VA/DoD Clinical Practice Guidelines

Management of Bipolar Disorder

Quick Reference Guide

Version 2.0 | 2023

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF BIPOLAR DISORDER

Department of Veterans Affairs

Department of Defense

Quick Reference Guide

Recommendations **Algorithm**

Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the GRADE approach (see *Summary of Guideline Development Methodology* on page 19 in full 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).

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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy	Acute Mania	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
		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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy (cont.)	*Prevention of Recurrence of Mania*	18.	We recommend lithium or quetiapine for the prevention of recurrence of mania.	Strong for	Reviewed, New-added
		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
	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

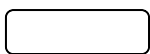
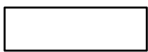
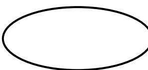
Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Other Somatic Therapies		31.	For individuals with bipolar 1 disorder with acute severe manic symptoms, we suggest electroconvulsive therapy in combination with pharmacotherapy when there is a need for rapid control of symptoms.	Weak for	Reviewed, 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
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
	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	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
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
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* on page 135 in the full CPG

[b] For additional information, see *Recommendation Categorization* on page 137 in the full CPG

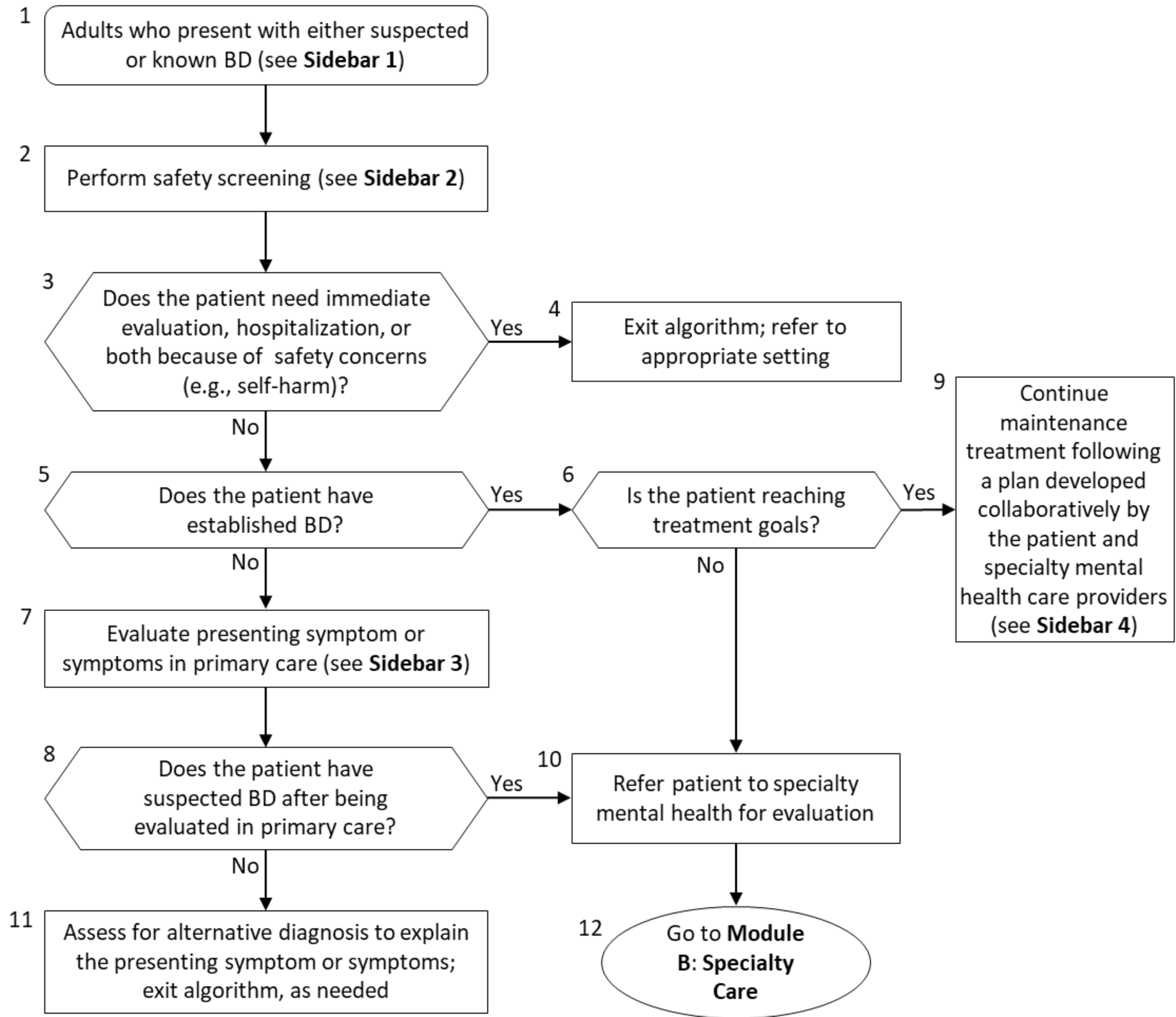
Algorithm

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.

The algorithm sidebars can be found on page 30 in the full CPG at https://www.healthquality.va.gov/.

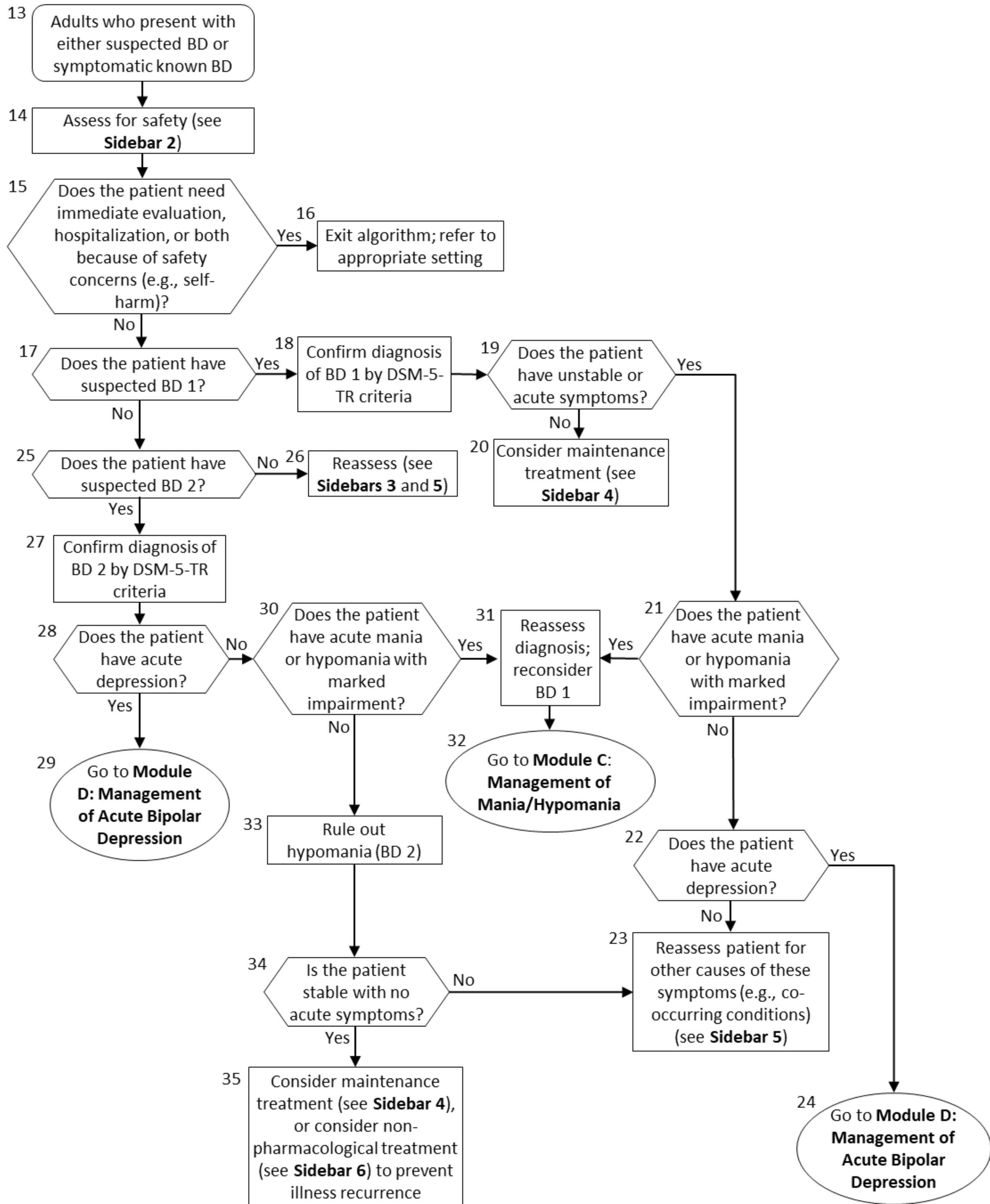
Appendix M (also in the full CPG) contains the alternative text descriptions of the algorithm.

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

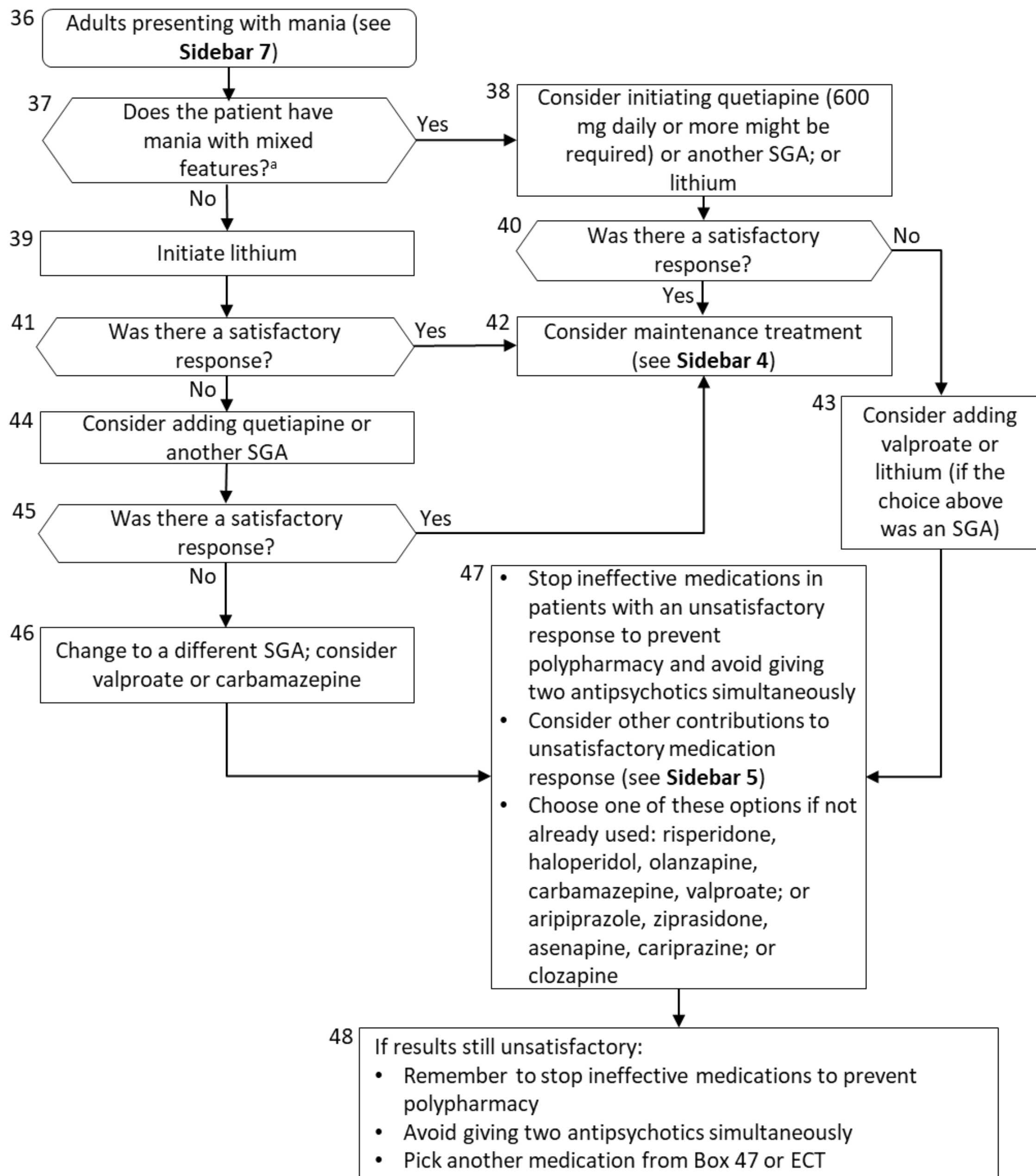
Module C: Management of Mania/Hypomania

Key Points

- Manage severe emergent agitation[a]
- 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) (**Sidebar 7** is located in the full CPG at https://www.healthquality.va.gov/.)

[a] Stetson SR, Osser DN. Psychopharmacology of agitation in acute psychotic and manic episodes. *Curr Opin Psychiatry*. 2022;35(3):171-6. Epub 2022/05/18. doi: 10.1097/yco.0000000000000787. PubMed PMID: 35579871.

Abbreviations: ECT: electroconvulsive therapy



[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

49. Adults who present with acute bipolar 1 depression

50. Is an urgent indication for ECT present (e.g., severe SI, catatonia, insufficient oral intake)?
 - Yes → 51
 - No → 52

51. Consider ECT, as recommended

52. Consider other non-pharmacological treatment (see **Sidebar 6**)

53. Consider ketamine if ECT is unacceptable, unsuccessful, or unavailable

54. Determine medications the patient is currently on

55. Patient is on lithium → 61

56. Patient is not on any medications used for BD → 64

57. Patient is on valproate, carbamazepine, or lamotrigine → 60

58. Patient is on quetiapine, lumateperone, lurasidone or cariprazine → 60

59. Patient is on olanzapine, the combination of olanzapine and fluoxetine, or one or more antidepressants → 64

60. Optimize dosage → 64

61. Optimize lithium to 0.6-0.8 mEq/L and add lamotrigine or quetiapine; or add lumateperone or lurasidone → 62

62. Did the patient respond?
 - Yes → 63
 - No → 66

63. Maintain therapy

64. Has the patient tried quetiapine, lurasidone, cariprazine, lumateperone, or the combination of lithium and lamotrigine?
 - Yes → 66
 - No → 65

65. Start one of these not previously tried; see text for help in selecting

66. Has there been a trial of one of the other drugs in Box 64?
 - Yes → 68
 - No → 67

67. Try another of the five choices not yet tried, or consider ECT

68. All options have either been tried or are unsuitable (see **Sidebar 5**)

69. Is the patient in a mixed state, or does the patient have a history of rapid cycling or a history of a manic or hypomanic or mixed state after receiving an antidepressant?
 - Yes → 70
 - No → 71

70. Continue to avoid antidepressants → 72

71. Has the patient had a trial of adjunctive antidepressants?
 - Yes → 72
 - No → 73

72. Has the patient tried combinations involving lithium, quetiapine, lamotrigine, lurasidone, cariprazine, and lumateperone?
 - Yes → 74
 - No → 75

73. Confirm adequate dose mood stabilizer; add antidepressant (bupropion or an SSRI)

74. Consider ECT or other strategies for refractory bipolar depression

75. Try one or combinations of these options

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

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