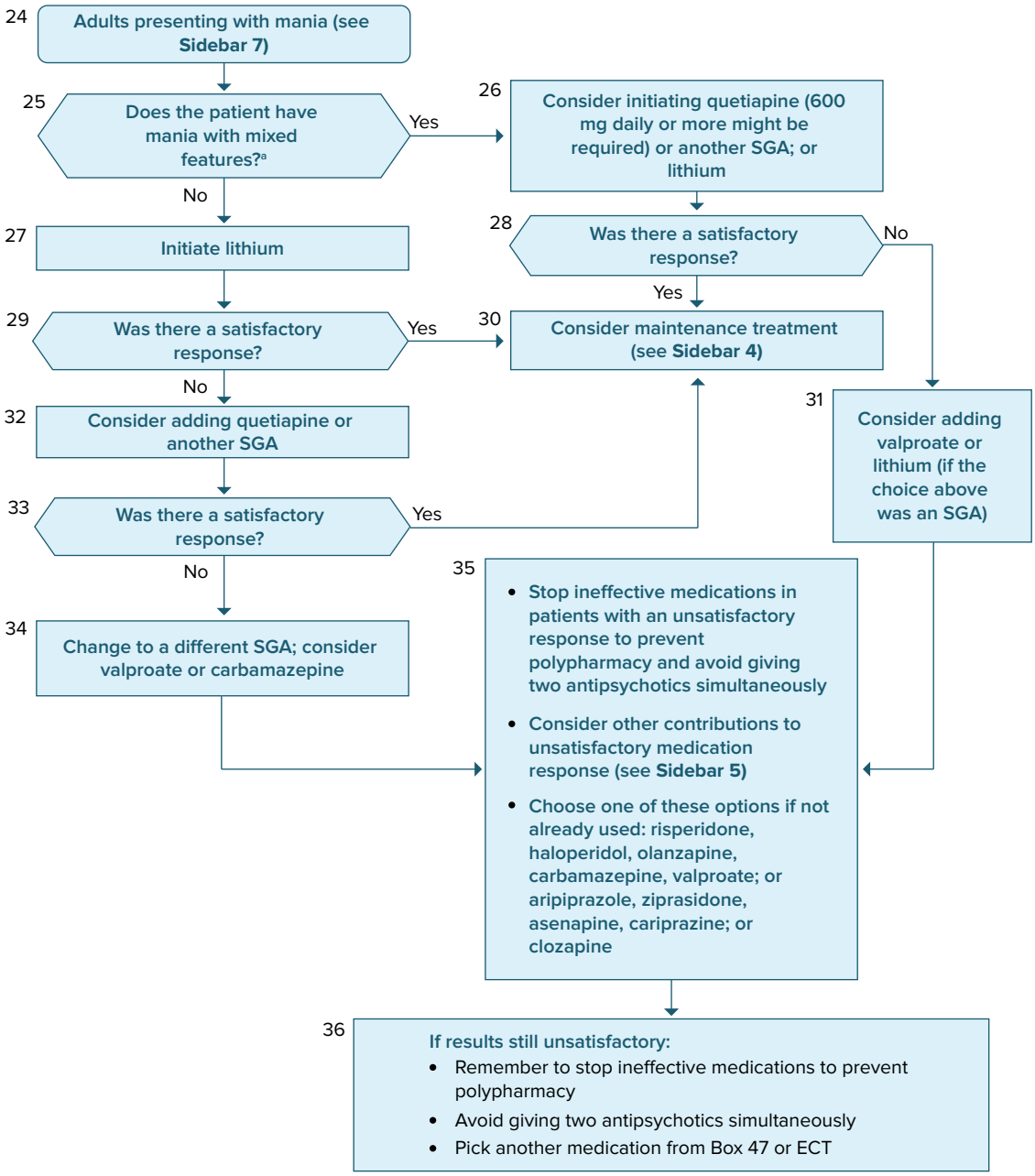
Figure 1.

## Specialty Care[a]




[a]Reprinted from the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder. The full Guideline (www.healthquality.va.gov) contains sidebars (see Figure 4) and additional modules referenced in this figure. See manuscript text for adjunctive psychosocial treatments.

Figure 2.
**Management of Mania/Hypomania**[a]



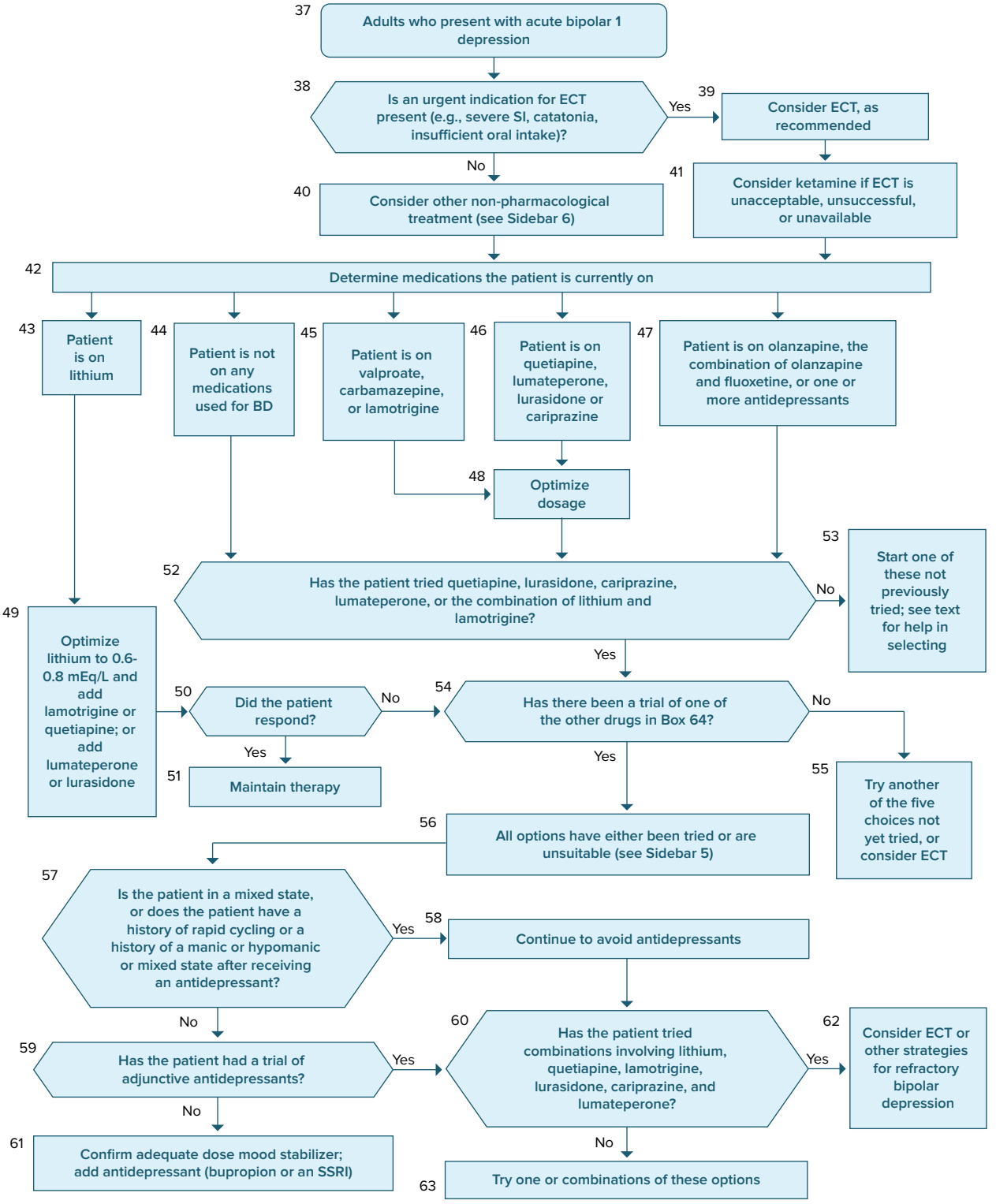

[a]Reprinted from the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder. The full Guideline (www.healthquality.va.gov) contains sidebars (see Figure 4) and additional modules referenced in this figure.

Our review finds that certain medications (quetiapine, lithium, olanzapine) are effective in preventing both manic and depressive episodes. In contrast, others (eg, risperidone, paliperidone) primarily prevent mania, while lamotrigine is more effective against recurrence of depression. For BD 1, agents effective against both manic and depressive episodes are preferred. For BD 2, the focus may shift based on the individual's history and risk factors, but with the main focus on the prevention and treatment of depressive episodes.

These recommendations are also tailored to individual patient characteristics, acknowledging that treatments with strong efficacy might not suit all due to side effects or interactions. This approach respects patient preferences and clinical variables such as coexisting conditions and past treatment experiences, ensuring a personalized and effective treatment strategy for BD.

Figure 3.

## Management of Acute Bipolar Depression[a]




[a]Reprinted from the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder. The full Guideline (www.healthquality.va.gov) contains sidebars (see Figure 4) and additional modules referenced in this figure. See manuscript text for adjunctive psychosocial treatment.

Figure 4.

## Sidebars From the VA/DOD Clinical Practice Guideline for the Management of Bipolar Disorder

**Sidebar 1: History and Symptoms Relevant to Identifying Possible Bipolar Disorder**

When gathering data on history and symptoms (e.g., by establishing medical history as well as personal and family history of mental health issues), the following might be especially relevant to identifying possible BD, particularly in combination.

- First-degree family member with BD
- Evidence of mania, hypomania, or both or of irritability, agitation, or both after antidepressant initiation
- Extended periods of functioning with high energy on little or no sleep
- Atypical depression, such as leaden paralysis, psychomotor retardation
- Other symptoms of mania or hypomania
- Severe initial onset of depression or onset of depression at a young age (≤25) or multiple prior episodes of depression (≥5)
- High levels of comorbid anxiety, substance use, depression with psychotic features
- Treatment resistant depression
- Sleep log/history with onset, maintenance, wake time, change in sleep pattern from work week to weekend, and change in energy levels

**Sidebar 2: Safety Assessment**

The VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide should be reviewed and used for this sidebar.[a] Safety assessment should include the following.

- Assess the patient for risk of harm to self or to others, including the need for hospitalization.
- Complete a validated suicide screening tool. VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide recommends PHQ-9 item 9 as a universal screening tool to identify suicide risk. Also consider C-SSRS or CAMS. When positive, continue to the following.
  - Assess modifiable and non-modifiable risk factors.
    - Self-directed violence
    - Current psychiatric conditions/current or past mental health treatment
    - Psychiatric symptoms
    - Recent bio-psychosocial stressors
    - Availability of lethal means
    - Physical health conditions
    - Demographic factors
  - Assess protective factors.
  - Create a crisis response plan with the patient.

**Sidebar 3: Primary Care Evaluation**

When there is suspicion for BD, conduct a primary care evaluation.

- Screen the patient with a validated instrument.
- Conduct a psychiatric and general medical history.
- Conduct a full medication reconciliation (including prescribed and nonprescribed medications, supplements, and vitamins), giving attention to neuropsychiatric side effects.
- Conduct a mental status and physical examination.
- Obtain a basic set of laboratory tests:
  - Thyroid stimulating hormone,
  - Complete blood count,
  - Comprehensive metabolic panel, and
  - Urine drug screening.

Reserve neuroimaging or advanced neurologic studies (e.g., EEG) for patients who have abnormal findings in the history or neurologic examination

*(continued)*

## Treatment of Acute Mania

The Work Group considered a constellation of factors in determining preferred treatments. Because lithium and quetiapine have demonstrated efficacy for acute mania, prevention of recurrence of episodes of mania, and prevention of recurrence of depression, the Work Group suggested their use as preferred or first-line monotherapies for the treatment of acute

**Figure 4 (continued).**

**Sidebar 4: Maintenance Treatment/Rehabilitation and Recovery**

When individuals with BD stabilize after an acute episode of mania/hypomania or depression, or when they present for treatment between episodes, there are opportunities and needs to plan for maintenance treatment to prevent recurrences and for the supports that might be needed to enhance living with and recovering from BD. The planning process should incorporate:

- Psychoeducation about BD, including information about the effectiveness of maintenance pharmacotherapy, psychotherapy and psychosocial rehabilitation, strategies for clinical management, and opportunities for recovery.
- Shared decision-making with the patient, the patient's social supports (where appropriate), and the treatment team.

Issues to think about include the following.

- Defining the relationship with the provider, treatment team, or both
  - Scheduling appointments, other contacts, and procedures for addressing urgent needs and emergencies
  - Specifying when and how caregivers, family members, and significant others should be involved with treatment
  - Considering whether care management (e.g., employing a non-physician health professional to coordinate interactions of the patient and providers, monitor symptoms and side effects, and promote self-management) is needed[b]
- Planning monitoring of moods, symptoms, and treatment adherence
  - Discussing methods and availability of tools to support day-to-day self-monitoring
  - Engaging caregivers, family members, and significant others in monitoring, when appropriate
  - Identifying early warning signs of possible recurrences and reporting them to providers
- Agreeing on a medication regimen with effectiveness for preventing mania and depression, including discussing side effects and their management
- Considering psychotherapy to build coping and self-management skills and to prevent recurrences
- Considering programs providing psychoeducation and support for caregivers, family members, and significant others
- Providing access to peer support in the care system or the community
- Addressing behavioral health comorbidities (e.g., mental health conditions, alcohol and drug use conditions, tobacco use, insomnia)
- Addressing specific problems (e.g., unemployment, problems at work or school, housing instability, relationships with family members and others)
- Addressing health and wellness
  - Engaging with primary care
  - Choosing among available programs to enhance wellness
- Specifying indications and timeframes for reevaluating the plan

**Sidebar 5: Reassessment after Specialty Evaluation**

- Repeat a full medication reconciliation (including prescribed and nonprescribed medications, supplements, and vitamins), giving attention to neuropsychiatric side effects.
- Investigate treatment non-adherence, using laboratory measurement when feasible.
- Consider repeat or expanded laboratory evaluation for nonmedical substance use.
- Consider the need for expanded neurologic workup.

**Sidebar 6: Non-pharmacological Therapy**

Outside acute manic episodes, the following psychotherapies might be considered as adjunctive treatments to psychopharmacology for individuals with BD 1 or BD 2 (not ranked).

- CBT
- Family or Conjoint Therapy
- IPSRT
- Psychoeducation lasting at least six sessions (Note that some types of psychoeducation [e.g., regarding possible costs of untreated mania, importance of medication adherence] might still be important even for patients with acute mania.)
- Consider light therapy as an augmentation for medication being used at any step of the algorithm.

The Work Group notes, as well, that other psychotherapeutic approaches might include components of these treatments (e.g., LGCC).

*(continued)*

**Figure 4 (continued).**

**Sidebar 7: Approach to Treating a Manic Episode**

- Taper and discontinue antidepressants.
- Address medical factors.
- Address substance intoxication and withdrawal, and treat active SUDs[c]
- Avoid carbamazepine, topiramate, and valproate if the patient is of child-bearing potential.
- Assess the effectiveness and tolerability of previous treatments for the current and past manic episodes.
- Consider mandatory referral to a behavioral health prescriber for DoD patients; if unavailable, use the nearest telepsychiatry MTF for confirmation.

[a]See the VA/DOD CPG for the Assessment and Management of Patients at Risk for Suicide, https://www.healthquality.va.gov/.
[b]See Kilbourne AM, Post EP, Nossek A, et al. *Bipolar Disord*. 2008;10(6):672–683.
[c]See the VA/DOD CPG for the Management of Substance Use Disorders, https://www.healthquality.va.gov/.
Abbreviations: BD = bipolar disorder, BD 1 = bipolar 1 disorder, BD 2 = bipolar 2 disorder, CAMS = Collaborative Assessment and Management of Suicidality, CBT = cognitive behavioral therapy, CPG = Clinical Practice Guideline, C-SSRS = Columbia-Suicide Severity Rating Scale, DOD = Department of Defense, EEG = electroencephalogram, IPSRT = interpersonal and social rhythm therapy, LGCC = Life Goals Collaborative Care, MTF = military treatment facility, PHQ-9 = Patient Health Questionnaire-9, SUD = substance use disorder, VA = Department of Veterans Affairs.

mania.[19,20] If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania.[19] Risperidone and paliperidone lack evidence supporting the use as maintenance treatments to prevent episodes of bipolar depression.[20] Olanzapine is included in this recommendation rather than in the first-line recommendation because of concerns about the burden of side effects and the risk for adverse reactions.

For third-line monotherapy for acute mania, the CPG suggests aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone due to the lack of evidence from the systematic evidence review supporting the use of these drugs as maintenance treatments for BD.[20] Evidence suggests that treatment with lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone improves mania symptom severity in individuals with BD who had an unsatisfactory response or a breakthrough episode on monotherapy.[21]

Evidence for brexpiprazole, topiramate, and lamotrigine suggests that they do not differ from placebo in improving mania symptom severity.[19] Given the lack of evidence of benefit for reducing mania and because of known harms, we suggest against their use. Similarly, evidence suggests that the addition of aripiprazole, paliperidone, or ziprasidone to a mood stabilizer is no different than a mood stabilizer alone in improving mania severity.[21] Given the known side effects associated with these agents, we suggest against their use after unsatisfactory response to lithium or valproate monotherapy for acute mania.

There is insufficient evidence to recommend for or against other first-generation antipsychotics or second-generation antipsychotics, gabapentin, oxcarbazepine, or benzodiazepines as monotherapy or in combination for acute mania. The evidence review included no studies on gabapentin, oxcarbazepine, or benzodiazepines, while also making clear that antipsychotic medications cannot be considered as a medication class in the treatment of BD and that individual antipsychotic drugs have different effects across different phases of the illness.[19]

## Prevention of Recurrence of Mania

Lithium and quetiapine are the most effective medications for maintenance treatment to prevent recurrence of mania.[20,22] The efficacy of both medications appears to be similar,[20] but each has unique advantages and disadvantages that would be relevant to selection for the individual patient. If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest oral olanzapine, oral paliperidone, or risperidone long-acting injectable for the prevention of recurrence of mania.[20]

There is insufficient evidence to recommend for or against other first-generation antipsychotics, second-generation antipsychotics, and anticonvulsants (including valproate) for the prevention of recurrence of mania. Some evidence suggests that antipsychotics (asenapine, aripiprazole, lurasidone) and anticonvulsants (valproate, carbamazepine) might be effective for the prevention of recurrence of mania, but this evidence was considered insufficient to recommend for or against their use.[20]

Evidence does not support the use of lamotrigine to prevent recurrence of mania, even though evidence does support its use to prevent bipolar depressive episodes.[20,23] Additional medication must be used with lamotrigine if the goal is to prevent the recurrence of mania, or alternative monotherapy treatment should be

considered that can help treat both phases of BD. If polypharmacy must be considered for the prevention of recurrence of mania, we suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate.[20,24]

## Treatment of Acute Bipolar Depression

Bahji et al[25] reviewed 11 randomized controlled trials (RCTs) in a network meta-analysis of individuals with BD 1 and BD 2. That review found quetiapine to be effective in the treatment of acute depression, adding to the evidence supporting the recommendations for its use in maintenance treatment for the prevention of mania and for its use in the prevention of bipolar depression. When considered together, the breadth of effectiveness for quetiapine is high. Counterbalancing this evidence, the Work Group acknowledges that quetiapine can cause significant side effects. Sedation is often present and limits its use at therapeutic doses for depression, mania, or maintenance. Metabolic side effects can be significant and must be monitored longitudinally.

If quetiapine is not selected based on patient preferences and characteristics, the Work Group suggests cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy options for acute bipolar depression, all of which have evidence demonstrating efficacy.[25–28] Like quetiapine, however, these antipsychotics all have side effects that must be considered.[28,29]

The Work Group found insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression.[25] The Bahji et al[30] network meta-analysis included an evaluation of lamotrigine added to lithium or quetiapine and found significant efficacy though the quality of this evidence was low. Lamotrigine is usually well tolerated.

The use of adjunctive antidepressants in BD is an important question as they are widely prescribed for BD in practice, but the evidence is insufficient to recommend for or against them. This applies to the olanzapine/fluoxetine combination as well, despite its approval by the US Food and Drug Administration (FDA), because only 1 RCT compared olanzapine alone to the combination.[31,32]

The Work Group also evaluated the evidence on ketamine and esketamine in the management of acute bipolar depression and concluded that the evidence was of very low quality and was therefore insufficient to recommend for or against these products as either monotherapy or an adjunctive therapy in BD.[30,33–37]

## Prevention of Recurrence of Bipolar Depression

Lamotrigine received a strong recommendation for prevention of episodes of bipolar depression.[19,23] Lamotrigine monotherapy should be of value specifically in individuals who are not thought to be at risk of mania, including those with BD 2 from our review of recent network meta-analyses. While dosing requires slow titration over the course of many weeks to minimize the risk of Stevens-Johnson syndrome, this is less problematic when lamotrigine is used to prevent episodes rather than used acutely. There was limited evidence comparing lamotrigine to other medications in the prevention of depression; however, Kishi et al[19] did not find a difference when comparing lamotrigine to lithium.

For patients with BD, especially BD 1, we suggest lithium or quetiapine as monotherapy for the prevention of recurrence of depression.[20,38,39] These studies included and did not distinguish outcomes between BD 1 and BD 2; it is important to note that in patients who require maintenance treatment to prevent mania, lithium and quetiapine are preferable to lamotrigine as monotherapy to prevent episodes of depression. In the 1 placebo-controlled head-to-head comparison of quetiapine and lithium for maintenance efficacy over 2 years, they had equal efficacy.[40] However, study participants were enriched with acute responders to quetiapine, so it is unknown if lithium might be superior. If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine monotherapy, although it presents a much higher metabolic risk.

For combination therapy to prevent bipolar depression, the evidence appears strongest for lurasidone or quetiapine added to lithium or valproate.[19,20] The evidence was insufficient to recommend for or against any other medications for preventing depression in BD.[20]

## Pregnancy and in Patients of Childbearing Potential

We make two separate but important recommendations regarding the treatment of patients who are pregnant or may become pregnant. First, for patients are stabilized on lithium, we suggest continued treatment with lithium at the lowest effective dose in a framework that includes psychoeducation and shared decision-making, with a “weak for” recommendation. It is essential that for patients who are stabilized on lithium the opportunity to continue lithium be a first consideration, given the consequences of stopping lithium and understanding that, for some patients, lithium is the most effective treatment, with the patient making decisions about the risks and benefits of doing so. Second, the CPG makes a strong against recommendation for the use of valproate, carbamazepine, or topiramate in patients of childbearing potential. Because the known harms of these agents outweigh their limited potential benefits in BD, we recommend against their use in individuals of childbearing potential. This is especially important with regard to valproate, which is often used in BD and which has reproductive concerns in multiple domains. Valproate has an FDA “black box” warning against its

use in pregnancy because of teratogenicity and neurodevelopmental disorders, so we recommend against it, which is especially important given the limits of its utility in the CPG.[41]

## OTHER SOMATIC THERAPIES

Neuromodulation and other somatic therapies were reviewed. Electroconvulsive therapy (ECT) has been used to treat individuals with severe manic symptoms who have not responded to pharmacotherapy when there is a need to rapidly decrease symptoms or when the risks of medication might outweigh the benefits. The Work Group suggests ECT in combination with pharmacotherapy when there is a need for rapid control of symptoms in mania, a "weak for" recommendation.[42] The use of ECT for depression in BD was not reviewed by the Work Group because no research on this topic was identified in the update of the systematic evidence review.

Evidence suggests that treatment with light therapy, which consists of daily exposure to bright artificial light emitting up to 10,000 lux, improves depression and clinical response in a mixed population with BD 1 or BD 2 and bipolar depression.[43] A "weak for" recommendation was therefore made for offering short-term light therapy as augmentation to pharmacotherapy for treatment of bipolar depression in both of these subgroups.

Repetitive transcranial magnetic stimulation (rTMS) involves administering an induced magnetic field to a specific area of the brain, resulting in neuronal activation in the targeted cortical area. While the FDA has cleared rTMS for use in treatment-resistant depression, it is not cleared for use in BD. The Work Group, however, suggests offering rTMS as an adjunctive treatment for patients who have demonstrated partial or no response to pharmacologic treatment for depressive symptoms with a "weak for" recommendation.

## NONPHARMACOLOGIC RECOMMENDATIONS

The BD CPG reviewed literature comparing different psychotherapies for BD, typically as supplements to psychopharmacology. Much of the relevant literature was included in a recently published systematic review and network meta-analysis.[44] Thus, the Work Group suggests 4 manualized psychotherapies as adjuncts to medication: cognitive behavioral therapy (CBT), family or conjoint therapy, interpersonal and social rhythm therapy, and psychoeducation lasting at least 6 sessions. Improvements based on these treatments include reduced recurrence and decreased mania and depression severity at follow-up (typically 6–12 months). The Work Group concluded, however, that there was insufficient evidence to recommend any one of these four psychotherapeutic approaches above the others. Therefore, selection of a psychotherapy should be left to patient preference, while accounting for differing levels of availability for these treatments (eg, because not all clinicians may be trained in all these psychotherapies). Few qualifying studies directly compared two specific psychotherapies to one another as adjuncts to medications, meaning that the recommendations for these psychotherapies were primarily derived from studies that compared one or more of them to TAU or medication alone.

A host of other psychotherapies and related approaches, including dietary interventions, were not included in the systematic evidence review carried out as part of this CPG and were not considered in developing this recommendation. Some of these treatments, however, draw heavily from the principles underlying one or more of the psychotherapies described above (eg, Life Goals Collaborative Care, which incorporates elements of psychoeducation and behavioral therapy across 7 or more treatment sessions).[13]

### Telehealth and Apps

Technology-supported treatment has become a pillar of medical care. While there was no evidence to indicate any level of harm associated with web-based or smartphone-based applications, the BD CPG found that there was insufficient evidence to recommend for or against any particular application or computer- or web-based intervention. The studied applications and web programs were noted to vary widely, and no head-to-head comparisons were found. The Work Group notes that there is wide variation in both patient and provider preferences regarding these types of interventions. And while video-based mental health care has become common, the Work Group found insufficient evidence to recommend any one specific approach to providing video-based services to veterans or active-duty personnel. Thus, patient preference should be considered when deciding upon a treatment modality. Ideally, future research will provide more information on the best ways to meet patient needs through apps, video telehealth, or other computer- or web-based approaches to providing or supplementing mental health care for BD.

### Supportive Services and Models of Care Delivery

Other aspects of care examined by the BD CPG included wrap-around and family support services. These included housing support, vocational/educational support, caregiver models, and collaborative care. While the Work Group felt strongly that providing safe and affordable housing to persons diagnosed with BD

involves little to no harm, there was insufficient evidence to recommend any specific supported housing intervention. Vocational or educational support with "Individual Placement and Support" (IPS) or "Individual Placement and Support-Enhanced" (IPS-E),[45,46] caregiver support programs,[47,48] and clinical management in a collaborative care model[49–52] all earned "weak for" recommendations.[53–55] In aggregate, these recommendations emphasize the importance of providing assistance above and beyond evidence-based medications and/or psychotherapy: support in the domains of housing, employment, caregiver functions, and care coordination may all be helpful for people with a diagnosis of BD.

## COMPARISON TO OTHER GUIDELINES

The VA/DOD CPG on BD has numerous similarities and differences with other major guidelines. Three relevant comparators have been published since 2000. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) last updated their guidelines in 2018.[56] BD treatment guidelines from the UK National Institute for Health and Care Excellence (NICE) were last updated in 2016.[57] The American Psychiatric Association last published bipolar disorder guidelines in 2002.[58]

Methodological differences between the VA/DOD CPG and these other treatment guidelines may explain some differences in recommendations. Similar to the CANMAT and ISBD guidelines, the VA/DOD guideline is aligned around pharmacologic interventions, but the search strategy and the use of levels of evidence differentiate them. The VA/DOD CPG is an update of a prior guideline with a strict evidence-based strategy. It does not use expert opinion where the evidence is absent or inconclusive, for either harms or benefits. This approach differentiates it from CANMAT/ISBD, for example, which uses expert opinion and consensus outside of established evidence.

The evidence for the treatment of BD is limited, and our use of it is limited in this CPG by the rigorous search strategy used to identify studies to include in the review. Because of this, there are limitations to using a strictly evidence-based guideline as many clinicians and patients may find that the highest rated options are either ineffective or not preferred by the patients. There is an argument for including expert opinion treatment recommendations outside the evidence and some may wish to do so, but this was not the charge of this Work Group. A limitation of expert opinion is that it is inherently biased and not evidence based; nevertheless, clinicians might choose to follow expert opinion recommendations, especially in areas in which evidence is lacking or next-step treatments are unclear.

Although both the NICE and CANMAT/ISBD guidelines were published within the past decade, much continues to evolve in the treatment of this complex illness. The VA/DOD guideline is now the most recently published evidence review. It should be noted that other institutional, local, and national guidelines do exist (eg, American Academy of Family Physicians),[59] although they are not as rigorous or comprehensive as those mentioned above.

## DISCUSSION

This Clinical Practice Guideline for Bipolar Disorder, developed by the VA/DOD Evidence-Based Practice Work Group (EBPWG), is a standardized, evidence-based delineation of treatments for BD, tailored for use within the military and veteran populations, but with evidence that can be generalized to the civilian population. This CPG embodies a comprehensive approach to treatment, integrating both pharmacologic and nonpharmacologic interventions and underscoring the importance of patient-centered care and shared decision-making in a complex, lifelong condition often co-occurring with other medical, psychiatric, and addictive disorders.

One of the main strengths of this CPG is its foundation in rigorous, systematic evidence review, adhering to the GRADE approach. This ensures that the treatment strategies are based on the highest quality of current scientific evidence. It also marks a significant effort to go beyond mere symptom control by including a range of treatment modalities, from pharmacologic interventions to psychotherapies and somatic treatments like ECT and rTMS to recovery-focused care. The CPG's design not only focuses on the acute management of BD but also makes maintenance treatment and overall wellness primary goals, incorporating strategies for long-term management and recovery. At its core, the CPG promotes shared decision-making, ensuring that care plans align with patient values and preferences, thereby enhancing treatment effectiveness and patient outcomes. The development of the CPG involved a wide array of stakeholders, including health care providers from various disciplines and patient representatives, ensuring a well-rounded perspective in its recommendations.

However, the CPG is not without its limitations. A key limitation is that it serves as an update to an earlier guideline that considered only RCTs or systematic reviews published between January 1, 2012, and December 31, 2021. This temporal scope means that any new studies or findings published after this period could not be included, potentially omitting recent advancements or updates in BD treatment. Recommendations for BD 2 are necessarily limited because of large gaps in the literature, especially for the treatment of hypomania and for maintenance treatment,

although the treatment of depression in BD 2 is also understudied. Additionally, while the evidence derives from studies in the general population, the CPG's recommendations are primarily tailored to the military and veteran populations, which may limit their applicability to broader patient groups. The evolving nature of evidence in the field also implies that the CPG will require regular updates to stay current. Additionally, the successful implementation of these guidelines requires resources, training, and coordination across various levels of health care, which might be a challenge outside of well-resourced medical centers.

The VA/DOD CPG for Bipolar Disorder is a robust, evidence-based tool that makes a significant contribution to the standardization and improvement of care for individuals with BD, with a mandate to focus on the needs of military and veteran populations. It effectively balances clinical expertise with patient preferences, promoting a holistic and individualized approach to treatment. Nonetheless, its relevance and effectiveness in the rapidly evolving landscape of mental health care depend on continuous updates and the inclusion of emerging research findings.

## Article Information

**Published Online:** January 13, 2025. https://doi.org/10.4088/JCP.24cs15546


**Submitted:** August 9, 2024; accepted October 25, 2024.

**To Cite:** Ostacher MJ, Miller CJ, Edwards-Stewart A, et al. Synopsis of the 2023 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for the Management of Bipolar Disorder. *J Clin Psychiatry.* 2025;86(1): 24cs15546.

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**Author Contributions:** Concept and design: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors.

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**Relevant Financial Relationships:** The authors have no relevant financial disclosures.

**Funding/Support:** This Clinical Practice Guideline was funded by the US Department of Veterans Affairs.

**Role of the Sponsor:** US Department of Veterans Affairs oversaw the development of the Clinical Practice Guideline and had final decision to submit the manuscript for publication.

**Disclaimer:** The views expressed in this article are those of the authors and do not reflect the official policy of the US Department of the Army, the US Department of the Navy, the US Department of the Air Force, the US Department of Defense, the US Department of Veterans Affairs, or the US Government.

**Previous Presentation:** Poster presented at the American Psychological Association Annual Meeting; August 8–10, 2024; Seattle, Washington.

**Acknowledgments:** The authors thank all US Department of Veterans Affairs and US Department of Defense Work Group members who developed this Clinical Practice Guideline. The full Work Group list can be found in the guideline at www.healthquality.va.gov.

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