

VA/DoD Clinical Practice Guidelines



Management of Bipolar Disorder



VA/DoD Evidence-Based Practice

Provider Summary

Version 2.0 | 2023



VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF BIPOLAR DISORDER

Department of Veterans Affairs

Department of Defense

Provider Summary

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DoD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

Version 2.0 – May 2023

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Introduction

The VA and DoD Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the VA/DoD Health Executive Committee “on the use of clinical and epidemiological evidence to improve the health of the population . . .” across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPG) for the VA and DoD populations.⁽¹⁾ Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and wellbeing.

The VA/DoD EBPWG initiated the creation of the VA/DoD Bipolar Disorder (BD) CPG in 2021. This CPG provides an evidence-based framework for evaluating and managing care for individuals with BD toward improving clinical outcomes. Successful implementation of this CPG will

- Assess the patient’s condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care;
- Emphasize the use of patient-centered care and shared decision making;
- Minimize preventable complications and morbidity; and
- Optimize individual health outcomes and quality of life (QoL).

The full VA/DoD BD CPG, as well as additional toolkit materials including a Quick Reference Guide and Patient Summary, can be found at:

<https://www.healthquality.va.gov/index.asp>.

Scope of the CPG

This CPG is based on published clinical evidence and related information available through December 31, 2021. It is intended to provide general guidance on best evidence-based practices (see Appendix A in the full VA/DoD BD CPG for additional information on the evidence review methodology). Although the CPG is intended to improve the quality of care and clinical outcomes (see [Introduction](#)), it is not intended to define a standard of care (i.e., mandated or strictly required care).

This CPG is intended for use by VA and DoD primary care providers (PCPs) and others involved in the healthcare team caring for individuals with BD. It is tailored to be of greatest value to mental health providers. Additionally, this CPG is intended for community-based clinicians involved in the care of Service members, beneficiaries, or Veterans with BD.

The patient population of interest for this CPG is adults (age 18 years and older) treated with any diagnosis covered within “bipolar and related disorders” of the DSM-5-TR. It includes Veterans and Service members as well as their dependents. Recommended interventions in this CPG are applicable regardless of care setting.

Guideline Development Team

Table 1. Guideline Work Group and Guideline Development Team

| Organization | Names* |
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*Additional contributor contact information is available in Appendix K (in the full VA/DoD BD CPG)

Patient-centered Care

Intended to consider patient needs and preferences, guideline recommendations represent a whole/holistic health approach to care that is patient-centered, appropriate for diverse patient populations, and available to people with limited literacy skills and physical, sensory, or learning disabilities. In addition, VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and wellbeing.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.^(2, 3) A whole/holistic health approach (<https://www.va.gov/wholehealth/>) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences.

Shared Decision Making

This CPG encourages providers to practice shared decision making, which is a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.⁽⁴⁾ Shared decision making is emphasized in *Crossing the Quality Chasm*, an Institute of Medicine (IOM), now NAM, report in 2001 ⁽⁵⁾ and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care, especially where patient heterogeneity in weighing risks and benefits might exist. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

Algorithm

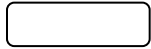
This CPG’s algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in managing individuals with BD. This algorithm format represents a simplified flow of the management of individuals with BD and helps foster efficient decision making by providers. It includes

- Steps of care in an ordered sequence,
- Decisions to be considered,
- Decision criteria recommended, and
- Actions to be taken.

The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.⁽⁶⁾ Sidebars 1–7 provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape

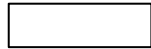
Description



Rounded rectangles represent a clinical state or condition.



Hexagons represent a decision point in the process of care, formulated as a question that can be answered “Yes” or “No.”



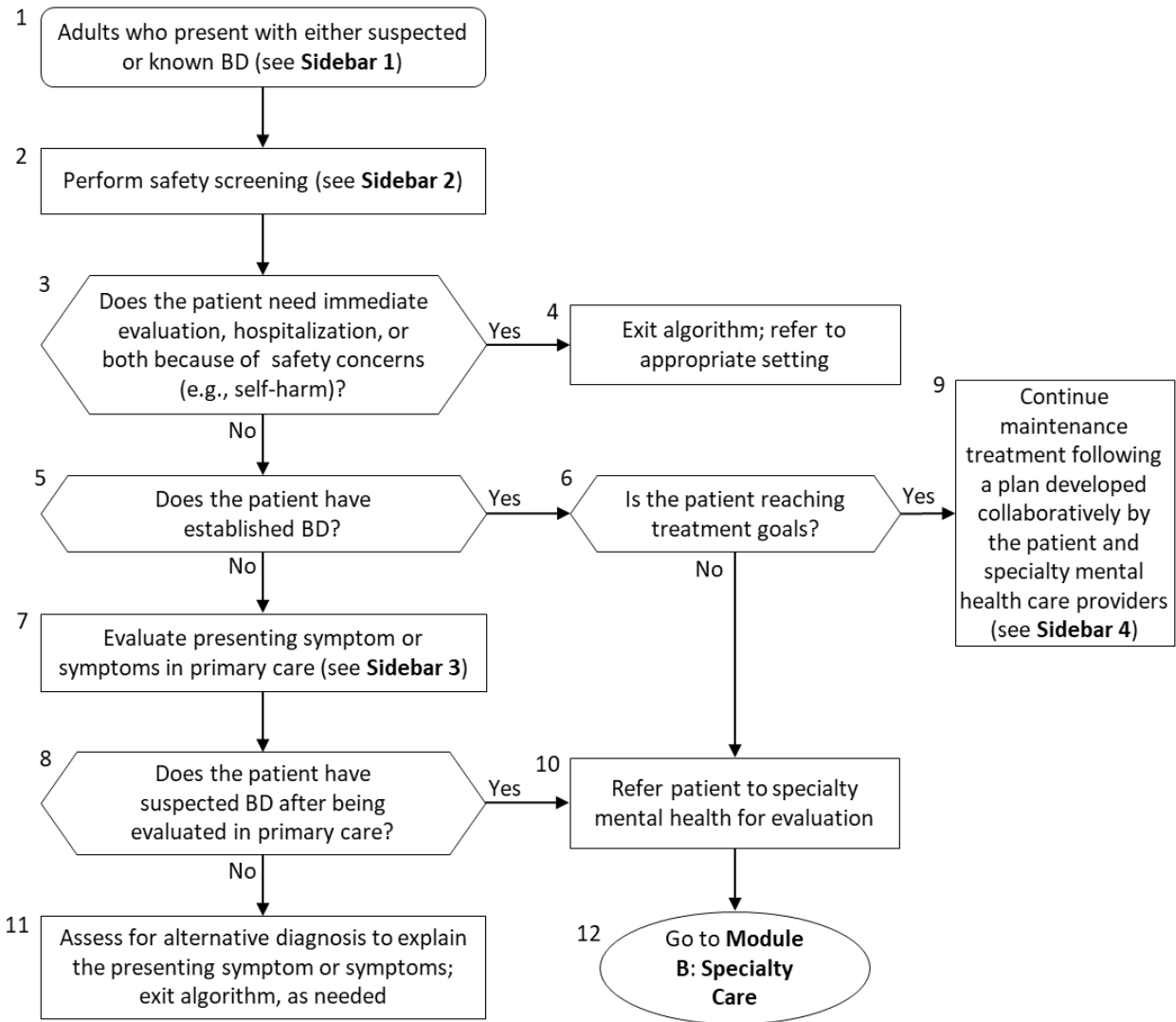
Rectangles represent an action in the process of care.



Ovals represent a link to another section within the algorithm.

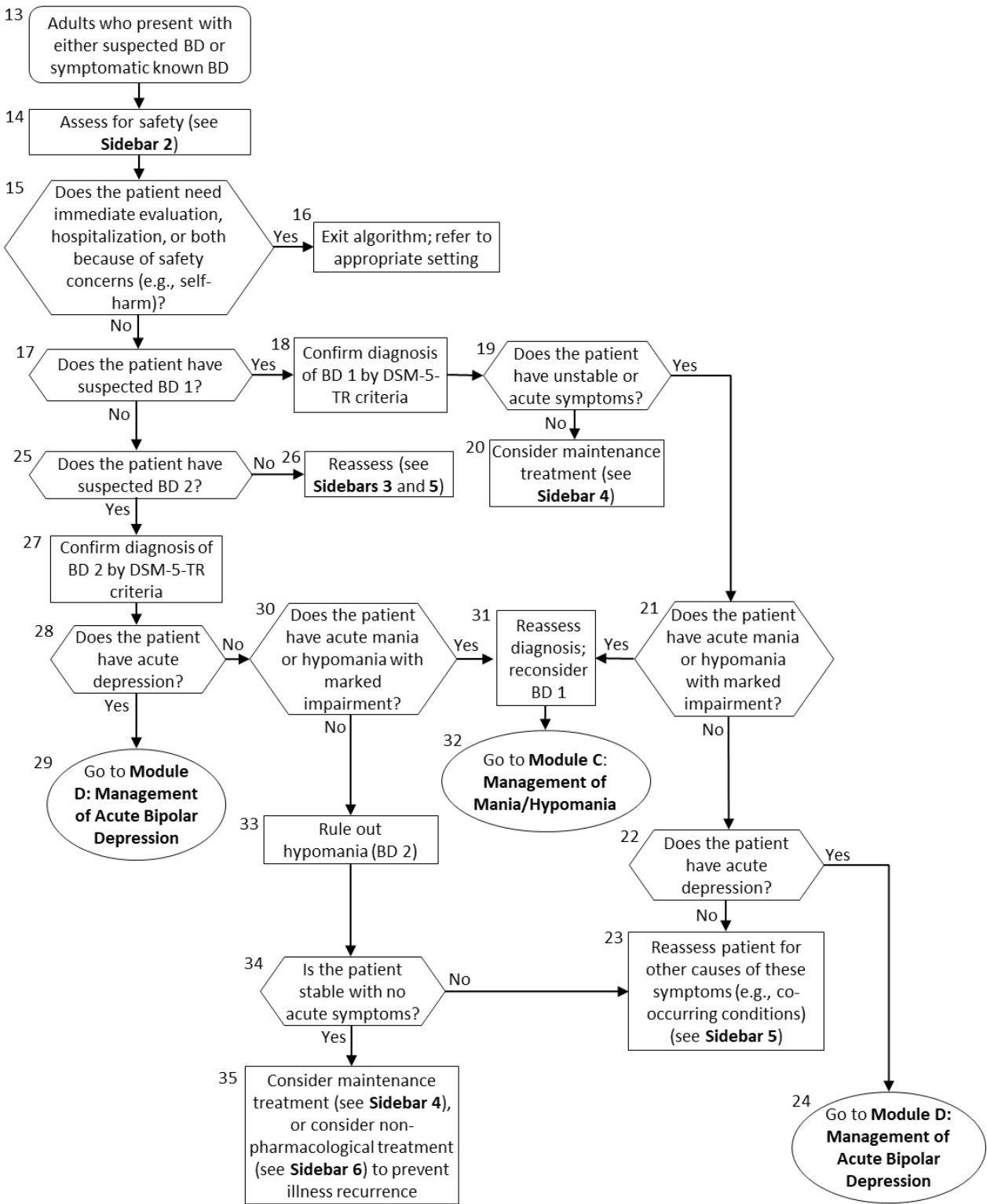
Appendix M in the full VA/DoD BD CPG contains alternative text descriptions of the algorithms.

Module A: Diagnosis and Triage



Abbreviations: BD: bipolar disorder

Module B: Specialty Care

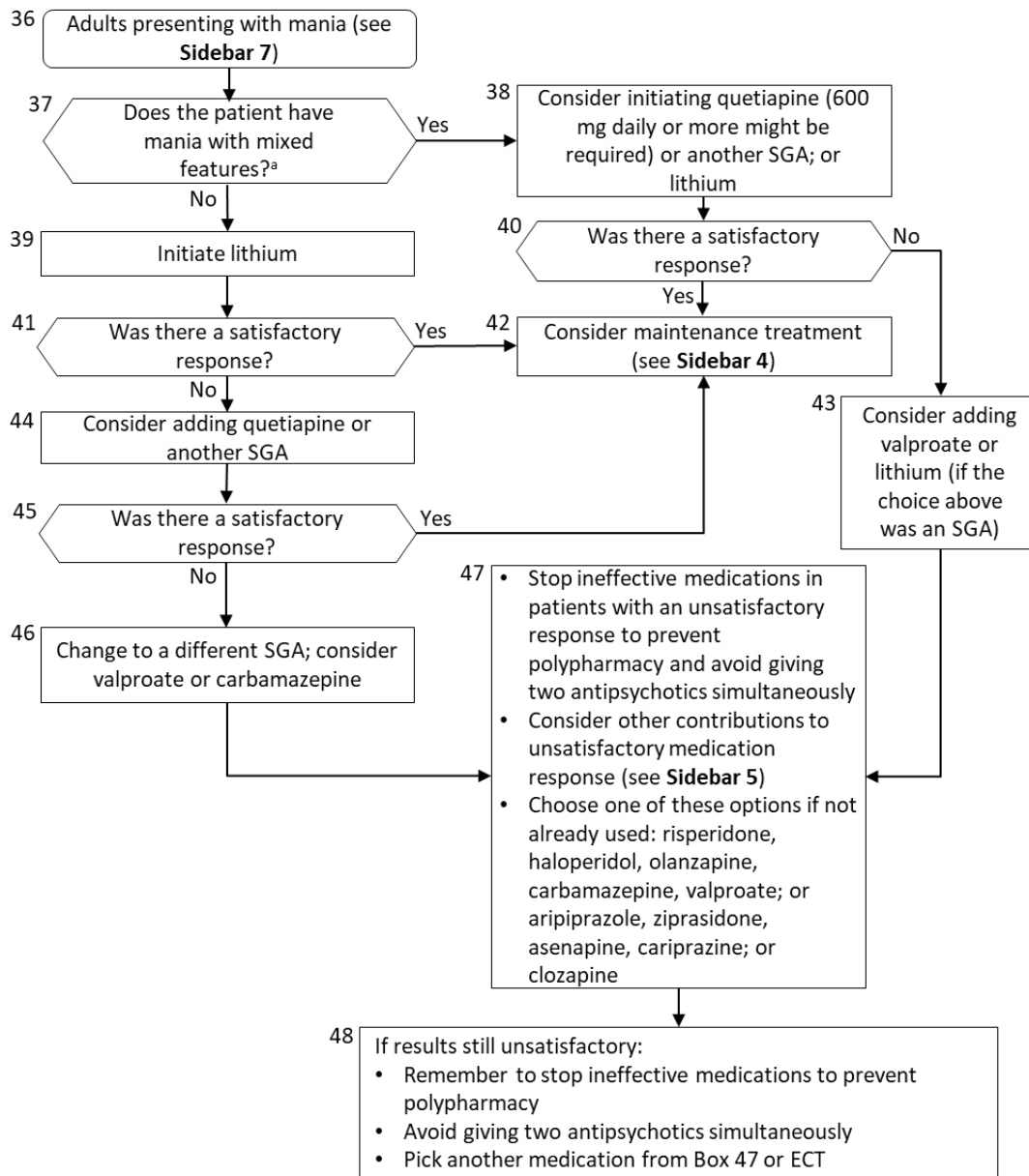


Abbreviations: BD: bipolar disorder; BD 1: bipolar 1 disorder; BD 2: bipolar 2 disorder; DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision

Module C: Management of Mania/Hypomania

| Key Points |
|--|
| <ul style="list-style-type: none"> • Manage severe emergent agitation.(7) • Consider ECT for patients resistant to pharmacotherapy, with history of positive response to ECT, or with adverse effects or intolerable side effects to medications. • See Sidebar 7 before proceeding with treatment (especially considerations for individuals of child-bearing potential). |

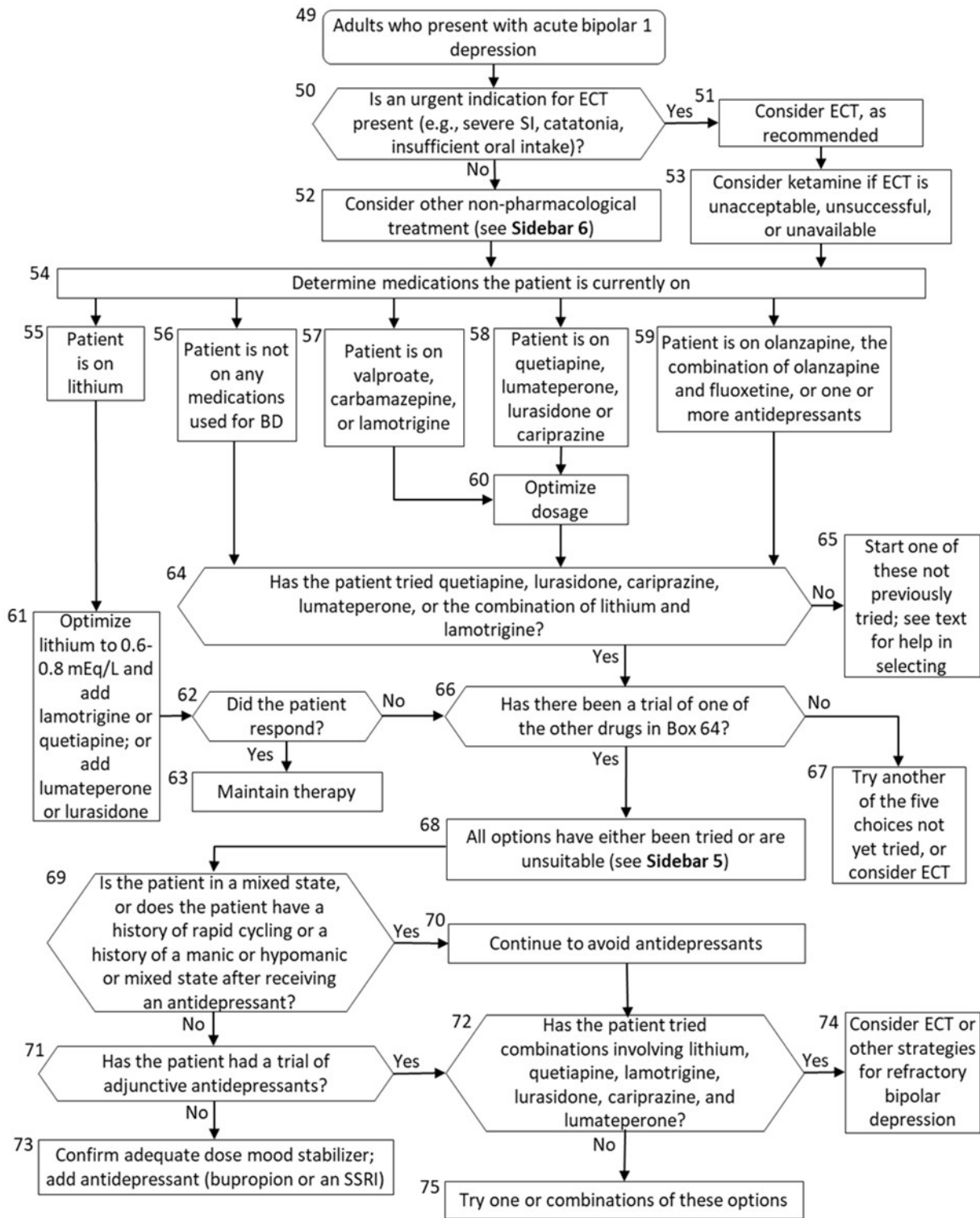
Abbreviations: ECT: electroconvulsive therapy; IM: intramuscular



^a Mixed episodes as defined before DSM-5 in 2013 are no longer part of the diagnostic system. Mixed features as a course specifier was added in DSM-5, but this approach has not been studied systematically in mania or depression, so the ability to make evidence-based recommendations for patients with mixed features is limited.

Abbreviations: ECT: electroconvulsive therapy; mg: milligram; SGA: second-generation antipsychotic

Module D: Management of Acute Bipolar Depression



Abbreviations: BD: bipolar disorder; ECT: electroconvulsive therapy; mEq/L: milliequivalents per liter; SI: suicidal ideation; SSRI: selective serotonin reuptake inhibitor

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

Abbreviations: BD: bipolar disorder

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.

^a See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: <https://www.healthquality.va.gov/>.

Abbreviations: CAMS: Collaborative Assessment and Management of Suicidality; CPG: clinical practice guideline; C-SSRS: Columbia-Suicide Severity Rating Scale; DoD: Department of Defense; PHQ-9: Patient Health Questionnaire-9; VA: Department of Veterans Affairs

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

Abbreviations: BD: bipolar disorder; EEG: electroencephalogram

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 ([8](#))
- 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

Sidebar 4: Maintenance Treatment/Rehabilitation and Recovery

- 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

Abbreviations: BD: bipolar disorder

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).

Abbreviations: BD 1: bipolar 1 disorder; BD 2: bipolar 2 disorder; CBT: cognitive behavioral therapy; IPSRT: interpersonal and social rhythm therapy; LGCC: Life Goals Collaborative Care

Sidebar 7: Approach to Treating a Manic Episode

- Taper and discontinue antidepressants.
- Address medical factors.
- Address substance intoxication and withdrawal, and treat active SUDs^a
- 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 Management of Substance Use Disorders, available at:

<https://www.healthquality.va.gov/>.

Abbreviations: DoD: Department of Defense; MTF: military treatment facility; SUD: substance use disorder

Recommendations

The evidence-based clinical practice recommendations listed (see [Table 2](#)) were made using a systematic approach considering four domains as per the GRADE approach (see Methods and Appendix A in the full VA/DoD BD CPG). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Note: Although the systematic evidence review carried out as part of the development of this CPG included a search for schizoaffective disorder, no evidence was retrieved. Therefore, the recommendations in this CPG do not cover patient populations with schizoaffective disorder. Unless otherwise specified, the recommendations below for the treatment and prevention of mania are for patient populations with BD 1, and those for the treatment and prevention of bipolar depression are for patient populations with BD 1 and BD 2.

Table 2. Evidence-based Clinical Practice Recommendations with Strength and Category

| Topic | Sub-topic | # | Recommendation | Strength ^a | Category ^b |
|---------------------------------|--------------------|----|--|-------------------------|-----------------------|
| Screening and Evaluation | | 1. | We suggest against routine screening for bipolar disorder in a general medical population. | Weak against | Reviewed, New-added |
| | | 2. | In specialty mental health care, when there is suspicion for bipolar disorder from a clinical interaction, we suggest using a validated instrument (e.g., Bipolar Spectrum Diagnostic Scale, Hypomania Checklist, Mood Disorder Questionnaire) to support decision making about the diagnosis. | Weak for | Reviewed, New-added |
| | | 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 (e.g., Hypomania Checklist, Mood Disorder Questionnaire) as part of the evaluation for mania/ hypomania. | Weak for | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| Pharmacotherapy | <i>Acute Mania</i> | 5. | We suggest lithium or quetiapine as monotherapy for acute mania. | Weak for | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |

| Topic | Sub-topic | # | Recommendation | Strength ^a | Category ^b |
|-------------------------|--------------------------|-----------------------------------|---|---|-----------------------|
| Pharmacotherapy (cont.) | Acute Mania (cont.) | 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 | Reviewed, New-added |
| | | 9. | We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania. | Weak against | Reviewed, New-added |
| | | 10. | We suggest against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy for acute mania. | Weak against | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | Acute Bipolar Depression | 12. | We recommend quetiapine as monotherapy for acute bipolar depression. | Strong for | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | | 14. | There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression. | Neither for nor against | Reviewed, New-added |
| | | 15. | We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression. | Weak for | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | 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 | Reviewed, New-added |
| | 21. | | We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania. | Weak against | Reviewed, New-added |
| | 22. | | We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania. | Weak for | Reviewed, New-added |

| Topic | Sub-topic | # | Recommendation | Strength ^a | Category ^b | |
|-------------------------|--|-----|---|--|-----------------------|---------------------|
| Pharmacotherapy (cont.) | Prevention of Recurrence of Bipolar Depression | 23. | We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes. | Strong for | Reviewed, New-added | |
| | | 24. | We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes. | Weak for | Reviewed, New-added | |
| | | 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 | Reviewed, New-added | |
| | | 26. | We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes. | Weak for | Reviewed, New-added | |
| | | 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 | Reviewed, New-added | |
| | | 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 | Reviewed, New-added | |
| | Pregnancy/Child-bearing 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 | Reviewed, New-added | |
| | | 30. | We recommend against valproate, carbamazepine, or topiramate in the treatment of bipolar disorder in individuals of child-bearing potential. | Strong against | Reviewed, New-added | |
| | 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 | Reviewed, New-added |
| | | | 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 | Reviewed, New-added |
| 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 | Reviewed, New-added | |

| Topic | Sub-topic | # | Recommendation | Strength ^a | Category ^b |
|--|--|-----|--|-------------------------|-----------------------|
| 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 non-brief psychoeducation (not ranked). | Weak for | Reviewed, New-added |
| | | 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 non-brief psychoeducation. | Neither for nor against | Reviewed, New-added |
| | 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | Models of Care/ Care Delivery | 41. | For individuals with bipolar disorder, we suggest caregiver support programs to improve mental health outcomes. | Weak for | Reviewed, New-added |
| | | 42. | For individuals with bipolar disorder, we suggest that clinical management should be based on the collaborative care model. | Weak for | Reviewed, New-added |

| Topic | Sub-topic | # | Recommendation | Strength ^a | Category ^b |
|-------------------------|-----------|-----|---|-------------------------|-----------------------|
| 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 | Reviewed, New-added |
| | | 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 | Reviewed, New-added |
| | | 45. | For individuals with fully or partially remitted bipolar disorder and with residual anxiety symptoms, we suggest cognitive behavioral therapy. | Weak for | Reviewed, New-added |

^a For additional information, see Determining Recommendation Strength and Direction in the full VA/DoD BD CPG.

^b For additional information, see Recommendation Categorization in the full VA/DoD BD CPG.

Pharmacotherapy

Table 3. Monotherapies for Bipolar Disorder^a

| Medication | Effective for Bipolar Disorder Phase/Indication ^b | | | |
|---------------|--|---------------------|---------------------------------------|----------------------------------|
| | Acute Treatment of Mania | Prevention of Mania | Acute Treatment of Bipolar Depression | Prevention of Bipolar Depression |
| Quetiapine | x | x | x | x |
| Olanzapine | x | x | x | x |
| Lithium | x | x | | x |
| Cariprazine | x | | x | |
| Paliperidone | x | x | | |
| Risperidone | x | x | | |
| Aripiprazole | x | | | |
| Asenapine | x | | | |
| Carbamazepine | x | | | |
| Haloperidol | x | | | |
| Valproate | x | | | |
| Ziprasidone | x | | | |
| Lumateperone | | | x | |
| Lurasidone | | | x | |
| Lamotrigine | | | | x |

^a For information on adverse events, see Table E-2: Antipsychotic Adverse Event Profiles in the full VA/DoD BD CPG.

^b An “X” indicates an agent with demonstrable evidence of effectiveness for a specific phase/indication; a blank space indicates that an agent has been studied and not found effective for a specific phase/indication or lacks evidence of effectiveness based on the evidence reviewed.

Table 4. Combination Therapies for Bipolar Disorder

| Medication | | Effective for Bipolar Disorder Phase/Indication ^a | | | |
|--------------|-----------------------|--|---------------------|---------------------------------------|----------------------------------|
| Medication 1 | Medication 2 | Acute Treatment of Mania | Prevention of Mania | Acute Treatment of Bipolar Depression | Prevention of Bipolar Depression |
| Quetiapine | Lithium or valproate | x | x | | x |
| Olanzapine | Lithium or valproate | x | x | | x |
| Haloperidol | Lithium or valproate | x | | | |
| Asenapine | Lithium or valproate | x | | | |
| Risperidone | Lithium or valproate | x | | | |
| Aripiprazole | Lithium or valproate | | x | | |
| Ziprasidone | Lithium or valproate | | x | | |
| Lurasidone | Lithium or valproate | | | | x |
| Lamotrigine | Quetiapine or lithium | | | x | |

^a An “X” indicates an agent with demonstrable evidence of effectiveness for a specific phase/indication; a blank space indicates that an agent has been studied and not found effective for a specific phase/indication or lacks evidence of effectiveness based on the evidence reviewed.

Methods

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.⁽⁵⁾ The *Guideline for Guidelines* is available at <http://www.healthquality.va.gov/policy/index.asp>. This CPG also aligns with the National Academy of Medicine’s (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).⁽⁶⁾ Appendix A in the full VA/DoD BD CPG provides a detailed description of the CPG development methodology.

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction in the full VA/DoD BD CPG): confidence in the quality of the evidence, balance of desirable and undesirable outcomes, patient values

and preferences, other considerations as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations).⁽⁹⁾

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.⁽⁸⁾ A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice even though it is unsupported by clinical evidence and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about an intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in [Table 5](#).

Table 5. Strength and Direction of Recommendations and General Corresponding Text

| Recommendation Strength and Direction | General Corresponding Text |
|---------------------------------------|--|
| Strong for | We recommend ... |
| Weak for | We suggest ... |
| Neither for nor against | There is insufficient evidence to recommend for or against ... |
| Weak against | We suggest against ... |
| Strong against | We recommend against ... |

The GRADE of each recommendation made in the 2023 CPG can be found in the section on [Recommendations](#). Additional information regarding the use of the GRADE system can be found in Appendix A in the full VA/DoD BD CPG.

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Access to the full guideline and additional resources is available at:
<https://www.healthquality.va.gov/>.

