VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF BIPOLAR DISORDER

Department of Veterans Affairs
Department of Defense

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 – 2023

Prepared by

Management of Bipolar Disorder Work Group

With support from

Office of Quality and Patient Safety, Veterans Health Administration

and

Clinical Quality Improvement Program, Defense Health Agency

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Based on evidence reviewed through December 31, 2021

[a] VA/DoD Clinical Practice Guideline. (2023). Management of Bipolar Disorder Work Group. Washington, DC: U.S. Government Printing Office.

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I. 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 CPGs 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).

II. Background

A. Description of Bipolar Disorder

Bipolar disorder is a serious mental health condition that affects more than 40 million people worldwide.(2) It is marked by fluctuations in mood, thought, energy, behavior, and social functioning. Specific BD diagnoses depend on the severity, polarity, and duration of mood episodes. Within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR),(3) mania is a type of mood episode marked by some combination of elevated, expansive, or irritable mood; increased goal-directed activity or psychomotor agitation; decreased need for sleep; inflated self-esteem; pressured speech; racing thoughts; distractibility; or engagement in risky activities, such as reckless spending or sexual indiscretions. To qualify as a manic episode, symptoms must be present most of the day, nearly every day, for at least one week and result in significant impairment or negative consequences (e.g., hospitalization, arrest, psychotic features, harm to others, loss of a job or important relationships). However, many episodes (not only of mania, but also of hypomania and depression as described below) might last significantly longer than one week.

Hypomania might feature many of the same symptoms as mania and represents a marked change in behavior when compared with a person's normal functioning but, by definition, does not involve the same level of negative consequences.(3) In fact, some people might experience improved mood and productivity while hypomanic, potentially

complicating attempts to diagnose it accurately.(4) Furthermore, a mood episode might qualify as hypomania based on a duration of four days or longer, shorter than the seven days required for a manic episode.

Major depressive episodes, in contrast, are marked primarily by at least two weeks of depressed mood or a loss of interest or pleasure in activities, accompanied by appetite changes; psychomotor agitation or retardation; fatigue; concentration problems; feelings of worthlessness or guilt; or thoughts of death or suicide.(3) Major depressive episodes, by definition, cause significant distress or impairment. The clinical presentation of a major depressive episode in the context of bipolar depression is not reliably different from that of a major depressive episode in the context of major depressive disorder (MDD) (i.e., unipolar depression). Thus, a diagnosis of BD cannot be made based on the presence of particular features for any given patient's depressive episodes alone.(5)

A diagnosis of bipolar 1 disorder (BD 1) requires a history of at least one manic episode, with or without a history of depression.(3) Bipolar 2 disorder (BD 2) requires a history of at least one hypomanic episode and at least one depressive episode, without a history of mania. Finally, a diagnosis of cyclothymic disorder is assigned to individuals who experience frequent mood fluctuations over a period of two years or more, but who do not meet criteria for BD 1, BD 2, or a full hypomanic or major depressive episode. In DSM-5, people with BD who experience four or more episodes (depression, mania, or hypomania) per year are designated as rapid cycling.

We also note that mixed states had previously been defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) as involving symptoms that would meet full criteria for mania or depression. This aspect of the illness, however, has undergone significant revision in DSM-5.(6) Specifically, DSM-5 allows for specifiers for people who experience depressive episodes with co-occurring—but potentially subsyndromal—manic symptoms (depressive with mixed features) as well as for people who experience manic episodes with co-occurring—but potentially subsyndromal—depressive symptoms (manic with mixed features).

Diagnostic criteria for BD in the International Classification of Diseases, 10th Revision are similar to those listed in DSM-5-TR, albeit with some subtle differences.(7) Unfortunately, accurate diagnosis of BD might come years after the onset of symptoms,(8) which can contribute further to the instrumental and emotional costs of this condition for patients and their families. In summary, BD can be an extremely disabling condition that presents important clinical challenges related to assessment, diagnosis, treatment, and recovery.

B. Epidemiology and Impact on the General Population

Bipolar disorder has a lifetime prevalence of around 1% in adults in the United States (U.S.) with rates varying according to study sampling and geographical location.(9) Clinical estimates for bipolar spectrum disorders range as high as 2.4% globally,

according to large cross-sectional survey methods across 11 countries.(10) Using face-to-face household surveys, this study provided lifetime prevalence and point (12-month) prevalence estimates with BD 1 lifetime prevalence of 0.6%, and 0.4% for BD 2, whereas point prevalence was 0.4% and 0.3% for BD 1 and BD 2, respectively.(10) Estimates of BD vary notably related to stringency of criteria, to study methodologies, and by differences in race. For example, in one study, the prevalence of BD among individuals identifying as Native Americans was higher relative to self-identified Whites, whereas estimates of BD 1 were lower for self-identified Blacks, Asians and Pacific Islanders, and Hispanics. However, consistent findings across different racial, ethnic, and cultural backgrounds are lacking and further research is needed.(11-13) Additionally, studies examining differences across genders lack a consistent pattern.

Numerous factors associated with the risk of BD diagnosis have been examined, such as age, genetic influences, environmental exposures, substance use, comorbid preexisting psychiatric and medical conditions, infections (e.g., Toxoplasma gondii [*T. gondii*]/viral), prenatal and perinatal factors, and personality characteristics.(14) Age remains one of the most important clinical considerations when evaluating an individual for BD. A recent systematic review (SR) revealed evidence of a trimodal age-at-onset distribution with three different subgroups: early onset (mean age: 18.7 years; standard deviation [SD]: 1.52), mid-onset (mean age: 25.5 years; SD: 1.47), and late-onset (mean age: 29.4 years; SD: 2.21).(15) Historically, it has been thought that BD tends to present in a bimodal distribution. However, an SR revealed that when data supporting a bimodal model using early versus late-onset age cohorts were examined separately, only 20% of cases identified as BD 1 were recognized as occurring late-onset (over age 40).(15) Studies of first-degree family relatives of individuals with BD and several studies examining single genetic loci associations reveal promising findings to help improve the understanding of a genetic model of BD.(16, 17) Many of the single loci identified were correlated with loci associated with schizophrenia. Furthermore, 19 studies have examined the biological evidence of a *T. gondii* infection (e.g., IgG antibodies) and BD showing an association (odds ratio [OR]: 1.26–1.52; $p<0.05$).(18, 19) Directionality and causation of the relationship between *T. gondii* and BD remain elusive because of limitations in sample sizes and BD diagnostic methodologies.

Exposure to childhood trauma and stressful life events is associated with an increased likelihood of BD.(14) Increasingly, studies of substances associated with non-medical use, including cocaine, cannabis, nonmedical prescription opioids, stimulants, and sedatives/tranquilizers, have observed an association between these substances and BD diagnosis. For example, studies performed with robust methods revealed an association between BD and cannabis use (OR: 2.7–4.8; $p<0.05$),(20, 21) although studies with less stringent designs have examined non-medical use of prescriptions opioids, stimulants, and sedative/tranquilizers and have also found an association with BD.(22) Further, genetic correlations between disorders of alcohol use and BD have been found.(23) The range of psychiatric conditions associated with onset of BD include prior panic disorder,

anxiety disorder, suicide attempts, and rapid cycling mood symptoms. Medical conditions that have been found to be associated with the onset of BD include asthma, migraines, multiple sclerosis, prior traumatic brain injury (TBI), and irritable bowel syndrome.(18) The degree of evidence supporting associations with BD are the strongest for those listed above with many other associations under examination. Finally, clinical observations support a strong relationship between smoking and mental health disorders, relationships that invariably impact medical comorbidity and QoL findings. An SR by Jackson et al. (2015) identified 20 studies representative of 16 countries and revealed an overall prevalence of smoking was 49% among samples with BD;(24) a prevalence rate falling between rates of smoking among samples of individuals with a diagnosis of depression and those with a diagnosis of schizophrenia.

Bipolar disorder is among the most serious mental health disorders and, although relatively uncommon compared with MDD, BD has a sizable impact on measures of disability and years lost to disability (YLD). Measures of BD burden worldwide reveal that it is the 16th leading cause of YLD for all ages and ranks 6th globally among younger samples (ages 10–24). Estimates indicate that 9.9 million person-years are lost because of BD, representing 1.3% of the sum of global estimates of YLD among all diseases examined. An SR from 2022 reports on years of potential life lost associated with a diagnosis of BD that was estimated to be roughly 10 years (pooled life expectancy 66.9 years; 95% confidence interval [CI]: -69.6–72.4).(25) Notably, despite the much lower prevalence of BD relative to asthma, the high disability weight for an episode of mania meant that the global rate of BD YLD per 100,000 population was similar to prevalent conditions such as asthma (BD: 138.3; asthma: 147.9).(26) Among all mental health conditions, BD trails major depression, anxiety, schizophrenia, and alcohol use disorders (AUD) as the fifth most disabling condition globally. The costs of BD extend well beyond measures of individual disability and contribute to substantial total direct costs to the health care system (i.e., $202.1 billion in 2015) and high emotional and financial costs to families and social support systems managing BD.(27, 28)

It is critical that providers recognize the frequent pattern of co-occurring mental health conditions that accompany patients experiencing BD; findings show remarkable consistency across both U.S. and international samples.(10, 29) In U.S. epidemiological research, 92.3% of individuals with BD also reported another mental health condition. These included generalized anxiety disorder (GAD) (29.6%), panic disorder (20.1%), posttraumatic stress disorder (PTSD) (24.2%), obsessive-compulsive disorder (OCD) (13.6%), impulse control disorders (ICDs) (62.8%), and substance use disorders (SUD) (42.3%). International studies revealed a similar pattern albeit with lower frequencies, with any co-occurring mental health condition in 76.5% of individuals with BD. These included panic disorder (11.1%), GAD (20.5%), PTSD (18.9%), OCD (12.5%), ICDs (42.9%), and SUDs (36.6%).(10, 29)

C. Bipolar Disorder in the Department of Veterans Affairs Population

Based on VA administrative data,(30) VA cared for 134,748 Veterans with BD in 2021; this number represents 2.16% of all Veterans receiving VA care (see Table 1). Substantial proportions were elderly or with mental health or other medical comorbidities, or both. These features differ to some extent from the characteristics of the patients included in randomized clinical trials, signaling the need for caution in evaluating the fit of the evidence from clinical trials to the needs of VA's real-world patients.

a. Demographics

Of the individuals with BD receiving care in VA, 77.7% were men and 22.3% were women. Among this total, 13.6% were under age 35, 61.3% were age 35–64, and 25.2% were age 65 and older; 74.0% were White, 16.5% were Black, 0.8% were Asian, 0.9% were Native American, and the remainder were other, multiracial, or unknown. Finally, 6.9% were Hispanic, and 67.9% had some degree of service-connected disability.

b. Clinical Characteristics

Most of the VA patients with BD had a recurring condition with multiple episodes, and most experienced comorbidities or complications. The most common co-occurring mental health disorder in Veterans with BD was PTSD, which was present in 42.9% of that group. In addition, 34.1% had an SUD. Medical comorbidities were also common. The average body mass index was 30.5, indicating that a substantial proportion of VA patients with BD were obese. Further, 40.3% of the Veterans had hypertension, 21.8% had diabetes, and 4.4% had heart failure. During 2021, 2.1% of VA patients with BD died. As VA patients with BD age, they are at increased risk for being diagnosed with late life dementia (incidence risk ratio: 2.92).(31)

c. Health Care Use

Approximately 69.9% of the individuals with BD seen in VA were treated in VA general mental health clinics, with an average of nine visits during the year; 7.6% were treated in an inpatient VA mental health unit in 2021. During 2021, 73.1% of VA patients with BD filled one or more VA prescriptions for an oral mood stabilizer and 52.1% for an oral antipsychotic medication. Lastly, 7.8% of VA patients with BD received homeless services, 5.3% were identified and flagged as being at high risk for suicide, and 1.6% were identified as having disruptive behavior. The proportion of Veterans who receive rehabilitation-related services, such as Assertive Community Treatment (ACT), Supportive Employment, and care in a Psychosocial Rehabilitation and Recovery Center (PRRC), was low, under 3% for each of these programs.

Approximately 10% (9.9%) of the Veterans with BD were treated in a VA inpatient medical/surgical unit during the year, 79.5% received primary care services from VA, and 31.1% of the patients were seen in VA emergency departments for mental health or medical/surgical problems. In addition, 1.27% were seen in VA Community Living Centers (nursing homes), either for step down/rehabilitation services or long-term care.

d. Summary

Overall, VA patients with BD are likely to be middle-aged or elderly. They experience high degrees of mental health comorbidities, primarily related to PTSD and SUD, and high degrees of medical comorbidities, primarily associated with obesity, hypertension, and diabetes. A substantial proportion has been diagnosed with a tobacco use disorder. Most VA patients with BD receive both primary care and mental health services from VA. Therefore, VA has both the need and the opportunity to treat the patients' BD in the context of aging and both mental health and medical comorbidities. Table 1 breaks out the subgroups and percentages of VA's BD patient population in 2021.

Table 1. Characteristics of VA Patients with Bipolar Disorder, 2021

Category	Subgroup	Percentage
Demographics	Female	22.3%
	Male	77.7%
	Age <35	13.6%
	Age 35–49	26.7%
	Age 50–64	34.6%
	Age 65–79	23.4%
	Age ≥80	1.8%
	White	74.0%
	Black	16.5%
	Asian	0.8%
	Native American	0.9%
	Other, multiracial, or unknown	7.8%
	Hispanic	6.9%
Comorbidity	PTSD	42.9%
	SUD	34.1%
	Tobacco Use Disorder	17.9%
	Hypertension	40.3%
	Diabetes	21.8%
	Heart Failure	4.4%
Past-Year VA Service Use	Inpatient Mental Health	7.6%
	ACT	2.0%
	PRRC	2.8%
	Supportive Employment	1.7%
	Homeless Services	7.8%
	High Risk Flag –Suicide	5.3%
	High Risk Flag–Disruptive Behavior	1.6%

Category	Subgroup	Percentage
Past-Year VA Service Use (continued)	Inpatient Medical/Surgical	9.9%
	Emergency Department	31.1%
	Primary Care	79.5%
	Community Living Center (Nursing Home)	1.3%

Abbreviations: ACT: Assertive Community Treatment; PRRC: Psychosocial Rehabilitation and Recovery Center; PTSD: posttraumatic stress disorder; SUD: substance use disorder; VA: Department of Veterans Affairs

D. Bipolar Disorder in the Department of Defense Population

Psychiatric disorders are an important source of morbidity in the DoD population, with BD representing a significant proportion of those disorders. Among U.S. Service members, BD presents serious occupational problems, disrupts military readiness, and can consume large amounts of administrative and medical resources. From 2006–15, affective psychoses (including severe depression and manic episodes with and without psychotic features) were the second leading cause of hospitalizations for U.S. Service members (n=43,742; incidence rate [IR]: 3.18 per 1,000 person years [PY]) with a primary diagnosis of BD accounting for approximately 10% of these hospitalizations (n=4,663; IR: 0.34 per 1,000 PY).(32) From 2016–20, the rate of hospitalizations with a primary discharge diagnosis of BD remained unchanged (n=2,238; IR: 0.34 per 1,000 PY).

In the first two years after entering the military, mental disorders are the primary cause of hospitalization, likely in part because of a modal peak incidence in psychotic disorders among the most common ages at enlistment, despite the requirement of a pre-accession medical evaluation. Among those hospitalized with a primary discharge diagnosis of any mental disorder, the rate of separation from the military is 45% within six months after the first hospitalization.(33, 34) In the ambulatory setting, from 2006–15, 140,340 encounters with a primary diagnosis of BD (IR: 10.21 per 1,000 PY) occurred and from 2016–20, 126,451 encounters (IR: 19.42 per 1,000 PY) occurred.(32) From 2016–20, 1.5% (n=11,886) of ambulatory encounters for BD indicated a primary diagnosis of a hypomanic episode, and 27.8% (n=35,192) of encounters indicated a primary diagnosis of BD 2. It should be noted that DoD Instruction 6130.03 indicates that BD 1 is incompatible with retention in service, whereas BD 2 will be considered case by case.(35) Rates of ambulatory care in the MHS for BD 1 likely do not reflect the total burden of individuals who have separated from service and are receiving care outside the MHS. IRs of BD were highest among female military members, younger than 20–24 years, who identified as White; however, it was noted that the incidence of BD 2 increased in males over time.(36, 37) It is important to note that although epidemiologic data is readily accessible in the VA health system, the information available from DoD is relatively limited in comparison, thereby preventing direct alignment and comparison of data at times. Alignment in data collection and storage is a focus for improvement in DoD and is supported by the planned adoption of a shared electronic health record system.

E. Recovery Movement

a. Mental Health Recovery and this Clinical Practice Guideline

The term “recovery” has been interpreted in multiple ways. The earliest meaning of recovery was seen as remission of an illness or the elimination of symptoms. SUDs seen in remission are often equated with recovery. For the purpose of this CPG, we will focus on mental health recovery. The current focus on mental health recovery is on the process in which individuals living with mental illnesses, such as BD, live meaningful lives of their choosing. Both systems and individuals are a part of an orientation to recovery.(38) Given the context of CPGs,(39) this review focuses on the individual. The concept of mental health recovery is vital because it relates to wellbeing in addition to the care process of individuals living with BD and their families. Addressing stigma as it relates to BD is part of recovery focused care.(40) Self-stigma can prevent individuals from seeking care, and stigma from others potentially interferes with engagement in care.(41)

Recommendations in this CPG aim to support mental health recovery of individuals with BD and do not fully capture the range of current research and scholarship as it relates to recovery. This brief overview of mental health recovery provides a broader focus on how mental health services might support individuals with BD beyond the scope of these CPG recommendations and outlines some of the limitations of this CPG process in understanding and promoting recovery in BD.

b. What is Mental Health Recovery?

The Substance Abuse and Mental Health Services Administration (SAMHSA) defines recovery in both behavioral health and substance use as a process of change through which people improve their health and wellness, live self-directed lives, and strive to reach their full potential.(42) Four major dimensions support recovery.

- **Health** – overcoming or managing one’s disease or diseases or symptoms and making informed, healthy choices that support physical and emotional wellbeing
- **Home** – having a stable and safe place to live
- **Purpose** – having meaningful daily activities and the independence, income, and resources to participate in society
- **Community** – having relationships and social networks that provide support, friendship, love, and hope

Frameworks such as POETIC (purpose and meaning, optimism and hope, empowerment, tensions, identity, and connectedness) (43) speak to the ongoing evolution in semantics and approach in recovery. Jagfeld et al. (2021) used the POETIC framework to conduct a systematic review of qualitative data for individuals recovering from BD.(43) In the process, the authors pointed out a need to address tensions in addition to the more optimistic portions of the framework. Across the literature on recovery there were notable differences in definitions of recovery between the individual

(44) and the systems of care.(45) Recovery approach at the system level describes a philosophy or orientation, such as "person-centered care." Although considered influential, person-centered care is not an endpoint or outcome of recovery for individuals. Operationalizing the concept of recovery can lead to challenges if no consensus on a definition is reached. Further difficulty in defining and operationalizing the recovery model can be seen with the diversity of measurement approaches. Problems in measurement can lead to inability to draw conclusions about "evidence" on both the individual and system of care,(46) making it challenging to incorporate the recovery concept as an outcome in SRs and CPGs such as this one.

c. What is the Recovery Movement?

Historically, the evolution of recovery can be traced back to the 1800s with Phillippe Pinel and moral treatment for mental illness.(46) Social justice movements of the 1860s and 70s brought recovery closer to the individually driven intention and systems collaboration of modern recovery. In 2002, the President's New Freedom Commission took a closer look at mental health treatment in the U.S. In 2003, the final report of the New Freedom Commission summarized goals for mental health in America.(47) The underlying theme of recovery was evident in testimonies presented to the commission and in the resulting goals.

- Goal 1 – Americans Understand That Mental Health Is Essential to Overall Health
- Goal 2 – Mental Health Care Is Consumer and Family Driven
- Goal 3 – Disparities in Mental Health Services Are Eliminated
- Goal 4 – Early Mental Health Screening, Assessment, and Referral to Services Are Common Practice
- Goal 5 – Excellent Mental Health Care Is Delivered and Research Is Accelerated
- Goal 6 – Technology Is Used to Access Mental Health Care and Information

In 2004, the VHA Mental Health Strategic Plan was developed based on the above recommendations, including recovery-oriented initiatives. In 2006–08, VHA established the role of local recovery coordinators as part of its mental health strategic plan. The VHA used SAMHSA's definition of recovery and recovery-oriented care to focus their actions.(48). The incorporation of Wellness Recovery Action Planning, Illness Management and Recovery, Integrated Peer Support Services, supported employment and evidence-based practices in therapy identified to assist individuals with BD in meeting their goals has been part of the ongoing evolution in the VHA to provide recovery focused care. SAMHSA's recent creation of an Office of Recovery in 2021 is part of the ongoing focus in the U.S. government to help shape systems care to meet individual recovery needs. The adoption of more pragmatic and non-theoretical psychiatric rehabilitation practices focusing on improving life roles and community status through employment, housing, friendship, leisure activities and wellness management, activities of daily living, nutrition, and exercise are evident in the mental health system at large.

This CPG does address some of the more pragmatic practices, such as housing and care management. However, the Work Group had a limit to the number of key questions (KQ) that could be asked. Moreover, methodological challenges in measuring and studying recovery limited the ability to include more recovery specific evidence in this CPG.

d. Challenges in Incorporating Recovery into This Clinical Practice Guideline

Recovery appears as an individual process where individuals with psychiatric disabilities can personalize their recovery experience. Although potentially beneficial in clinical practice, the ongoing difficulty in consistent operationalization leads to challenges in collecting systematic evidence supporting the recovery concept. The range and diversity of definitions of recovery can be seen in researchers' efforts.(49) The evidence reviewed for this CPG rarely included definitions and measures of recovery, making it difficult to draw meaningful conclusions about the effect of interventions on mental health recovery itself. The systematic evidence drawn for KQs related to screening, diagnosing, and treating individuals with BD was not focused on recovery itself. Additional challenges in delineating the full range of evidence about interventions designed to promote recovery are present in this CPG. The systematic evidence review for this CPG included only studies of individuals with BD and excluded studies where participants were diagnostically heterogeneous, so studies of interventions designed to improve recovery-oriented domains, such as housing, employment, social connectedness, and peer support, were limited. Studies of stigma and BD were not part of the evidence retrieved for this CPG. Stigma related to mental illness can be self-stigma and stigma generated by others. The patient focus group for this CPG discussed thoughts that would be considered related to stigma. Future CPGs might consider addressing stigma as it relates to recovery and best practices. Conducting research on heterogeneous populations is often an appropriate way to develop evidence on recovery-promoting interventions. When symptoms no longer are the primary target of the intervention, testing interventions on diagnostically narrow groups might be unnecessary. However, the large body of evidence on recovery-oriented treatments conducted with diagnostically diverse individuals could not be included here because of the diagnostically homogeneous protocols adopted by the CPG, which might have influenced the Work Group's ability to make recommendations on recovery-oriented treatments.

III. Scope of This Guideline

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 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).

A. Guideline Audience

This CPG is intended for use by VA and DoD primary care providers (PCP) and others involved in the health care 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 providers involved in the care of Service members, beneficiaries, or Veterans with BD.

B. Guideline Population

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.

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline

In 2010, VA/DoD initially developed a BD CPG; however, it was archived. Therefore, this document is the second version of the VA/DoD BD CPG. This CPG provides recommendations for providers on identifying and treating individuals with BD. Generally, the strengths of the CPG consist of the involvement of a broad spectrum of interested parties, which include consumers and experts in retrieving and summarizing clinical evidence as well as providers from across the disciplines from both VA and DoD engaged in direct clinical care and administration. Moreover, as with other CPGs, the recommendations consider factors beyond the strength of the evidence. These factors include balancing desired outcomes with potential harms, supporting equity across subgroups, recognizing the potential for variation in patient values and preferences, and considering both feasibility for implementation and acceptability for the full range of stakeholders.

Specifically, highlights are as follows.

- The CPG recognizes the realities and complexities of BD as it occurs in military and Veterans populations while, at the same time, it bases its recommendations rigorously on the evidence.
- The recommendations and the algorithm for pharmacological treatment go beyond controlling symptoms and promoting wellness. They include maintenance treatment and staying well in the hope that treatment planning, from the start, will focus on both components of care.
- Some recommendations are also based on evidence for the effectiveness of somatic treatments, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and bright light therapy for subgroups of patients in specific contexts.

- However, the CPG acknowledges that although pharmacological treatment for BD is, in general, necessary, and that other somatic treatments might, at times, be effective, medications and somatic treatments alone are often insufficient. Accordingly, the CPG focuses on psychotherapy and other psychosocial treatments and on recovery as well as biomedical treatments.

B. Components of the Guideline

This CPG provides clinical practice recommendations for the care of patients with BD (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, a patient summary, and a quick reference guide, which can be found at https://www.healthquality.va.gov/index.asp.

C. Racial and Ethnic Demographic Terminology in This Guideline

Demographic terms referring to an individual's race or ethnicity (e.g., Hispanic, Latino or Latina, Asian, Native American, Black, African American, White, Caucasian) can be ambiguously defined and understood, reflecting diverse geographies, histories, cultures, and experiences. Aligned with the recent Executive Order on Further Advancing Racial Equity and Support for Underserved Communities through the Federal Government,[a] the Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and to promote inclusivity, clarity, and consistency. However, to represent accurately the evidence on which this CPG is based, the Work Group generally deferred to racial and ethnic terminology as reported in the published SRs, clinical trials, and other studies comprising that evidence when summarizing or otherwise referring to those studies. Consequently, usage of demographic terms in this CPG might appear inconsistent.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Ira Katz, MD, PhD, and Christopher Miller, PhD, from VA; and Jeffrey Millegan, MD, MPH, DFAPA, and Amanda Edwards Stewart, PhD, ABPP, from DoD.

The Work Group comprised individuals with the following areas of expertise: psychiatry, psychology, internal medicine, nursing, primary care, pharmacy, mental health

[a] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government | The White House

counseling, and social work. Table 2 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with

- Determining the scope of the CPG;
- Crafting clinically relevant KQs to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting was contracted by VA to help develop this CPG.

Table 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Ira Katz, MD, PhD (Champion)**
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VI. Summary of Guideline Development Methodology

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.(50) 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, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(51) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

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).(52)

1. Confidence in the quality of the evidence
2. Balance of desirable and undesirable outcomes
3. Patient values and preferences
4. Other considerations, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

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.(53) 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 3.

Table 3. 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 . . .

That a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence based and still important to clinical care) is important to note. The strength of each recommendation is shown in Recommendations.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., randomized controlled trials [RCT]) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(54, 55) For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(56) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(57)

Recommendation categories are used to track how a previous CPG's recommendations can be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(58, 59) Table 4 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2023 CPG recommendation categories can be found in Recommendations.

Table 4. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (58) and Garcia et al. (2014) (59)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(50) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care)(60) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(50) The disclosure form inquires regarding relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(54, 61) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on October 13, 2021. The focus group aimed to gain insights into patients with BD of potential relevance and incorporate these insights into the CPG, as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and impacts of their care on their lives.

The patient focus group comprised a convenience sample of three people, and all were male. Two participants were Veterans, and one participant was an active duty Service member. All participants received care from the VA health system, and one participant also received treatment from non-government community providers. The Work Group acknowledges this convenience sample is not representative of all patients with BD within the VA and DoD health care systems and, thus, findings are ungeneralizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix I. Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from the VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with BD. The Work Group submits suggested performance metrics for VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. 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 providers, and improve treatment adherence.(62, 63) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and wellbeing 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 gender, culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making, 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.(64) Shared decision making is emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM), now NAM, report in 2001 (65) 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 or both, 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.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to managing BD. Many Veterans, Service members, and their families have one or more co-occurring conditions. Because BD is sometimes accompanied by co-occurring conditions, managing BD collaboratively with other care providers is often best. Some co-occurring conditions might require early specialist consultation to

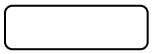
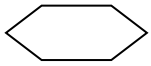
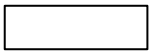
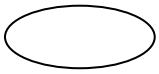
determine necessary changes in treatment or to establish a common understanding of how care will be coordinated. This approach might entail reference to other VA/DoD CPGs (e.g., for Suicide Risk, SUD, Opioids, MDD).[b]

VIII. 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.

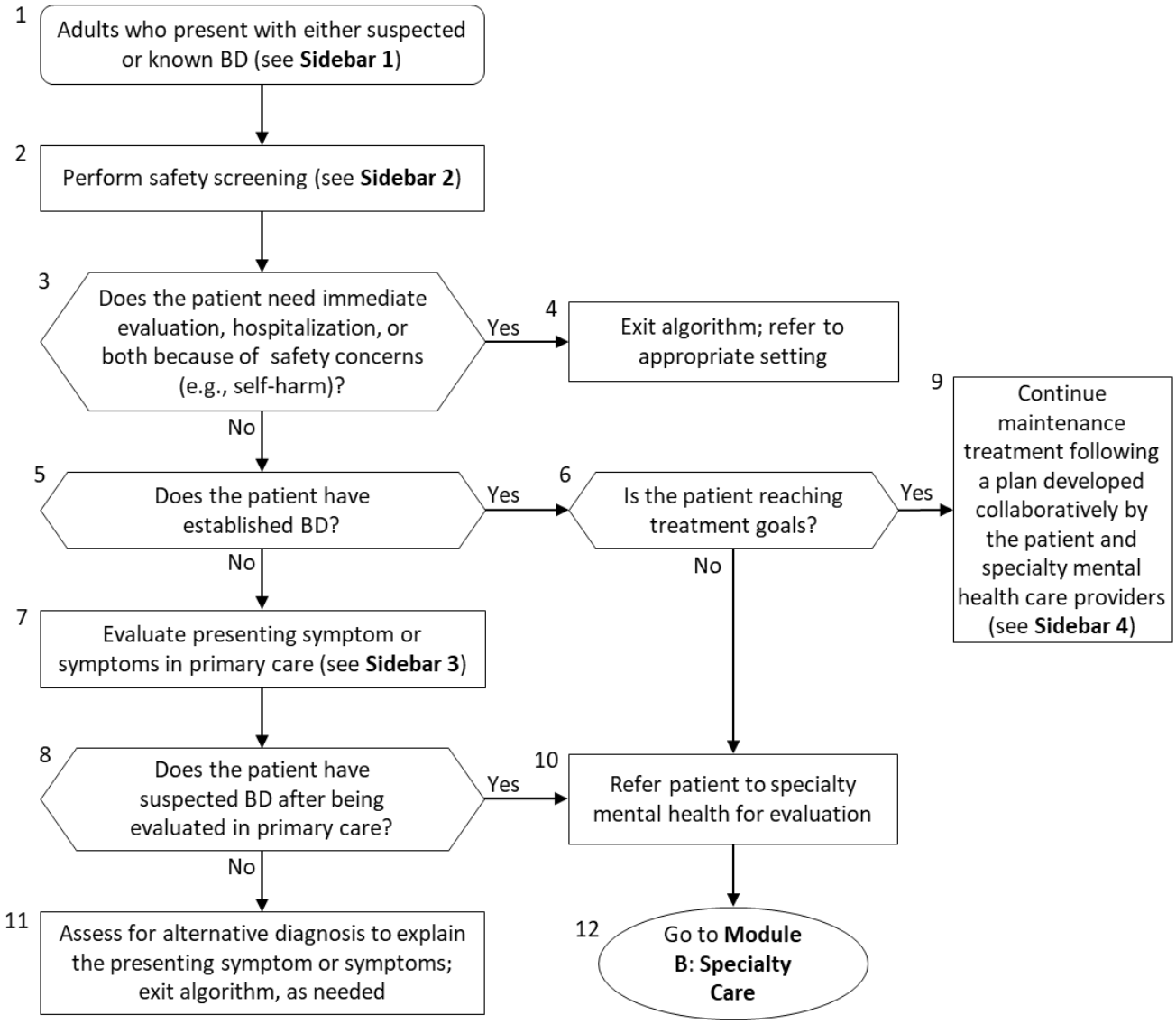
The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(66) Sidebars 1–7 provide more detailed information to assist in defining and interpreting elements in the boxes.

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 contains alternative text descriptions of the algorithm.

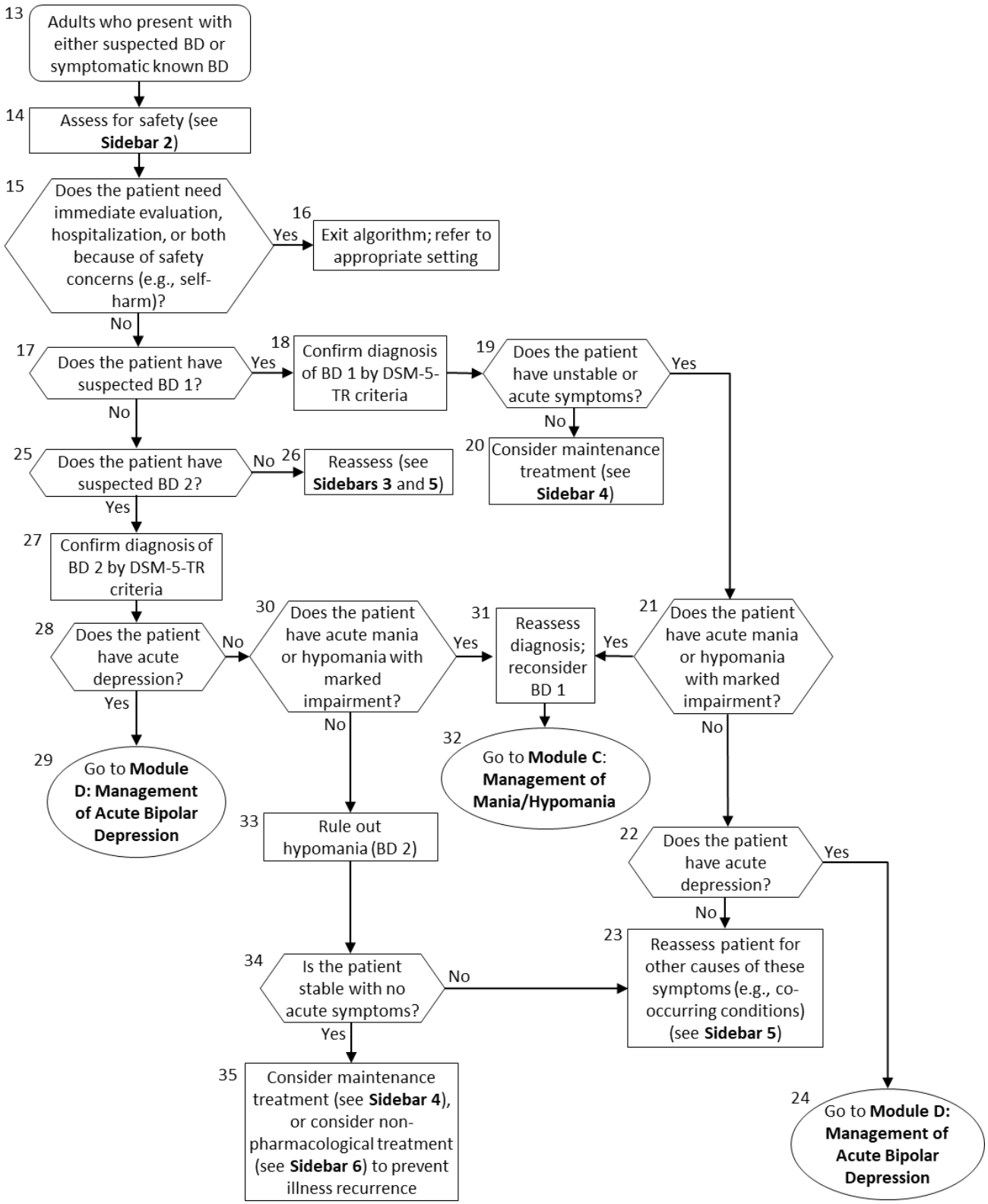
[b] The VA/DoD Clinical Practice Guidelines are available at: https://www.healthquality.va.gov/

A. Module A: Diagnosis and Triage



Abbreviations: BD: bipolar disorder

B. Module B: Specialty Care

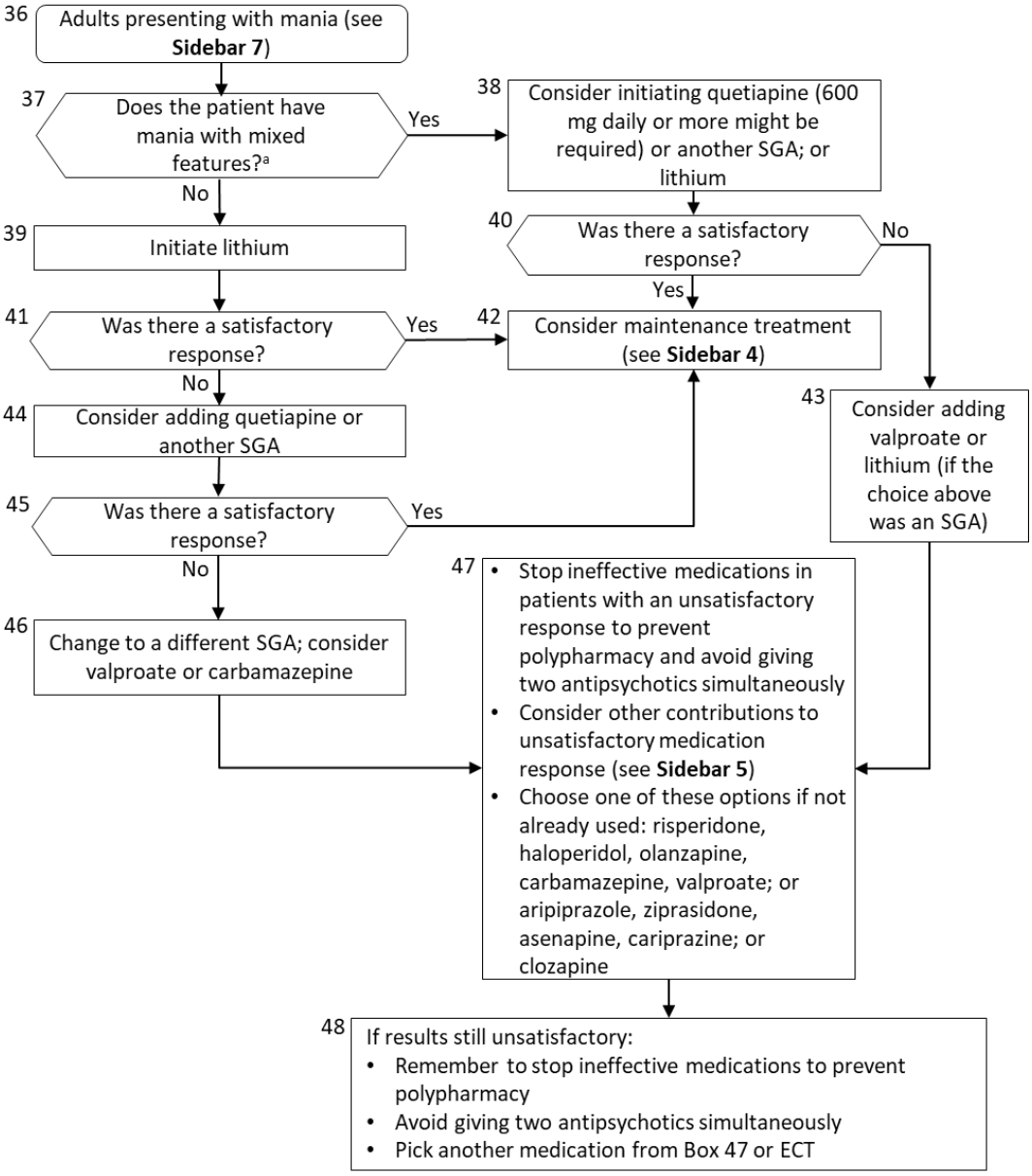


Abbreviations: BD: bipolar disorder; BD 1: bipolar 1 disorder; BD 2: bipolar 2 disorder; DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision

C. Module C: Management of Mania/Hypomania

Key Points
• Manage severe emergent agitation.(67) • 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).

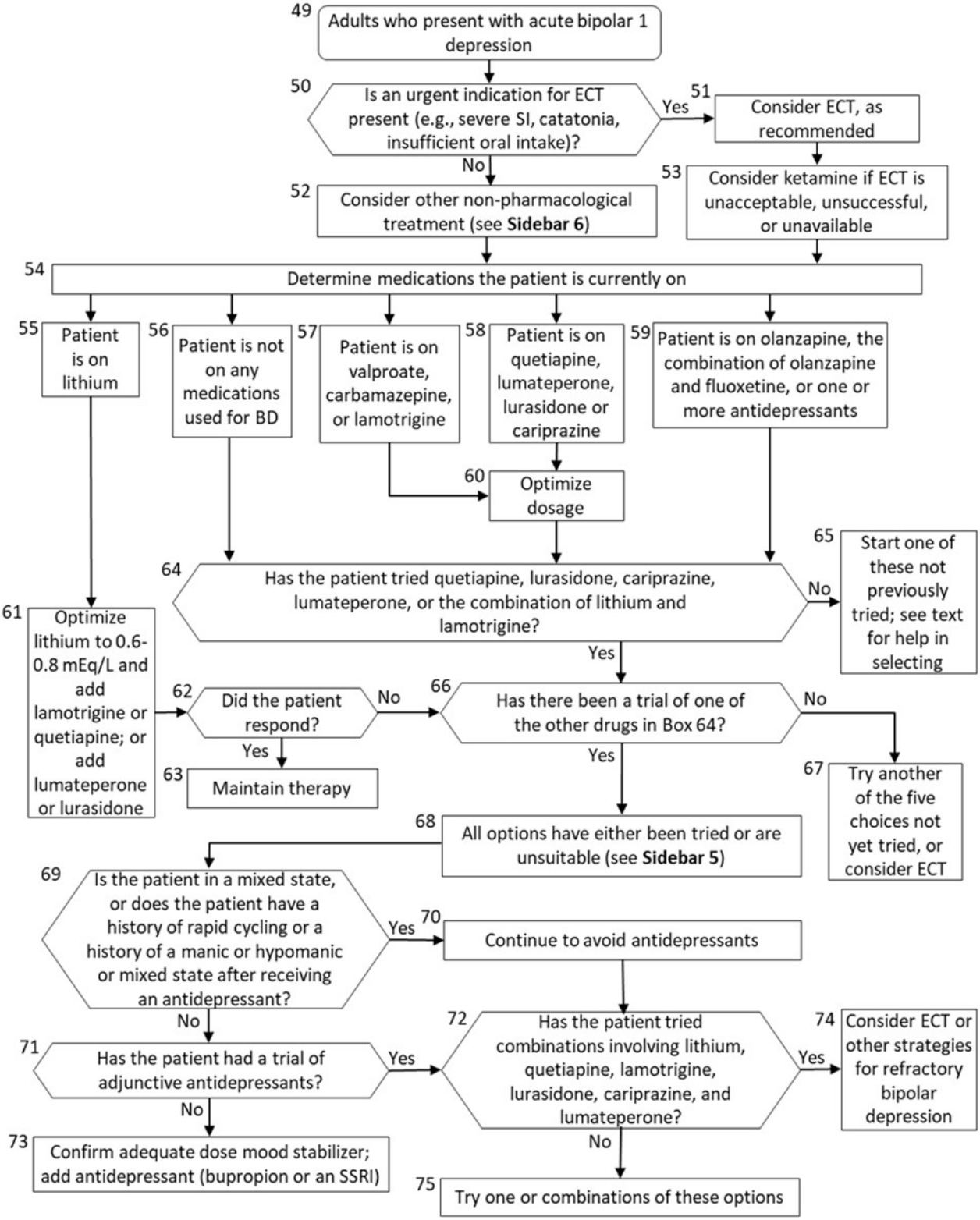
Abbreviations: ECT: electroconvulsive therapy



[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

D. 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 (68)
- 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

IX. Recommendations

The following evidence-based clinical practice recommendations (see Table 5) were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). 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 5. 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	*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

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	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

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
	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
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.

[b] For additional information, see Recommendation Categorization.

A. Screening and Evaluation

Recommendation

1. We suggest against routine screening for bipolar disorder in a general medical population.
   (Weak against | Reviewed, New-added)

Discussion

Evidence from Carvalho et al. (2015) (69) and Cerimele et al. (2014) (70) (both included in the more recently published SR by Wang et al. [2019]) (71) suggests that performing routine screening for BD in primary care or general populations will lead to high rates of false positive results requiring additional mental health resources to confirm the diagnosis. The Work Group recognizes that general populations differ relative to populations accessing primary care. The evidence base included study samples from both primary care and the general population. Although different patient factors are associated with populations accessing primary care, because of the rates of high false positives in the instruments studied the Work Group suggested against routine screening in general populations when accessing primary care. The strength of the evidence for the Carvalho et al. (2015) SR was weak because of the limited number of studies specifically focused on general populations or primary care samples.(69) Studies included in this SR examined the performance of individual instruments in primary care settings,(72-76) which was found to vary according to the instrument and study population in three of the studies (73-75) but generally had either low sensitivity or low positive predictive value (PPV).(73-75)

The systematic evidence review revealed that most studies investigating screening instruments for BD were in subjects in mental health clinical settings; thus, they had limited ability to address the topic of this recommendation. From the available evidence addressing primary care, BD was found to occur in 0.5–4.3% of primary care

populations using structured interviews.(70, 77) Given this relatively low prevalence of BD in primary care populations, the evidence retrieved for this recommendation suggests that systematic screening for BD in primary care clinics with the Mood Disorder Questionnaire (MDQ) leads to low sensitivity of 28%,(73) and low PPV of 16.8% (74) and 28% (75). Furthermore, these estimates varied according to clinical and demographic factors (e.g., race, trauma history, gender). Another study examined the use of the 32-item Hypomania Checklist (HCL-32) and demonstrated reasonable sensitivity (82%).(77) However, this study had limitations because it was based on a survey (non-clinical sample) and was limited to participants age 35–66 years.

In the SR by Cerimele et al. (2014),(70) of the 12 studies included that examined the prevalence of BD in primary care populations, 3 studies using the MDQ screening instrument found that 7–10% of the individuals had a positive screen for BD.(78-80) The authors of the SR noted that the low PPV of the MDQ in primary care would likely translate into high rates of false positive findings. Considering the performance characteristics of available valid instruments when applied to primary care populations, the Work Group suggested against routine screening for BD because of the high likelihood of false positive rates leading to inappropriate referrals to mental health or non-accurate diagnoses of BD appearing in medical charting.

The Work Group expects that patient preference varies little regarding this type of routine screening. No notable suggestions from the patient focus group indicated variability regarding the use of screening instruments at clinic visits because health questionnaires are commonly given. There are important resource considerations for the costs associated with large population screening for BD given the low prevalence (1–4%) and poor performance characteristics in primary care populations.(70) Furthermore, although some studies have examined postpartum women (81) and Black individuals with histories of trauma,(74) more studies are needed to explore if the instruments perform equally across populations with differing risk. Finally, considerable resources must be devoted to improving the primary care training for delivering and interpreting BD screening instruments.

The Work Group systematically reviewed evidence related to this recommendation.(69, 71, 77, 81) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a limited number of studies using a general population sample (77) and an overall limited number of studies examining non-depressed primary care clinical samples.(69, 70) The harms to a patient receiving a false positive BD diagnosis and the burden of the health system managing false positive screens slightly outweighed the potential benefit of BD screening in general on primary care populations. Patient values and preferences were similar because patients typically accept health screening instruments in clinic appointments. Thus, the Work Group made the following recommendation: We suggest against routine screening for bipolar disorder in a general medical population.

Recommendation

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)

Discussion

The utility of routine testing (i.e., screening) for relatively rare conditions in general populations requires careful consideration of benefits and downstream costs. The PPV of a screening test (i.e., the proportion of those testing positive that have the condition of interest) decreases with decreasing disease prevalence. For conditions such as BD, with a prevalence in the general population of 2.4%,(10) individuals who screen positive will require additional investigation to distinguish true positive and false positive cases. Therefore, the Work Group does not recommend routine screening of the general population (e.g., in primary care settings), but instead suggests using validated instruments for case-finding in specialty mental health settings or when suspected based on a clinical interaction.

Evidence suggests acceptable performance characteristics in the use of validated instruments when applied to populations accessing mental health clinical settings.(69, 71, 82) Limiting the application to populations seen in mental health services is an important distinction because when identifying potential BD in clinical populations considering the prevalence of the condition is necessary. Given the low prevalence of BD among general populations, the Work Group suggested limiting the use of validated instruments to samples of patients attending mental health clinical settings and presenting with a possible mood disorder. This suggestion reflects the wide range of populations with mental health conditions reported in the literature and the range of conditions represented in the protocols of the studies included in the systematic evidence review for this CPG (e.g., depression, cyclical mood disorders, recent psychiatric hospitalizations). The Work Group chose to eliminate the term “screening” in this recommendation because of the heterogeneity in the studies. The nuanced difference between screening and clinically indicated use of an instrument is an important distinction because higher costs are associated with false positive screens, and stigma associated with a diagnosis relying on only a cutoff score, instead of on a clinical assessment, is possible.

As noted above, when applying the evidence for the use of screening instruments among a population accessing mental health, the meta-analysis by Wang et al. (2019) demonstrated acceptable psychometric properties for the HCL-32 and the MDQ, with pooled sensitivity of 82% (95% CI: 72–89) and 80% (95% CI: 71–86), and specificity of 57% (95% CI: 48–66) and 70% (95% CI: 59–71), respectively.(71) The Youngstrom et

al. (2018) meta-analysis yielded 103 studies that examined a range of BD screening instruments.(82)

Of the available measures free of copyright requirements, four were highlighted as having the most useful characteristics related to discriminative performance (area under the curve [AUC]), availability in multiple languages, and reading level. These included the MDQ, Hypomania Checklist (HCL), Internal State Scale (ISS), and the Bipolar Spectrum Diagnostic Scale (BSDS). The study by Youngstrom et al. (2018) reported sensitivities of 0.41, 0.43, 0.38, and 0.44 at thresholds associated with a specificity of 0.90 for the MDQ, BSDS, HCL, and ISS, respectively.(82) Additionally, it reported AUC of 0.76, 0.77, 0.75, and 0.78 for the MDQ, BSDS, HCL, and ISS, respectively. Although some other studies had different findings, these studies were smaller and of lower quality. For example, the ISS was not included as an example in this recommendation because of limited studies examining the performance characteristics.

Further, two studies (72, 76) from the same SR (82) revealed a notable distinction when screening for BD among a sample of primary care patients with who had apparent unipolar depression. In the study by Hirschfeld et al. (2005), screening a primary care sample with apparent unipolar depression on antidepressants identified 21.3% of individuals with BD.(72) The study by Smith et al. (2011) used the HCL and the BSDS in a primary care sample of individuals with a working diagnosis of depression (n=154) and identified the frequency of individuals with possible unrecognized BD ranged between 3.3–21.6%.(76) The strength of these studies was low quality, was limited in the number of patients examined, and varied in rigorous application of a structured clinical exam.

Similar variation in patient preferences occurred regarding the practice of screening. The patient focus group did not specifically address routine screening questions, which, depending on length, can be burdensome, and positive findings would require more time for follow-up assessments. However, some individuals would potentially benefit from earlier diagnosis, and use of an instrument to detect true BD might balance overall burden. Additional considerations pertaining to feasibility, equity, and acceptability were considered. Variable valence attached to (self-report) scales in different specialties can impact feasibility. Equity might be impacted by more common use of instruments requiring licensing fees in larger volume clinics relative to smaller clinics. Further, the HCL and MDQ might be more acceptable and equitable because they are available in more than a dozen languages.(82)

The Work Group systematically reviewed evidence related to this recommendation.(69, 71, 82) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including heterogeneity in samples of patients in a variety of clinical settings or with varying mental health conditions.(69, 71, 82) The benefits of using a validated instrument when clinically indicated to identify BD in mental health populations appears

to have weak support based on the evidence; however, potentially earlier diagnosis of BD in mental health settings would slightly outweigh the potential harm. For example, mental health providers are well equipped to identify a false positive BD screening result based on a good clinical exam. The Work Group also anticipates that most mental health providers are well suited to incorporate an additional validated instrument into existing clinic workflow. Patient values and preferences were similar because patients are well adjusted to routine clinical instruments in practice. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)**

Discussion

The suggestion to use a validated instrument to check for BD in individuals initially diagnosed with MDD should they demonstrate signs of hypomania or mania while on antidepressants, stemmed from the review of evidence and discussion of benefits outweighing harms in adding an instrument to the existing standard of care. Evidence from the systematic evidence review was limited to four studies which looked at the use of screening tools, including the 13-item Hypomania Checklist (HCL-13), HCL-32, and MDQ, for identifying hypomania/mania in cohorts diagnosed with MDD and prescribed antidepressants.(83-86) The studies were unable to address whether the hypomania or mania identified were first episodes. Singh et al. (2017) noted that the HCL-13 has a fair facility to discriminate between individuals with MDD and BD (AUC: 0.72).(85) This study also reported that a brief three-item manic features questionnaire showed fair facility to discriminate between MDD and BD (AUC: 0.79). Evidence from another diagnostic cohort study, which compared scores for the HCL-32, noted that individuals with hypomania had higher total scores than individuals without hypomania.(84) Individuals in this study were also identified with treatment-resistant MDD. A larger cohort study (n=1,487) reported that an HCL-32 cutoff of 13 could distinguish between BD and MDD with acceptable diagnostic accuracy.(83) The MDQ was reviewed in the Chou et al. (2012) study; this study reported that a cutoff point of 6/7 for sensitivity and specificity on the MDQ provided optimal diagnostic accuracy for individuals diagnosed with MDD who had been taking antidepressants for at least three months.(86) The evidence retrieved did not specify monitoring approaches as compared with screening. However, continuing evaluation of individuals under medical care would be the implied standard. The Work Group also determined that the benefits for the two outcomes of

diagnostic accuracy and observing bipolar symptom change outweighed the potential harms of using validated instruments when suspecting hypomania or mania from a clinical interaction.

Participants in the patient focus group revealed a desire for improvements in BD diagnosis recognition. Providers for individuals diagnosed with BD prefer avoiding catastrophic harms for such individuals who might switch to a manic state. More importantly, evidence-based treatments for BD often differ from those for MDD or other disorders whose symptoms can be seen in individuals with BD; therefore, an accurate diagnosis can lead to more appropriate and effective treatment. Other implications for suggesting the use of validated instruments can include additional resource use in terms of time for the provider and the individual receiving care, access to the suggested measures, and sensitivity of the measures to subcultural concerns beyond language, such as willingness to share mood.(86) Acceptability to the individual could vary because of potential effects a BD diagnosis might have on employment and career trajectories (e.g., a diagnosis of BD could impact a future career in DoD). Additionally, clinical interviews and documentation might take more time to clarify diagnosis.

The quality of the data on diagnostic accuracy ranged from low to very low. The Francesca et al. (2014) study provided low quality evidence on diagnostic accuracy with the use of the HCL-32.(84) The study did not perform a clinical assessment (using a structured interview) of fully diagnosed BD to separate actual BD from subthreshold BD. Therefore, true diagnostic accuracy of HCL-32 cannot be determined in the study population. The Hu et al. (2012) study, although it had the largest cohort (n=1,487), provided very low quality evidence on the same test.(83) The Chou et al. (2012) and Singh et al. (2017) studies provided low quality evidence on diagnostic accuracy with the use of the MDQ and HCL-13, respectively.(85, 86)

The Work Group systematically reviewed evidence related to this recommendation.(83-86) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes for at least two of the four studies.(85, 86) All studies used an acceptable but imperfect reference standard that relied on the DSM-IV criteria; two studies were unclear about whether the reference test was interpreted independently of the index test. The benefits of using a validated instrument when there is suspicion of hypomania/mania in individuals diagnosed with MDD and treated with an antidepressant (e.g., could assist in clarifying diagnosis, which would help individuals receive appropriate treatment sooner) outweighed the potential harms, which were small (e.g., some individuals might object to more time needed during the clinical interview to clarify the diagnosis and a greater documentation time; some individuals in DoD might not want the BD diagnosis because of a potential negative impact on career trajectory). Patient values and preferences were similar because most individuals prefer the appropriate diagnosis and offer of related treatment versus the negative impact of mania and hypomania on behavior and relationships. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

There was insufficient evidence to suggest that the use of any specific quantitative treatment outcome measure affects patient outcomes, including mood episode occurrence, time to first recurrence of any mood episode, manic symptom change, depressive symptom change, or QoL. The systematic evidence review identified only one low quality RCT, which showed no differences between the intervention group, which received psychoeducation followed by close monitoring of symptoms and the group receiving treatment as usual (TAU).(87) No studies that evaluated in-office measurements as a monitoring strategy for improving treatment outcomes were included in the systematic evidence review. Validated scales that assess both manic and depressive symptoms could be used to provide measurement-based care for BD,(88) but the systematic evidence review did not identify any RCTs evaluating the outcomes of this practice.

Even so, the Work Group emphasizes that the purpose of this recommendation is not to discourage providers from using treatment outcome measures and ongoing monitoring of symptoms in the care of their patients with BD. Instead, this recommendation acknowledges that there is insufficient evidence to recommend one measure over another for these purposes. Thus, although the Work Group encourages the use of measurement to guide ongoing care, the Work Group remains agnostic regarding which specific validated measure or measures to use.(88)

Patient preferences vary little regarding treatment monitoring. The patient focus group noted a value for self-monitoring and provider monitoring for treatment effectiveness. Further, treatment monitoring that involves inputting measures into a digital platform requires access to a computing device, which raises concerns with equity. The frequency of the required input might also impact adherence to a monitoring strategy.

The Work Group systematically reviewed evidence related to this recommendation.(87) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including incomplete blinding and high attrition.(87) Because of insufficient evidence on this topic, the Work Group could not determine the balance of benefits and harms. Patient values and preferences were similar because individuals generally accept monitoring tools and value accuracy. Thus, the Work Group made the following

recommendation: For individuals with bipolar disorder, there is insufficient evidence to recommend for or against any specific treatment outcome measures to guide measurement-based care.

B. Pharmacotherapy

There are three distinct phases of the pharmacological management for BD, including (1) treatment for acute mania, (2) treatment for acute depression, and (3) maintenance treatment to prevent recurrences of both mania or depression. It has been common practice to treat individuals experiencing mania or bipolar depression with medications that have evidence of effectiveness for their current episodes and to continue them on agents to which they have responded without considering the impact on long-term outcomes. This approach is often taken even though most individuals with BD spend more time in the maintenance and prevention phases than in periods of acute illness. This practice could lead to greater risks for relapses if the medications used to treat acute episodes are not optimal for maintenance. Moreover, if additional medications are added when there are recurrences, it can lead to unnecessary polypharmacy and an increase in the burden of side effects.

When developing recommendations for the treatment of mania and depression, the Work Group viewed BD as a condition that would require lifelong treatment, and for which treatment planning, from the start, should extend beyond controlling episodes of mania or depression to include a longer-term perspective that considers the breadth of effectiveness of medications (i.e., the evidence for effectiveness of treatment for a current acute episode as well as for maintenance treatment to prevent recurrent episodes). To characterize differences between medications in their breadth of effectiveness, the Work Group first examined the evidence for the effectiveness of medications used in the maintenance phase of treatment, considering prevention of mania and of bipolar depression as separate outcomes. After identifying those that were effective for maintenance, the Work Group examined the evidence for treatment of acute phases. The Work Group then wrote the recommendations for monotherapies for the acute treatment phases to recognize those medications that demonstrated efficacy for both the acute and maintenance phases. The principle informing the recommendations was that treatments demonstrated to be effective for acute phases should be selected in accordance with their demonstrated effectiveness for the maintenance phase to improve long-term outcomes and to minimize the risk of harm (including side effect burdens) to individuals over the lifelong course of their illness.

As summarized in Table E-5. Monotherapies for Bipolar Disorder, there is, at this time, evidence that some agents (quetiapine, lithium, and olanzapine) are effective for preventing both manic and depressive episodes, others (risperidone and paliperidone) are effective for preventing mania but not depression, and another (lamotrigine) is effective for preventing depression but not mania. Based on these findings, when providers choose monotherapies to treat acute episodes of mania or depression,

medications with evidence of effectiveness for the acute episode, a breadth of effectiveness that includes prevention of both mania and depression, and a low side effect burden should be viewed as preferred or first line treatments. More specifically, when providers consider monotherapies for maintenance treatment for individuals with BD 1, agents with evidence for prevention of both manic and depressive episodes should be preferred; for others with BD 2 (and without a history or risk of severe hypomanic episodes associated with adverse consequences), effectiveness for prevention of mania may not be salient.

The recommendations in this guideline for monotherapies for the treatment of acute episodes of mania and depression and those for maintenance treatment are based, in part, on their breadth of effectiveness, as well as their effectiveness for acute treatment or prevention of mania or depression and their side effect profiles. For medications that are effective for treatment, prevention of acute episodes of mania or depression, or both, but are limited in their breadth of effectiveness or their relative safety, the recommendations include language stating that they are to be used if "patient preferences or characteristics" suggest that preferred or first line medications should not be used. Relevant clinical characteristics might include BD 1 versus BD 2 diagnosis, coexisting mental health and SUDs, possible drug-drug and drug-disease interactions, and experience with earlier treatments. This statement is meant to acknowledge that even treatments with the strongest evidence for efficacy and safety might have intolerable side effects or might not be effective for some patients. For additional details on how treatments might be sequenced in these circumstances, see the Algorithm.

a. Acute Mania

Recommendation

5. We suggest lithium or quetiapine as monotherapy for acute mania.
   (Weak for | Reviewed, New-added)

Discussion

Planning for the pharmacologic treatment of acute mania should always consider that the treatments effective acutely will most often be continued after the resolution of mania and will form the basis of maintenance treatment for BD to prevent the recurrence of mania. For most individuals receiving treatment for BD, prevention of depressive episodes should be considered when formulating any treatment plan. Because lithium and quetiapine have demonstrated efficacy for acute mania, prevention of recurrence of episodes of mania, and prevention of recurrence of depression (with quetiapine additionally having efficacy for acute depression), the Work Group suggested their use as preferred or first line monotherapies for the treatment of acute mania.(89, 90) The Work Group acknowledged that lithium is approved by the U.S. Food and Drug Administration (FDA) as maintenance monotherapy for BD; however, quetiapine is FDA-approved for maintenance treatment only as an adjunct to lithium or valproate.

Nevertheless, the systematic evidence review that informed this CPG identified evidence for its use as monotherapy in a broader range of contexts.

Patient preferences vary regarding quetiapine, primarily because of the drug's potential for sedation and weight gain and for metabolic concerns, such as the risk for diabetes and lipid abnormalities. The use of antipsychotic medications, even for BD, also might be associated with stigma because of the term "antipsychotic." Additionally, access to quetiapine might be limited in criminal justice settings because some jurisdictions consider the treatment a high diversion risk for misuse.(91, 92) The patient focus group noted that the use of lithium can be burdensome because it requires laboratory monitoring, and stigma might be associated with its use in BD. The adverse effects of lithium (e.g., tremors, need to keep blood levels within a narrow range, weight gain, potential for renal function impairment, and interactions with other drugs) are important to consider as is whether to use lithium when the patient is pregnant or is planning to become pregnant.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including questions regarding the reliability of the network meta-analyses used. The benefits of lithium and quetiapine as treatments for acute mania and maintenance treatments to prevent both manic and depressive episodes outweighed the potential harms, including the risk of QT corrected for heart rate (QTc) interval prolongation, sedation, and metabolic effects as well as (in the case of lithium) tremor, renal effects, hypothyroidism, and the need for close monitoring. Patient values and preferences varied because of the potential for side effects, but the preference for maintenance treatment to prevent mood episodes is strong. Thus, the Work Group made the following recommendation: We suggest lithium or quetiapine as monotherapy for acute mania.

Recommendation

6. If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania.
   (Weak for | Reviewed, New-added)

Discussion

Olanzapine, paliperidone, and risperidone each have evidence supporting their use for the treatment of acute mania from an updated network meta-analyses by Kishi et al. (2021a).(89) Because the lack of evidence from the systematic evidence review supporting the use of paliperidone and risperidone as maintenance treatments to prevent episodes of bipolar depression, the Work Group suggests use of these drugs as monotherapies if lithium or quetiapine is not selected.(90) Support for choosing these drugs for acute mania is strengthened by evidence of their effectiveness as

maintenance treatments to prevent episodes of mania. Additionally, support is limited by a lack of evidence demonstrating the effectiveness of paliperidone or risperidone in the prevention of recurrence of depression, and priority should be given to treatments effective for maintenance treatment to prevent the return of episodes of both mania and depression. Olanzapine is included in this recommendation rather than in Recommendation 5 because of concerns about the burden of side effects and the risk for adverse reactions. The metabolic effects of olanzapine are a strong counterbalance to its efficacy as monotherapy (even with evidence for the treatment of acute depression and maintenance to prevent depression) because antimanic treatments, when effective, tend to be continued by providers, increasing the risk of significant weight gain and metabolic disturbances, including diabetes and lipid abnormalities. Maintenance treatment is the cornerstone of treatment for BD, and prevention of depression should be prioritized when selecting treatments for acute mania in most individuals. The metabolic effects of olanzapine are ultimately the reason why the Work Group decided to suggest this drug alongside (and not higher than) risperidone and paliperidone.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including number of studies, ability of network meta-analyses to appropriately address transitivity (i.e., when direct comparisons have not been made, indirect comparisons are accepted), and breadth of the CIs in the results.(89) The benefits of these drugs outweighed the potential harms (e.g., weight gain, sedation, metabolic side effects). Patient values and preferences varied because of the potential for adverse effects. Thus, the Work Group made the following recommendation: If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania.

Recommendation

7. If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preferences and characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania.
   (Weak for | Reviewed, New-added)

Discussion

Aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, and ziprasidone each have evidence to support their use for the treatment of acute mania.(89) Because of lack of evidence from the systematic evidence review supporting the use of these drugs as maintenance treatments for BD, the Work Group decided to suggest these drugs as monotherapies if lithium, quetiapine, olanzapine, paliperidone, and risperidone are not selected.(90) Support for choosing these drugs for the treatment of acute mania is limited by lack of evidence for the effectiveness of these medications

for maintenance treatment. Priority should be given to treatments effective for maintenance treatment to prevent the return of mood episodes (see Recommendations 5 and 6); maintenance treatment is the cornerstone of treatment for BD.

Evidence suggests that aripiprazole has potentially less efficacy compared with other agents, with some negative studies and small effect sizes.(89) Valproate also appears to have a small effect size (0.26) along with a risk of liver toxicity and coagulopathy, so its use should be considered carefully.(89) Valproate should be prescribed only as a last resort to individuals of childbearing potential because of teratogenicity and other developmental harms to exposed fetuses and only after other treatments without those risks have been considered. Carbamazepine also poses severe risks to women of childbearing potential and has a Black Box warning recommending genomic testing (for HLA-B*1502) in certain populations, specifically for those of Chinese descent, because of the risk of a deadly rash (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]).(93) Carbamazepine also has many drug-drug interactions.

Patient preferences vary, primarily regarding the side effect profiles of these drugs, especially for haloperidol, which has a higher risk of extrapyramidal adverse effects (e.g., parkinsonism).(94) Some drugs, such as cariprazine, have a high incidence of neurological side effects, with a 29% incidence of extrapyramidal symptoms (EPS) and a 21% incidence of akathisia in trials in BD. Stigma is also associated with the use of antipsychotics, especially with the use of haloperidol and older antipsychotics. Asenapine requires sublingual administration for several minutes (twice daily), and whether manic individuals more severely ill than the subjects in placebo-controlled research studies could comply with that requirement is unclear. There is a lack of evidence for the effectiveness of the asenapine transdermal patch. Ziprasidone must be taken twice daily with 500 kilocalories of food for proper absorption, and adherence might be difficult for some individuals who skip meals or do not have their capsules with them when they have their meals. Further, the intramuscular formulation takes increased time to administer secondary to preparation.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small number of studies, limited reliability of the network meta-analysis to appropriately address transitivity, and limited certainty of the CIs in the authors' results.(89) The benefits of these drugs in the treatment of acute mania slightly outweighed the potential harm of adverse effects. Patient values and preferences varied because of adverse effects and stigma toward antipsychotics. Because these treatments have no evidence that they prevent the recurrence of mania or depression, these drugs are not recommended as preferred treatments for acute mania. Thus, the Work Group made the following recommendation: If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preferences and

characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania.

Recommendation

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)

Discussion

Evidence suggests that treatment with lithium or valproate in combination with either 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.(95) Evidence also indicates some level of harm exists with combination therapy because it was associated with more side effects, especially somnolence; however, it was not associated with treatment-emergent depression. Despite its side effects, research in individuals with schizophrenia (not included in the evidence base nor impacting the strength of the recommendation) has demonstrated that patients are less likely to discontinue olanzapine than other medications.(96)

The available evidence was limited in several ways. The systematic evidence review did not identify sufficient data to allow the Work Group to consider the comparative effectiveness of adding therapies versus switching between monotherapies in individuals who had an unsatisfactory response or a breakthrough episode. Additionally, the patient populations included in the SR by Ogawa et al. (2014) varied because some studies included individuals maintained on lithium and valproate before randomization, although others did not. Further, studies generally defined “unsatisfactory response” to monotherapy as a trial over two weeks,(95) which might be infeasible for many individuals experiencing uncontrolled manic symptoms.

Patient preferences vary regarding this treatment. Some individuals feel that taking multiple medications can be burdensome and can lead to more side effects, although others would prioritize the reduction in mania symptoms over increased medication loads. Further, most studies suggest that trials of monotherapy last two weeks before considering treatment failure, but this length is not always practical in individuals with mania.

The Work Group systematically reviewed evidence related to this recommendation.(95) Therefore, it is categorized as *Reviewed, New-added*. The Work Group’s confidence in the quality of the evidence was low. The body of evidence had some limitations including lack of head-to-head trials comparing the effect of these agents on mania severity.(95) The benefits of dual therapy with lithium or valproate in combination with either haloperidol, asenapine, quetiapine, olanzapine, or risperidone for acute mania

symptoms in individuals who had an unsatisfactory response or breakthrough episode on monotherapy slightly outweighed the potential harm of additional adverse events from add-on therapy. Patient values and preferences varied because some individuals would prefer monotherapy and might oppose the risks of potential side effects, although others would prioritize symptom control. Thus, the Work Group made the following recommendation: 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.

Recommendation

9. We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania.
   (Weak against | Reviewed, New-added)

Discussion

Evidence suggests that brexpiprazole is no different than placebo in improving mania symptom severity.(89) Kishi et al. (2021a) cites two RCTs, with follow-up between 2–12 weeks, that demonstrated no difference in manic symptom severity when compared with placebo (standardized mean difference [SMD]: -0.085; 95% CI: -0.354–0.184; p>0.05). These studies had serious limitations and imprecision, and the overall quality of the evidence was low. No studies included in the systematic evidence review carried out as part of this CPG showed evidence of benefit. Known potential harms for brexpiprazole include, but are not limited to, weight gain, akathisia, restlessness, sedation, headache, hyperglycemia, increased risk of death and cerebrovascular events in elderly individuals, and rare cases of seizures. Given lack of evidence of benefit for reducing mania, any associated harms become significant.

Evidence suggests that topiramate is no different than placebo in improving mania symptoms.(89) Kishi et al. (2021a) cites four RCTs with follow-up between 2–12 weeks, showing no difference in manic symptom severity when compared with placebo (SMD: 0.064; 95% CI: -0.129–0.256; p>0.5). These studies had serious study limitations and imprecision, and the overall quality of the evidence was low. No studies included in the systematic evidence review carried out as part of this CPG showed evidence of benefit in reducing manic symptom severity. Known potential harms for topiramate include, but are not limited to, sedation, asthenia, ataxia, nausea, weight loss, blurred vision, confusion, speech problems, metabolic acidosis, and kidney stones. Given lack of evidence of benefit for reducing mania, any associated harms become significant.

Evidence suggests that lamotrigine is no different than placebo in improving mania symptom severity.(89) Kishi et al. (2021a) cites two RCTs with follow-up between 2–12 weeks, showing no difference in manic symptom severity when compared with placebo (SMD: 0.002; 95% CI: -0.297–0.301; p>0.5). These studies had serious limitations and very serious imprecision, and the quality of the evidence was very low. No studies

included in the systematic evidence review carried out as part of this CPG showed evidence of benefit. Known potential harms for lamotrigine include, but are not limited to, rash, sedation, ataxia, nausea, and rare cases of SJS/TEN. Given lack of evidence of benefit for reducing acute mania, any associated harms become significant.

Patient preferences vary regarding this treatment. Some individuals are eager for any potential pharmaceutical intervention with the possibility of reducing manic symptoms, although others might be wary of taking any medication at all. Risk tolerance to the various potential adverse effects varies considerably in the patient population. Other considerations also include resource use. Brexpiprazole is more expensive than older generic options, while topiramate and lamotrigine are comparatively less expensive.

The Work Group systematically reviewed evidence related to this recommendation.(89) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations related to randomization and allocation procedures, which were rated as unclear in most of the studies. The potential harms of brexpiprazole, lamotrigine, or topiramate slightly outweighed the potential benefits because no benefit was observed over placebo. Patient values and preferences varied based on attitudes about taking psychotropic medications as well as on concerns about adverse effects and monetary cost. Thus, the Work Group made the following recommendation: We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania.

Recommendation

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)**

Discussion

Evidence suggests that the addition of aripiprazole to a mood stabilizer is no different than a mood stabilizer alone in improving mania symptom severity. Ogawa et al. (2014) cites two RCTs (n=652) that demonstrated no difference in manic symptom severity (SMD: -0.15; 95% CI: -0.51–0.22; p=0.43).(95) These studies had serious limitations and imprecision, and the overall quality of the evidence was low. No studies included in the systematic evidence review carried out as part of this CPG showed evidence of benefit. Known potential harms of aripiprazole include, but are not limited to, dizziness, weight gain, insomnia, akathisia, nausea, rare seizures, and impulse control problems. There is caution advised with the combination of aripiprazole and lithium, indicating that the combination might increase the risk of encephalopathic syndrome. The combination of aripiprazole and valproate might increase the risk of central nervous system (CNS) depression, psychomotor impairment, and altered seizure control.

Evidence suggests that the addition of paliperidone to a mood stabilizer is no different than a mood stabilizer alone in improving mania symptom severity. Ogawa et al. (2014)

cites one RCT (n=299) that demonstrated no difference in manic symptom severity (SMD: -0.10; 95% CI: -0.33–0.12; p=0.37).(95) This study had serious limitations and imprecision, and the overall quality of the evidence was low. No studies included in the systematic evidence review carried out as part of this CPG showed evidence of benefit. Known potential harms of paliperidone include, but are not limited to, EPS, hyperprolactinemia, and hyperglycemia. The combination of paliperidone and lithium might increase the risk of encephalopathic syndrome. The combination of paliperidone and valproate might increase the risk of CNS depression, psychomotor impairment, and altered seizure control.

Evidence suggests that the addition of ziprasidone to a mood stabilizer is no different than a mood stabilizer alone in improving mania symptom severity. Ogawa et al. (2014) cites one RCT (n=525) that failed to reach statistical significance (SMD: -0.18; 95% CI: -0.37–0.00; p=0.06).(95) This study had serious limitations with imprecision and the overall quality of the evidence was low. No studies included in the systematic evidence review carried out as part of this CPG showed evidence of benefit. Known potential harms of ziprasidone include, but are not limited to, QT prolongation, asthenia, dizziness, and orthostatic hypotension. The combination of ziprasidone and lithium might increase risk of serotonin syndrome and encephalopathic syndrome. The combination of ziprasidone and valproate might increase the risk of CNS depression and alter seizure control.

Patient preferences vary regarding comfort with taking psychotropic medications in general. Some might have increased somnolence with polypharmacy, although for others the desire for relief from the problems of mania might outweigh other potential concerns.

The Work Group systematically reviewed evidence related to this recommendation.(95) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including incomplete data on dropouts and selection bias. The potential harms slightly outweighed the potential benefits because no benefit was observed in reducing mania severity with the addition of either aripiprazole, paliperidone, or ziprasidone to a mood stabilizer over a mood stabilizer alone. Patient values and preferences varied based on desire for psychotropic medications and comfort with polypharmacy. Thus, the Work Group made the following recommendation: We suggest against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy for acute mania.

Recommendation

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)**

Discussion

The systematic evidence review informing this CPG included no studies on gabapentin, oxcarbazepine, or benzodiazepines. Although evidence exists to support the efficacy of various second-generation antipsychotics (SGA) (quetiapine, olanzapine, paliperidone, risperidone, asenapine, cariprazine, ziprasidone) and a first-generation antipsychotic (FGA) (haloperidol) in reducing mania severity, evidence also exists that brexpiprazole, another SGA, was not more efficacious than placebo in reducing mania severity.(89) This evidence suggests that FGA and SGA medications cannot be considered as a medication class.

Although low quality RCTs included in an SR by Kishi et al. (2021a) comparing oxcarbazepine to valproate showed no difference for mania symptoms,(89) no studies comparing oxcarbazepine to placebo were included in the systematic evidence review. One RCT comparing gabapentin to placebo, included in an SR by Bahji et al. (2020), found no difference for mania severity.(97) This study had serious limitations and very serious imprecision with a very low quality of evidence.

The available studies on combinations of various antipsychotics with mood stabilizers yielded mixed results. The available literature demonstrated benefits in reducing manic severity with a combination of mood stabilizers with haloperidol, asenapine, quetiapine, olanzapine, ziprasidone, or risperidone; whereas no evidence of benefit was found in studies combining a mood stabilizer with aripiprazole or paliperidone.(95)

Patient preferences vary regarding comfort with taking psychotropic medications in general. Some individuals might experience increased somnolence with polypharmacy, although for others the desire for relief from the problems of mania might outweigh other potential concerns.

The Work Group systematically reviewed evidence related to this recommendation.(89, 95, 97) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including lack of adequate studies for several antipsychotics and other medications of interest. Although the medications enumerated in this recommendation had little to no evidence included in the systematic evidence review, the Work Group decided they still warranted a recommendation because these medications are commonly prescribed within the wider clinical community. The mixed evidence of the several similar medications to include those with evidence of no difference negated the possibility of making broad recommendations for medication classes. The potential benefits of these medications in treating acute mania were balanced with the potential harms. Patient values and preferences varied based on desire for psychotropic medications and comfort with polypharmacy. Thus, the Work Group made the following recommendation: 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.

b. Acute Bipolar Depression

Recommendation

12. We recommend quetiapine as monotherapy for acute bipolar depression. **(Strong for | Reviewed, New-added)**

Discussion

Evidence from randomized, placebo-controlled clinical trials demonstrates that quetiapine is effective for the acute treatment of bipolar depression. Bahji et al. (2020) reviewed 11 RCTs in an SR and network meta-analysis of individuals with BD 1 or mixed populations of BD 1 and BD 2.(97) This study provided evidence of moderate quality to support this recommendation. The SMD for quetiapine versus placebo for the improvement in depressive symptoms over 2–36 weeks was 0.48 (95% CI: 0.14–0.82), consistent with a moderate effect size. Other findings included odd ratios (OR) of 1.87 (95% CI: 1.62–2.17) for response to treatment and of 1.93 (95% CI: 1.50–2.49) for remission when all the included studies were considered; however, analyses of studies limited to individuals with BD 1 found no significant differences from placebo in either response or remission. The evidence for quetiapine was strengthened by findings from a more recent RCT of a mixed sample of individuals with BD, with a high quality of evidence, that reported effectiveness for both BD 1 and BD 2.(98)

The findings on quetiapine's effectiveness for acute episodes of bipolar depression must be interpreted in the context of the evidence supporting Recommendation 18, for its use in maintenance treatment for the prevention of mania, and Recommendation 24, for its use in the prevention of bipolar depression. When considered together, this evidence indicates that the breadth of effectiveness is high; treatment of bipolar depression with quetiapine can reduce current symptoms, and, when continued, can prevent recurrences of depression as well as the onset of mania. Further support for its utility comes from evidence from 1 RCT (99) included in an SR by Cullen et al. (2021),(100) suggesting it might also be effective for alleviating comorbid symptoms of anxiety in individuals with BD; although this study included individuals with both BD 1 and BD 2, it did not report on effects for the two subtypes.

Quetiapine can cause significant side effects. Avoiding excess sedation at the onset of treatment might require starting treatment at subtherapeutic doses and titrating up to doses that are effective for the treatment of bipolar depression. Over the longer term, weight gain, hyperlipidemia, and related metabolic side effects can be significant. Nevertheless, the benefits of treatment outweigh the harms and burdens.

Recommending treatments with evidence of effectiveness for acute depression and for preventing both manic and depressive episodes is aligned with patient preferences. However, weighing the potential benefits versus the risks requires input from the individual, and, where appropriate, from associated caregivers, family members, and significant others. Some individuals might express preferences for other agents, such as

antidepressants or newer agents currently being promoted through direct-to-consumer marketing. Decision making about the use of quetiapine should be conducted within the context of psychoeducation and shared decision making.

The Work Group systematically reviewed evidence related to this recommendation.(97, 98, 100) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The benefits of quetiapine for the treatment of bipolar depression outweighed the potential harms. Patient values and preferences varied. Preferences for specific treatments and the balance between benefits and risks must be viewed from the individual's perspective; however, concerns should be addressed through psychoeducation and shared decision making. Thus, the Work Group made the following recommendation: We recommend quetiapine as monotherapy for acute bipolar depression.

Recommendation

13. If quetiapine is not selected based on patient preferences and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression.
    (Weak for | Reviewed, New-added)

Discussion

Evidence from randomized, placebo-controlled clinical trials demonstrates that olanzapine, cariprazine, lumateperone, and lurasidone are all effective for the acute treatment of bipolar depression.

For olanzapine, Bahji et al. (2020) reviewed three RCTs for individuals with unspecified BD in an SR and network meta-analysis with moderate quality evidence.(97) The SMD for the improvement in depressive symptoms over 2–36 weeks was 0.72 (95% CI: 0.09–1.35), consistent with a moderate to large effect size. Other findings included ORs of 1.49 (95% CI: 1.19–1.86) for response to treatment and 1.66 (95% CI: 1.07–2.58) for remission; findings for studies limited to BD 1 were similar.

The findings on olanzapine's effectiveness for acute episodes of bipolar depression must be interpreted in the context of the evidence supporting Recommendation 19, for its use as maintenance treatment for the prevention of mania, and Recommendation 25, for its use for the prevention of episodes of bipolar depression. When considered together, the evidence indicates that treatment of bipolar depression with olanzapine can reduce current symptoms of depression, and, when continued, prevent recurrences of depression as well as the onset of mania, and, therefore, the breadth of effectiveness is high.

Olanzapine frequently causes significant side effects, most significantly, weight gain, hyperlipidemia, and related metabolic side effects. An SR and a meta-analysis of studies on individuals with BD by Kadakia et al. (2021) considered three studies of

olanzapine, all limited to individuals with BD 1 and demonstrated that olanzapine is associated with significantly greater weight gain than all of the other SGAs evaluated for the treatment of acute bipolar depression.(101) An alternative agent with less severe metabolic side effects, quetiapine, is effective for treatment of bipolar depression and for preventing both mania and depressive episodes. Therefore, the consensus of the Work Group was that the benefits and harms of olanzapine treatment were balanced, as the metabolic effects of olanzapine are a strong counterbalance to its efficacy as monotherapy. The metabolic effects of olanzapine are ultimately the reason why the Work Group decided to suggest this drug alongside (and not higher than) the other medications in this recommendation.

For cariprazine, an SR and network meta-analysis of studies on individuals with unspecified BD, by Bahji et al. (2020), evaluated two RCTs providing moderate quality evidence.(97) The SMD for the improvement in depressive symptoms over 2–36 weeks was 0.85 (95% CI: 0.08–1.62), consistent with a large effect size. Other positive findings included an OR of 1.58 (95% CI: 1.19–2.08) for response to treatment but no significant effect for remission. Findings for studies limited to BD 1 were similar. The evidence was strengthened by similar findings from another network meta-analysis that also had a moderate quality of evidence.(101) Kadakia et al. (2021) identified four RCTs, three limited to individuals with BD 1 and one for which 77% of participants were BD 1, and found significant drug-placebo differences for changes in depressive symptoms. None of the available studies evaluated efficacy specifically in individuals with BD 2.

For lurasidone, Bahji et al. (2020) evaluated two RCTs providing moderate quality evidence for effectiveness for acute bipolar depression.(97) The SMD for the improvement in depressive symptoms over 2–36 weeks was 1.15 (95% CI: 0.37–1.92), consistent with a large effect size. Other findings included an OR of 2.53 (95% CI 1.88–3.39) for response and 1.78 (95% CI: 1.04–3.03) for remission; findings for studies limited to BD 1 were similar. In another SR, Wang et al. (2020) identified seven randomized, placebo-controlled clinical trials evaluating individuals with BD 1 with six weeks follow-up.(102) It provided low quality evidence for effect on acute bipolar depression and moderate quality of evidence for other outcomes; both the number of clinical trials and the quality of the evidence varied depending on the outcome measured. Findings included significant improvements in provider-rated depressive symptoms relative to placebo. Relative risks (RR) were 1.73 (95% CI: 1.46–2.05) for treatment responses, and 1.57 (95% CI: 1.38–1.79) for remission. These findings were strengthened by an additional moderate quality RCT, by Rajagopalan et al. (2016), that included individuals with unspecified BD and found significant benefits for provider-rated depressive symptoms at six weeks follow-up.(103) None of the available studies evaluated efficacy specifically in individuals with BD 2.

For lumateperone, Calabrese et al. (2021) conducted a randomized placebo-controlled clinical trial with individuals with BD 1 and BD 2 with six weeks follow-up.(104) This study found significant drug-placebo differences for bipolar depression in both provider-

rated depressive symptoms and clinical global improvements. The study sample was 80% BD 1; the medication was effective for both subtypes, and the drug is approved by the FDA for the treatment of both BD 1 and BD 2.

The findings on the effectiveness for cariprazine, lurasidone, and lumateperone for the treatment of acute episodes of bipolar depression must be interpreted in the context of the current lack of evidence for their effectiveness as monotherapies for maintenance treatment for the prevention of mania or bipolar depression. In this regard, the breadth of effectiveness is lower, and the established benefits for these agents are less comprehensive than those for quetiapine (see Recommendation 12). Treatment with each of these agents can reduce symptoms associated with acute episodes of bipolar depression. However, in contrast to treatment with quetiapine or olanzapine, evaluating the drug regimen for individuals treated with cariprazine, lurasidone, or lumateperone after they stabilize might be necessary to ensure they are receiving effective maintenance treatment.

Cariprazine, lurasidone, and lumateperone all have side effects. The SR by Kadakia et al. (2021) demonstrated that weight gains associated with cariprazine and lurasidone were less than for olanzapine, and those associated with lurasidone were also less than for quetiapine; lumateperone was not included in this SR.(101) Calabrese et al. (2021) reported that the proportion of individuals with significant weight gain during a six-week clinical trial of lumateperone was similar in the medication and placebo groups.(104) The duration of this trial, however, was short, and the longer term effects of this drug on weight in BD are not currently known. Side effects of cariprazine include akathisia and other activating side effects (consistent with its activity as a partial dopamine agonist, like aripiprazole), nausea and vomiting, sedation, and (as with all antipsychotics) tardive dyskinesia. Side effects of lurasidone include parkinsonism, akathisia, sedation, prolactin elevation, and tardive dyskinesia. Side effects of lumateperone include parkinsonism, akathisia, sedation, hypotension, dry mouth, and tardive dyskinesia. However, for each of these agents the benefits of treatment outweigh the harms and burdens.

Treatments with evidence of effectiveness for acute depression are aligned with patient preferences. However, when quetiapine is not selected for treatment due to patient preferences or characteristics, weighing the potential benefits versus the risks of other medications requires input from the individual, and, where appropriate, from associated caregivers, family members, and significant others. Many individuals with BD would prefer treatments for which there is evidence of effectiveness for acute episodes and for prevention of both manic episodes and recurrences of bipolar depression; they may prefer treatment with olanzapine over cariprazine, lurasidone, and lumateperone. However, many would prefer to avoid treatments that have a substantial risk for weight gain and metabolic side effects; they may prefer treatment with cariprazine, lurasidone, and lumateperone over olanzapine. Some individuals might express preferences for other agents, such as antidepressants. Treatment planning for use of these medications should be conducted within the context of psychoeducation and shared decision making.

The Work Group systematically reviewed evidence related to this recommendation.(97, 101-104) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. Patient values and preferences varied. Preferences for specific treatments and the balance between benefits and risks must be viewed from the individual's perspective; however, these concerns should be addressed through psychoeducation and shared decision making. The consensus of the Work Group was that the benefits of olanzapine, cariprazine, lurasidone, and lumateperone for bipolar depression slightly outweighed the potential harms. However, the balance between the benefits and harms is less favorable than for quetiapine. For olanzapine, the difference is due to the higher risk for metabolic side effects. For cariprazine, lurasidone, and lumateperone, it is due to the current lack of evidence for prevention of mania and depression. The Work Group recognized that absence of evidence for prevention does not imply lack of effectiveness. However, we also recognized that the CPG must be based on the available evidence, and that, after treatment of acute episodes of bipolar depression with these agents, providers might have to consider additional strategies for maintenance treatment. Based on all these considerations, the Work Group made the following recommendation: If quetiapine is not selected based on patient preferences and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression.

Recommendation

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)

Discussion

An SR and network meta-analysis of studies including individuals with BD 1 and mixed samples of BD 1 and BD 2, by Bahji et al. (2020), evaluated the use of antidepressants and lamotrigine as monotherapies for the treatment of bipolar depression.(97) In interpreting the findings from this SR, the Work Group focused primarily on the outcome of changes in symptoms of depression. The quality of the evidence for the effectiveness of antidepressants for acute bipolar depression was low to very low. The only antidepressant medication with evidence suggesting effectiveness for decreasing depressive symptoms was fluoxetine. The effect size was large (SMD: 1.41; 95% CI: 0.27–2.55), but the quality of evidence was low, with serious risks of bias and imprecision. The antidepressants for which there were no significant drug-placebo differences for changes in depressive symptoms included paroxetine (one study), sertraline (one study), escitalopram (one study), venlafaxine (one study), imipramine (two studies), tranylcypromine (one study), phenelzine (one study), and moclobemide (one study). In analyses of all the available studies, Bahji et al. (2020) noted that fluoxetine, venlafaxine, and tranylcypromine demonstrated increased rates of treatment responses and remission relative to placebo, and imipramine demonstrated increased rates of treatment response. In analyses of studies limited to individuals with BD 1,

fluoxetine and imipramine demonstrated increased rates of response and remission.(97) To summarize, other than fluoxetine, no selective serotonin reuptake inhibitor (SSRI) or agent from another class of antidepressants was associated with improvements in depressive symptoms during a clinical trial. Several of the agents appeared to be associated with increased rates of response and remission in the absence of differences in symptoms; however, the inconsistencies among findings for improvements, responses, and remissions, in addition to the limited number of studies and the low or very low quality of evidence, suggests the need for caution in recommending any of the antidepressants.

In evaluating the safety of antidepressant medications in individuals with bipolar depression, it is important to consider adverse effects identified for these agents for other indications, as well as the risks, unique to BD, of inducing a switch from depression into mania or hypomania. The systematic evidence review identified one RCT comparing rates for switches into hypomania for individuals with BD 2 treated with lithium, sertraline, or a combination of the two.(105) The rate for switching was 14%, without differences between groups. The quality of the evidence was low, and the study might not have had adequate statistical power for detecting moderate differences between treatments. At this time, the available evidence does not provide a reliable estimate of the switching rate in individuals with BD 2 (or even in BD 1) receiving antidepressant monotherapy. However, even with uncertainty in estimates for switching, the limited and inconsistent evidence on effectiveness would not support a conclusion that the benefits of antidepressants outweigh the risks and potential harms.

For lamotrigine, Bahji et al. (2020) reviewed six placebo-controlled clinical trials with very low GRADE evidence.(97) No significant drug-placebo differences for changes in depressive symptoms were found. In analyses of all available studies, lamotrigine was associated with increased rates of treatment response and remission. In studies limited to individuals with BD 1, lamotrigine was associated with increased rates of response but not with remission. However, given the inconsistencies between outcomes and the very low quality of the evidence, caution is necessary in interpreting the findings. As with antidepressants, it is impossible to conclude that the benefits of lamotrigine monotherapy for the treatment of acute bipolar depression outweigh the harms.

Patient values and preferences vary regarding this recommendation. Individuals with depression might request an antidepressant medication and they might expect a prescription for one. However, the options should be addressed in the context of psychoeducation and shared decision making.

The Work Group systematically reviewed evidence related to this recommendation.(97, 105) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence on the effectiveness of antidepressant and lamotrigine monotherapy was very low. Concerns arose about differences in the findings reported for symptom change and treatment response or remission, and

concerns also were expressed that the benefits of treatment might not outweigh the risks or harms. The Work Group determined that because of mixed and limited evidence, the benefits of using antidepressants or lamotrigine as monotherapy were balanced with the potential harms. Patient values and preferences varied because some individuals with depression might expect to receive an antidepressant, although others might not want to use medications. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression.

Recommendation

15. We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression.
    (Weak for | Reviewed, New-added)

Discussion

Some individuals with BD might experience breakthrough episodes of depression while receiving antipsychotic medications or mood stabilizers. Others might be non-responders, delayed-responders, or partial-responders to treatment. In any of these contexts, individuals might experience bipolar depression while receiving antipsychotic medications or mood stabilizers. Recognizing that providers require guidance about treatment planning, Bahji et al. (2021a) conducted an SR and network meta-analysis of studies on individuals with BD that included an evaluation of the effectiveness of adding adjunctive lamotrigine to these “on-board” medications.(106) There were five studies of adjunctive lamotrigine in mixed samples of individuals with BD, of which two were versus placebo, one versus citalopram, and one versus two other comparators—risperidone and inositol. Findings for the primary analysis, rates of treatment response, favored lamotrigine (RR: 1.43; 95% CI: 1.00–2.04). There were no significant effects for analyses limited to individuals with either BD 1 or BD 2. The quality of evidence was very low, and no significant differences were found in secondary analyses of changes in symptoms and rates of remission.

The placebo-controlled studies included in Bahji et al. (2021a) evaluated lamotrigine as an adjunct to lithium and quetiapine with mixed study samples of individuals with both BD 1 and BD 2.(106) The study examining lamotrigine as an adjunct to lithium found that changes in provider ratings of symptoms and response rates, based on >50% reductions in provider rated symptoms (but not clinical global impressions), were significant at 6 and 8 weeks.(107) The RCT that evaluated lamotrigine as an adjunct to quetiapine found that changes in patient-reported symptoms were significantly greater than placebo at one year, but the quality of evidence was low.(108) Additionally, rates for remission for lamotrigine were significantly greater than placebo at 12 weeks and one year, but not at 22 weeks. Neither of these studies reported on outcomes specifically for BD 1 or BD 2 subtypes.

In general, lamotrigine is well tolerated, but its use is associated with the rare occurrence of a serious and potentially fatal dermatological condition, SJS/TEN. Based on guidance from FDA approved product labeling, minimizing this risk requires that lamotrigine treatment starts at low, subtherapeutic doses with slow titration over 6 weeks to effective target doses. The need for slow titration might limit its utility for the treatment of severe bipolar depression and for individuals at increased risk for suicide, where timing of improvements might be critical. Overall, though, the Work Group concluded that, the benefits of adjunctive treatment with lamotrigine for individuals with bipolar depression outweigh the harms and burdens.

In addition to its effectiveness as an adjunctive treatment of acute bipolar depression, lamotrigine has also demonstrated effectiveness as a monotherapy for the prevention of recurrent episodes of bipolar depression in BD 1 (see Recommendation 23) but not for mania (see Recommendation 21). Early use during an acute episode might simplify long-term management by establishing a treatment regimen effective for maintenance as well as acute treatment.

Patients' values and preferences vary regarding acute, adjunctive treatment with lamotrigine because of potential preferences for simple drug regimens that minimize polypharmacy. Treatment planning should be conducted within the context of psychoeducation and shared decision making.

The Work Group systematically reviewed evidence related to this recommendation.(106, 108) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence on the effectiveness of adjunctive therapy with lamotrigine was very low. However, the Work Group attached great importance to the findings that evidence exists supporting effectiveness both as an adjunctive treatment for acute episodes of bipolar depression and for maintenance treatment to prevent recurrent depression. The benefits of treatment outweighed the harms and burdens. Patient values and preferences varied because some individuals might prefer simple drug regimens. Thus, the Work Group made the following recommendation: We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression.

Recommendation

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)

Discussion

Few drugs alleviate depressive symptoms in individuals with acute bipolar depression. Therefore, new treatment approaches are needed. Evidence suggests that ketamine, an N-Methyl-D-Aspartate receptor antagonist, might be an effective agent. Dean et al.

(2021) found that ketamine was more effective than placebo 24 hours after a single intravenous (IV) infusion for improving response rate (OR: 11.61; 95% CI: 1.25–107.74; p=0.03) and reducing depression rating scale scores (mean difference: -11.81; 95% CI: -20.01 to -3.61; p=0.005) in bipolar depression.(109) They found non-significant evidence of ketamine's efficacy in producing remission over placebo at 24 hours (OR: 5.16; 95% CI: 0.51–52.30; p=0.72). These data were derived from two studies (n=33) included in the SR by Dean et al. (2021).(110, 111) These results were also supported by an SR and network meta-analysis conducted by Bahji et al. (2021a), which evaluated the comparative efficacy and tolerability of adjunctive pharmacotherapies for acute bipolar depression.(106)

Dean et al. (2021) also evaluated one trial by Grunebaum et al. (2017) comparing a single IV ketamine infusion with an active comparator midazolam.(112) They reported that differences in response, remission, or depression rating scale scores between ketamine and midazolam were indeterminate at 24 hours because of very low–certainty evidence (OR: 3.20; 95% CI: 0.23–45.19).

Bahji et al. (2021b) assessed the comparative efficacy and tolerability of adjunctive ketamine and esketamine for the treatment of unipolar and bipolar major depression.(113) Of the total participants studied (n=1,877), only a small subset (n=40; 2.1%) was diagnosed with a BD spectrum depression and received ketamine. Two studies (n=24) included in the SR by Bahji et al. (2021b) evaluated individuals with BD 1 or BD 2 and treatment resistant depression using crossover designs.(110, 111) One study (n=16) evaluated individuals with BD and a current major depressive episode (non-treatment resistant) in a parallel design study.(112) Ketamine was associated with short-term benefit for response(110, 111) and remission.(111, 112) However, long-term risk and benefits have not been fully elucidated. No studies of adjunctive intranasal esketamine for the treatment of bipolar depression were identified.

Patient preferences varied regarding this treatment. Some individuals without adequate response to previous treatment might actively seek new novel treatments for their depression. Others might be concerned about potential adverse effects from unproven therapies and the need to receive in-person treatment two to three times weekly lasting a minimum of two hours. In addition, esketamine is a risk evaluation and mitigation strategy (REMS) drug with pharmacy, dispensing, and monitoring requirements. Further, access to treatment with ketamine and esketamine is limited because trained staff and space might be unavailable at some treatment facilities.

The Work Group systematically reviewed evidence related to this recommendation.(106, 109, 113) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample size of individuals with BD, lack of long-term maintenance benefit, risk of bias, and imprecision.(106, 109, 113) The benefits of ketamine and esketamine for the treatment of acute depression in individuals with BD

were balanced with the potential harm (e.g., adverse events). Patient values and preferences varied because some individuals prefer non-invasive treatments, although others desire novel treatments. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against ketamine or esketamine as either a monotherapy or an adjunctive therapy for acute bipolar depression.

Recommendation

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)

Discussion

Evidence that evaluates the use of antidepressant medications in combination with antipsychotic medications or mood stabilizers comes from several SRs. McGirr et al. (2016) summarized findings from six RCTs: two with BD 1, three with a mixed sample of BD 1 and BD 2, and one with unspecified BD.(114) Overall, 83% of the participants had BD 1. The SR found that antidepressants plus either mood stabilizers or antipsychotic medications led to slightly greater reductions in depressive symptoms than placebo.(114) The quality of the evidence was moderate with a very small effect size (SMD: 0.165; 95% CI: 0.165–0.278). Additional analyses providing low quality evidence indicated that the differences in symptoms were not associated with increased rates of clinically meaningful treatment response or remission. There were no reports on outcomes for individuals with BD 1 or BD 2 subtypes. Analyses of subsets of the clinical trials suggested differences between the augmentation of antipsychotic medications and mood stabilizers. In the two trials that studied the augmentation of antidepressants with antipsychotic medications, rates for treatment response and remission were greater for the drug combination than placebo. However, in the four trials that studied augmentation with mood stabilizers, no significant differences were found.

The combination of olanzapine and fluoxetine has been approved by the FDA for the acute treatment of depressive episodes associated with BD 1 in adults. Bahji et al. (2020) identified clinical trials of olanzapine plus fluoxetine versus placebo in BD.(97) Low quality evidence from two RCTs included in the SR by Bahji et al. (2020) suggested that there was no difference between treatments in the reduction of depressive symptoms; however, moderate quality evidence from three RCTs included in the SR by Bahji et al. (2020) suggested that rates of treatment response and remission were greater with the combination. The apparent effects for response and remission remained significant in subtype analyses for studies limited to BD 1, but similar analyses could not be conducted for BD 2. Similarly, Silva et al. (2012) (115) identified one clinical trial by Tohen et al. (2003) (116) that compared olanzapine plus fluoxetine versus olanzapine alone, but the study was limited to individuals with BD 1. The study

provided low quality evidence for the effectiveness of the combination for changes in symptoms, response, and remission. Given that the systematic evidence review found only one RCT that contained evidence on olanzapine plus fluoxetine versus olanzapine alone, the Work Group did not develop a recommendation specifically for the combination. Instead, the Work Group opted to include it in this recommendation about augmentation by antidepressants as a class.

Some individuals with BD might experience breakthrough episodes of depression while receiving antipsychotic medications or mood stabilizers. Others might be non-responders, delayed responders, or partial responders to treatment. In any of these contexts, individuals might experience bipolar depression while receiving antipsychotic medications or mood stabilizers. Recognizing that providers require guidance about treatment planning, Bahji et al. (2021a) conducted an SR and network meta-analysis that included evaluations of the effectiveness of adding adjunctive antidepressants versus placebo to other "on-board" treatments for (unspecified) BD.(106) Findings were negative, and the quality of the evidence ranged from low to very low for sertraline (two studies), citalopram (one study), paroxetine (one study), venlafaxine (three studies), bupropion (one study), desipramine (one study), imipramine (two studies), amitriptyline (one study), and tranylcypromine (one study). There were positive findings for analyses of four studies on fluoxetine that provided evidence for greater reductions in depressive symptoms (low quality), response (moderate quality), and remission (low quality). There were similar findings for analyses limited to BD 1. Therefore, the evidence suggests that fluoxetine might be effective. However, the apparent differences between fluoxetine and other agents with similar mechanisms of action raise concerns that translating these findings into a specific recommendation might be premature.

In evaluating the safety of antidepressant medications among individuals with bipolar depression, it is important to consider adverse effects identified using these agents for other indications, as well as the risks, unique to BD, of inducing a switch from depression into mania. The systematic evidence review identified one SR and network meta-analysis, by Taylor et al. (2014), that included an evaluation of switches in individuals with bipolar depression.(117) Taylor et al. (2014) identified three clinical trials reporting on SSRIs versus placebo, one in combination with an SGA and two on tricyclic antidepressants (TCA) versus placebo. Patient populations in the TCA studies and the SSRI-only studies included unspecified BD or a mix of BD 1 and BD 2, although those in the study that included an SGA agent had BD 1 only. The SR was based on the definitions of a switch to mania used in the individual studies; it might have included switches into hypomania, as well. Very low-quality evidence suggested that switch rates did not differ from rates for placebo for either SSRIs (OR: 1.06; 95% CI: 0.48–2.34) or TCAs (OR: 2.57; 95% CI: 0.48–13.8). The SR did not report on any subtype-specific analyses. The findings are consistent with those observed in an RCT of individuals with BD 2, which was also included in the systematic evidence review.(105) However, the estimates from Taylor et al. (2014) might have been affected by the criteria for

considering clinical trials in the SR because it allowed studies that included individuals taking mood stabilizers.(117) McGirr et al. (2016), an SR of 6 RCTs, found that there was no short-term risk of a switch to mania after adding an antidepressant.(114) However, in two studies that extended treatment to 52 weeks, one limited to BD 1 and one with a mixed sample, there was a statistically significant 1.8-fold increase in the odds of switching by one year, suggesting that long-term use of antidepressants might have a destabilizing effect. There was no report of analyses by subtype.

Patient values and preferences vary regarding this recommendation. Individuals with depression might request an antidepressant medication, and they might expect a prescription for one. However, the options should be addressed in the context of psychoeducation and shared decision making.

The Work Group systematically reviewed evidence related to this recommendation.(97, 105, 106, 114, 115, 117) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence on the effectiveness of adjunctive treatment with antidepressants was very low. Concerns also arose that the benefits of treatment might not outweigh the risks or harms. Given the questions about the evidence for effectiveness and concerns about risks, the Work Group concluded that the potential benefits of adjunctive treatment with antidepressants were balanced with the harms or burdens. Patient values and preferences varied because some individuals with depression might expect to receive antidepressants, although others might not want to use medications. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against antidepressants to augment treatment with second-generation antipsychotics or mood stabilizers for acute bipolar depression.

c. Prevention of Recurrence of Mania

Recommendation

18. We recommend lithium or quetiapine for the prevention of recurrence of mania. **(Strong for | Reviewed, New-added)**

Discussion

Evidence from recent SRs and network meta-analyses suggests that lithium and quetiapine are the most effective medications for maintenance treatment to prevent recurrence of mania.(90, 118) The efficacy of both medications appears to be similar,(90) but each has unique advantages and disadvantages that would be relevant to selection for the individual patient.

Although other SRs and meta-analyses have found that lithium has an anti-suicide effect, the analysis by Kishi et al. (2021b) did not confirm this benefit.(90) In the network meta-analysis, most studies were relatively short-term RCTs with stringent exclusion criteria (e.g., excluding individuals with suicidal ideation and attempts) resulting in study populations that were often not representative of those seen in clinical practice. The

authors did not include non-RCT observational studies with longer mean follow-up times that might have captured an anti-suicide effect. A recent review by Del Matto et al. (2020), which was outside the scope of the systematic evidence review carried out as part of this CPG, included larger observational studies (n=200,000) with longer mean follow-up times and found a significant anti-suicide effect.(119) As of 2022, lithium is FDA-approved as a maintenance monotherapy for BD whereas quetiapine is not, though quetiapine is approved for maintenance therapy as an addition to lithium or valproate. Nevertheless, the systematic evidence review carried out as part of this CPG identified studies supporting the effectiveness of monotherapy for both agents.

All-cause discontinuation rates in maintenance studies were greater with placebo than with lithium, and no difference in all-cause discontinuation rates with lithium was found when compared with quetiapine.(90, 120)

The disadvantages of lithium include greater potential for kidney harm, though kidney harm was not an outcome measure in the studies reviewed. Kidney harm can be minimized by maintaining patients' lithium plasma levels in the optimal range of 0.6–0.8 mEq/L, which, in a recent SR outside the scope of the evidence review carried out as part of this CPG and not considered in developing this recommendation, was determined to offer the optimum balance of efficacy and side effects.(121)

One review captured in the evidence base found that individuals were more likely to discontinue lithium because of side effects than they were to discontinue placebo, but individuals were equally likely to discontinue lithium or quetiapine because of side effects.(90)

Another review by Kishi et al. (2021a) found that quetiapine has acute efficacy for treatment of bipolar depression whereas lithium does not.(89) The Work Group puts a strong emphasis on the selection of medications that will have acute and maintenance benefits for both the manic and depressive phases of BD. Other studies from an SR (not included in the evidence base nor impacting the strength of the recommendation) have demonstrated a significant effect of quetiapine on comorbid anxiety, which is a common occurrence in individuals with BD.(122) Disadvantages of quetiapine include sedation and weight gain/metabolic syndrome, which are commonly known side effects but were not outcome measures in the SRs that were retrieved.

Patient preferences vary largely regarding these treatments. Lithium has a reputation among individuals that can be favorable (e.g., liking that it occurs in nature, is similar to table salt, and is not a manufactured product) or unfavorable because of stigmatizing side effects, including tremor, weight gain (which can be rapid from water retention), hair loss, and a requirement for periodic blood tests. Lithium might also have an unfavorable reputation among some individuals because of the potential for more serious harms, including kidney and thyroid dysfunction, gastrointestinal symptoms, and toxicity associated with high blood levels. Quetiapine might be less controversial among

patients, though there may be concerns that it can cause excessive sedation and appetite stimulation that can lead to weight gain.

Explaining use of lithium to patients can be time intensive. Also, the prescribing process and monitoring of lithium might take more time than with quetiapine and most other bipolar mania medications. Therefore, providers might be reluctant to prescribe lithium and might prefer simpler medications to administer even if they are less evidence based. More resources are needed to complete the required monitoring, laboratory testing, and education for the proper use of lithium to maximize effectiveness and safety. However, both lithium and quetiapine are available as inexpensive generic products.

Neither lithium nor quetiapine has long-acting injectable (LAI) formulations, so if that kind of formulation is needed for adherence, other options must be considered.

The Work Group also noted that in some prison settings, the use of quetiapine might be restricted or prohibited because of the reputation for its being subject to diversion and nonmedical use.(92, 123, 124)

Finally, in comparing the two medications, large observational studies from U.S. and European sites found that in community samples of individuals with BD individuals receiving lithium as monotherapy were less likely to need additions to their drug regimens in a one-year follow-up than individuals on other bipolar medications.(125, 126) These studies were outside the scope of the systematic evidence review carried out as part of this CPG and were not considered in developing this recommendation, but they add support for the use of lithium as a maintenance treatment.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90, 118, 120) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including many relatively short-term industry-sponsored studies that might have biases in favor of the sponsor's product over lithium (i.e., the use of 100% enriched samples of responders to the sponsor's product). Many studies also had strict inclusion criteria that made the patient samples atypical of patients seen in usual practice.(90) The benefits of both lithium and quetiapine as maintenance treatments for mania outweighed the potential harms from adverse effects. Patient values and preferences varied considerably with lithium; it is fairly well known in the community because it has been available for more than 50 years, and patients might have a favorable or unfavorable opinion regarding its use. Thus, the Work Group made the following recommendation: We recommend lithium or quetiapine for the prevention of recurrence of mania.

Recommendation

19. 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.
(Weak for | Reviewed, New-added)

Discussion

The systematic evidence review conducted to inform this CPG provides some support for olanzapine, paliperidone, and risperidone LAI as maintenance medications for the prevention of recurrence of mania, but this support is weaker than that for lithium and quetiapine (see Recommendation 18).(90) Olanzapine seemed as or more effective in preventing mania (RR for mania: 0.35) when compared with lithium (RR: 0.54) and quetiapine (RR: 0.56);(90) however, the Work Group decided to prioritize treatments for preventing mania that also demonstrated effectiveness in treating or preventing bipolar depression or both. Olanzapine has some evidence of effectiveness as treatment for acute bipolar depression, but there are suggestions from a network meta-analysis that the effect size for olanzapine is smaller than for quetiapine;(89) also, olanzapine is not FDA-approved as a monotherapy for this indication. The Work Group also determined that olanzapine has more severe weight gain and related metabolic side effects than quetiapine or lithium. No studies comparing the weight gain from olanzapine with that from quetiapine or lithium met inclusion criteria for the systematic evidence review. However, one study by Tohen et al. (2005),(127) included within the SR by Kishi et al. (2021b),(90) found significantly greater weight gain with olanzapine than with lithium. Another SR of RCTs (not included in the evidence base nor impacting the strength of the recommendation) included comparisons of olanzapine with lithium and quetiapine and found substantially more weight gain and metabolic side effects with olanzapine compared with lithium or quetiapine.(128) The metabolic effects of olanzapine are a strong counterbalance to its efficacy as monotherapy and are ultimately the reason why the Work Group decided to suggest this drug alongside (and not higher than) the other medications in this recommendation.

Paliperidone (oral) and risperidone LAI have less substantial metabolic side effects and have shown effectiveness for preventing mania in maintenance studies for BD (RR: 0.59 and RR: 0.37, respectively); however, at this time, no evidence exists that either medication is effective for preventing or treating bipolar depression.(89, 90)

Paliperidone LAI has been studied in the maintenance treatment of schizoaffective disorder by the DSM-IV criteria and was shown to be effective.(129) However, the criteria for schizophrenia and schizoaffective disorder changed significantly in the DSM-5 and DSM-5-TR as follows: in the C Criterion for schizophrenia in DSM-IV, the patient might meet the criteria for a major mood episode at times, but the duration had to be “brief” compared with the total duration of the illness, including active and residual phases; the definition of brief was provided in the text as 2.5% of the time. If the duration was “more than brief” then the diagnosis could be schizoaffective disorder. In DSM-5 and DSM-5-TR, the duration of major mood episodes that was allowed for a diagnosis of schizophrenia was enlarged to a “minority” of the total duration of illness (i.e., it could be as high as 49%). Thus, many individuals who would have been diagnosed with schizoaffective disorder will now meet the criteria for schizophrenia. Whether the previous results with paliperidone LAI treatment of schizoaffective disorder

will be the same when treating schizoaffective disorder according to the DSM-5 and DSM-5-TR is unknown.

Patient preferences varied largely regarding these three medications. Many individuals (though not all) might not want an LAI medication. Metabolic side effect and weight gain differences will influence preferences. A small but significant risk of tardive dyskinesia occurs with SGAs. Thus, this risk should be discussed with patients. Risperidone LAI was associated with a higher incidence of prolactin level elevation than placebo,(90) and the Work Group is aware of evidence, outside the scope of the systematic evidence review and not specifically based on studies of individuals with BD, that demonstrates prolactin elevation is greater with risperidone and paliperidone than with olanzapine.(130) This side effect can also influence adherence. Added costs of the product itself and administrative requirements to have appointments and staff to administer the injections will be associated with risperidone LAI. The two oral medications are generic products of much lower cost.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90, 129) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including limited information on comparative side effects and exclusion, based on quality criteria, of possibly relevant studies. The benefits of olanzapine, paliperidone, and risperidone LAI slightly outweighed the potential harms, which mostly include adverse effects (especially for olanzapine) and potential failure to prevent episodes of depression (especially for oral paliperidone, or risperidone LAI). Patient values and preferences varied largely due to side effect differences and routes of administration for the different medications. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

Some evidence suggests that these 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.(90) Also, the Work Group prioritizes maintenance treatments for mania that also demonstrated effectiveness in treating or preventing bipolar depression or both, but none of these antipsychotics and anticonvulsants has been found to have

efficacy for preventing depressive episodes. The Work Group suggests that prescribers refer to the options presented in Recommendation 18 (lithium and quetiapine) and Recommendation 19 (olanzapine, paliperidone, and risperidone LAI) for medications determined to be effective for the prevention of recurrence of mania and also to have other advantages.

The effect size in mania prevention varied among these antipsychotics and anticonvulsants. Asenapine ranked the highest in efficacy in this group for relapse prevention when compared with placebo (RR: 0.21), but this ranking was based on only one 26-week trial.(90) The authors also noted that this study might be subject to performance and detection biases because of asenapine's distinctive side effect of oral hypoesthesia, which made the study difficult to blind. Aripiprazole monthly LAI also ranked high in efficacy (RR: 0.30); however, this ranking was based on only one study in which more than half the patients on aripiprazole dropped out.(131) Similarly to the other medications in this recommendation, it showed no efficacy for preventing depression. Oral aripiprazole was slightly lower in efficacy for mania maintenance, also for this medication, the estimate was based on only one study. The lowest ranking medication in this group for mania prevention was valproate (RR: 0.64); the estimate is also based on only one placebo-controlled study. The use of valproate is off-label and the Work Group, acknowledging the common use of this medication in clinical practice, wanted to emphasize that evidence supporting the use of valproate was marginal. Therefore, other options with greater efficacy should be considered instead. Carbamazepine has not been studied as a maintenance monotherapy versus placebo, but in a comparison trial with lithium, both medications appeared equally effective.(90) Lurasidone had no demonstrated efficacy for maintenance.(118)

Side effects vary among these treatment options. The antipsychotics can cause metabolic side effects, extrapyramidal movement disorders, tardive dyskinesia, and prolactin elevation (though aripiprazole is usually an exception). Valproate might cause weight gain, tremor, hair loss, liver dysfunction, and pancreatitis. Carbamazepine might cause sedation, dizziness, unsteadiness, gastrointestinal complaints, and blood dyscrasias. Further, valproate and carbamazepine should not be used in individuals of child-bearing potential (see Recommendation 30). Patient preferences varied regarding these treatments based on side effects. However, costs are usually low because all are generic products, except lurasidone.

The Work Group systematically reviewed evidence related to this recommendation.(90, 118) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including the limited number and quality of existing studies of the medications pertinent to this recommendation. The few benefits of the treatments in this recommendation were balanced with their potential harms, which were mostly side effects. Patient values and preferences varied because of differential preferences, vulnerabilities for the possible side effects, and mixed preferences for oral or LAI routes

of administration. Thus, the Work Group made the following recommendation: 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).

Recommendation

21. We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania.
    (Weak against | Reviewed, New-added)

Discussion

Evidence does not support the use of lamotrigine to prevent recurrence of mania.(90) However, the evidence does support the use of lamotrigine to prevent bipolar depressive episodes.(90, 120) The FDA has approved lamotrigine for the "maintenance treatment of BD 1," but the Work Group noted that this wording might have contributed to some confusion among providers and might have fostered the use of lamotrigine to prevent both depressive and manic episodes for some individuals.(132) Therefore, the Work Group decided to have a separate recommendation that recommends against the use of lamotrigine for the prevention of manic episodes. Additional medication must be added to lamotrigine to prevent the recurrence of mania, or alternative monotherapy treatment should be prescribed that can help treat both phases of BD as proposed in Recommendation 18.

The side effects of lamotrigine tend to be mild for most individuals, with no difference from placebo in discontinuation because of side effects.(90) However, rare, but serious, side effects have been reported in other studies (not included in the evidence base nor impacting the strength of the recommendation), including potentially fatal SJS/TEN. Further, milder rashes occur in 10% of individuals and blurred vision, ataxia, headaches, and nausea might occur, as well. Hence, given the lack of efficacy for mania prevention, these adverse effects led the Work Group to conclude that the harms exceed the benefits for this indication.

Patient preferences vary regarding use of lamotrigine. Patients might be disturbed by the risk of rash and SJS/TEN. If an individual is on valproate, the drug might raise lamotrigine levels and can increase the risk of rashes, including dangerous ones. Lamotrigine requires a slow titration (to minimize the rash risk) that usually takes at least six weeks. Frequent follow-up with the prescribing provider is needed, which can be difficult when Veterans are in prison or in short-term residential treatment programs or are experiencing homelessness. Patients must carefully adhere to the titration without missing doses or re-titration might be necessary.

The Work Group systematically reviewed evidence related to this recommendation.(90, 120) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some

limitations including a small number of studies. The harms of significant adverse events were rare but, overall, slightly outweighed the potential benefit of lamotrigine, given that the SRs did not demonstrate benefits for mania prevention. Patient values and preferences varied because the side effects and risks can be frightening for some individuals. Thus, the Work Group made the following recommendation: We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania.

Recommendation

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)

Discussion

Evidence suggests using the following antipsychotics in combination with lithium or valproate as maintenance medication for the prevention of recurrence of mania: aripiprazole, olanzapine, quetiapine, and ziprasidone.(90, 133) Kishi et al. (2021d) found that aripiprazole had a hazard ratio (HR) of 0.66 for reducing rates of mania in three pooled studies (n=771).(133) Aripiprazole also decreased relapses to depression (HR: 0.46), which was considered a "novel" finding given that this medication has not been found effective as a monotherapy for acute bipolar depression.(89) The studies assessing olanzapine were small (n=187 in two studies), but the authors found that olanzapine increased the time to recurrence of any mood episode.(133-135) The benefits of olanzapine come at the cost of its considerable metabolic side effects, with 35% of participants gaining significant weight.(134, 135) Quetiapine had the strongest evidence for preventing mania (HR: 0.27) and depression (HR: 0.29) in the studies (n=1,246), but the medication also caused weight gain.(133) Only one study investigated ziprasidone, but the authors found that this medication prevented mania (HR: 0.46) with no effect on depression.(133)

Notably, haloperidol and asenapine have not been studied in combination with lithium or valproate for the prevention of the recurrence of mania. Risperidone and paliperidone were studied, but neither added benefit for the prevention of mania.(134, 135) Notably, asenapine, paliperidone, risperidone, and haloperidol are suggested as possible options for treating acute mania alone or in combination with lithium or valproate (see Recommendations 6–8). Yet, support for their effectiveness beyond the acute episode, when combined with lithium or valproate, is unavailable.

Patient preferences vary regarding adding another medication. Many individuals seek to be on the fewest possible medications, and adherence can suffer when they feel they are prescribed too many. Side effects can vary, which also affects preference and adherence. Generally, there are more side effects when a second medication is added compared with taking one medication. Some SGAs, noted above, cause weight gain and metabolic side effects, whereas others might cause unwanted stimulation or akathisia. With long-term use, all these antipsychotics can cause tardive dyskinesia.

The decision to add a second medication should be made in the context of psychoeducation, informed consent, and shared decision making. There are no particular issues with cost because all the suggested medications are generic products.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90, 133-135) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including (1) very few studies, (2) small sample sizes, (3) short mean study durations (approximately one year), which would not capture long-term efficacy and safety well, (4) few evaluated side effects, and (5) potential confounders, including differences in the minimal period of clinical stability on monotherapy before adding the second medication, which could have affected the outcomes.(90, 133) The benefits of adding one of these SGAs slightly outweighed the potential harm from adverse effects. Patient values and preferences varied because of patient issues with being on multiple medications, suffering additional side effects, and opposing any medications for maintenance treatment. Thus, the Work Group made the following recommendation: We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania.

d. Prevention of Recurrence of Bipolar Depression

Recommendation

23. We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes.
    (Strong for | Reviewed, New-added)

Discussion

Evidence suggests that treatment with lamotrigine can help prevent the recurrence of depressive episodes in individuals with BD. Kishi et al. (2021a, 2021c) found that treatment with lamotrigine demonstrated efficacy for preventing not just mood episodes in general, but depressive episodes in particular.(89, 120) There was limited evidence comparing lamotrigine to other medications in the prevention of depression; however, Kishi et al. (2021a) demonstrated no difference when comparing lamotrigine to lithium.(89) Of note, these studies included both individuals with BD 1 and BD 2 and did not distinguish between the groups when presenting the results. As lamotrigine monotherapy has demonstrated effectiveness for prevention of depression but not mania, the Work Group acknowledged that it should be of value specifically in individuals with BD 2.

Patient preferences vary regarding this treatment. In general, the medication is well tolerated, a risk of serious side effects (e.g., SJS/TEN) exists. Many individuals prefer not to take maintenance medication. In addition, the medication titration can be cumbersome because it requires slow titration over the course of many weeks. Additionally, if multiple dosages have been missed, medication titration must be

restarted. Consequently, it is imperative that individuals have regular access to a prescribing psychiatric provider and take this medication consistently.

The Work Group systematically reviewed evidence related to this recommendation.(89, 120) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including minimal research comparing lamotrigine directly to other monotherapies, specifically for the maintenance and prevention of depression. The benefits of using these medications to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide and hospitalization) outweighed the potential harm of medication side effects. Patient values and preferences varied because of the potential side effects of lamotrigine as well as some individuals' resistance to taking medications for maintenance treatment. Thus, the Work Group made the following recommendation: We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes.

Recommendation

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 preferences and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests that treatment with lithium, quetiapine, or olanzapine can help prevent the recurrence of depressive episodes in individuals with BD. Kishi et al. (2021b), Suttajit et al. (2018), and Murasaki et al. (2018) found that treatment with any of these medications demonstrated efficacy for preventing not just mood episodes in general, but depressive episodes in particular.(90, 98, 136) Evidence regarding which of the three medications is the most efficacious is mixed, though there is some evidence that quetiapine and olanzapine performed better than other SGAs in the prevention of depression.(90) Of note, the studies referenced above included individuals with BD 1 and BD 2 and did not distinguish between the groups when presenting the results.

Patient preferences vary regarding these treatments. These medications have side effect profiles that include sedation, risk of prolonged QTc intervals, and metabolic syndrome; however, olanzapine carries a much higher metabolic risk than quetiapine or lithium. The metabolic effects of olanzapine are a strong counterbalance to its efficacy as monotherapy and are ultimately the reason why the Work Group decided to suggest this drug as a less favorable alternative than lithium and quetiapine (please refer to the introduction of the Pharmacotherapy section of the CPG for more clarification on this

ranking). Many individuals prefer not to take maintenance medication. Further, individuals using these medications require some laboratory monitoring, which can be burdensome.

The Work Group systematically reviewed evidence related to these recommendations. (90, 98, 136) Therefore, they are categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low for Recommendation 24, and moderate for Recommendation 25. The body of evidence had some limitations because no studies directly compared the effectiveness of these medications against each other, so ascertaining whether one of these medications is more effective than the other is difficult. Regarding Recommendation 24, the benefits of using lithium or quetiapine to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide, hospitalization) outweighed the potential harm of medication side effects. Regarding Recommendation 25, the benefits of using olanzapine to prevent depressive episodes and other outcomes slightly outweighed the potential harm of medication side effects. Patient values and preferences varied because of the potential side effects of these medications, the need for occasional laboratory monitoring, and the preference of some individuals against taking medications for maintenance treatment. Thus, the Work Group made the following recommendations: We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes; and if lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.

Recommendation

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)**

Discussion

Evidence suggests that treatment with olanzapine, lurasidone, or quetiapine with lithium or valproate can help prevent the recurrence of depressive episodes in individuals with BD. Kishi et al. (2021a; 2021b) found that treatment with a combination of lurasidone or quetiapine and one of these mood stabilizers (lithium or valproate) demonstrated efficacy for preventing future depressive episodes.(89, 90) Yatham et al. (2016) and Kishi et al. (2021a; 2021b) found that treatment with olanzapine and a mood stabilizer (lithium or valproate) demonstrated efficacy for preventing any future mood episode.(89, 90, 134) The evidence presented limitations, however, because the authors did not specify which mood stabilizer was added to each antipsychotic being evaluated. Additionally, the studies above included patients with both BD 1 and BD 2 and did not distinguish between the two when presenting the results.

Patient preferences vary regarding these treatments. Most of the medications have moderate side effect profiles, including sedation, risk of prolonged QTc (with olanzapine and quetiapine), and metabolic syndrome. Many individuals prefer not to take

maintenance medication. Those who do choose to receive maintenance medications likely prefer to be on fewer medications. Further, individuals might require some lab monitoring, which can be burdensome. Therefore, it is imperative that individuals have regular access to a psychiatric prescribing provider and PCP.

The Work Group systematically reviewed evidence related to this recommendation.(89, 90, 134) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including difficulties discerning which mood stabilizers were being used in the studies reviewed as part of the Kishi et al. (2021b) meta-analysis. The benefits of using these medications to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide and hospitalization) slightly outweighed the potential harm of medication side effects. Patient values and preferences varied because of the potential side effects of these medications, the need for occasional laboratory monitoring, and some individuals' resistance to taking medications (or for taking as few medications as possible) for maintenance treatment. Thus, the Work Group made the following recommendation: We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes.

Recommendation

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)

Discussion

There is insufficient evidence to recommend for or against the use of any of the medications listed above as monotherapy or in combination with other medications for the prevention of the recurrence of depressive episodes in individuals with BD. Although many studies examined the efficacy of these medications, both as monotherapies and in combination, most demonstrated no efficacy or provided low to very low quality evidence for the outcomes of interest.(90) Newer medications, such as cariprazine, lurasidone, and lumateperone, which have FDA approval for the treatment of acute depression in individuals with BD, have limited maintenance evidence at this time, possibly because of the relatively short amount of time these medications have been available.

Patient preferences vary regarding these treatments. Most of the medications have moderate side effect profiles, including sedation, risk of prolonged QTc (with some antipsychotics), and metabolic syndrome. Many individuals prefer not to take maintenance medication. Those who do choose to receive maintenance medications likely prefer to be on fewer. Further, individuals require occasional lab monitoring, which can be burdensome. Therefore, it is imperative that individuals have regular access to a psychiatric prescribing provider and PCP.

The Work Group systematically reviewed evidence related to these recommendations.(90) Therefore, they are categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence was limited for these medications, including the evidence on their efficacy for preventing the recurrence of bipolar depressive episodes. The benefits of using these medications to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide and hospitalization) slightly outweighed the potential harm of medication side effects. Patient values and preferences varied because of the potential side effects of these medications, the need for occasional laboratory monitoring, and some individuals' resistance to taking medications (or for taking as few medications as possible) for maintenance treatment. Thus, the Work Group made the following recommendations: 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; and 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.

e. Pregnancy/Child-bearing Potential

Recommendation

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)

Discussion

Evidence suggests that discontinuing lithium during pregnancy is associated with an increased risk of relapse and recurrence of bipolar symptoms.(137, 138) However, evidence demonstrates that lithium use in pregnancy is associated with a statistically significant increased risk for congenital and cardiac malformations, yet with low absolute risk.(137) Although the potential harms to the developing fetus and newborn infant are of substantial importance, they are likely to be slightly outweighed in many cases by

symptoms and behaviors associated with BD relapse that can also be dangerous to the pregnant individual, developing fetus, and newborn infant.

Before initiating therapy with lithium, prescribers should have a clear discussion on pregnancy intention, contraception, or both; the risks of withdrawing lithium therapy; alternative medications; and the potential benefits of continuing lithium therapy versus the potential harms of the medication. Prescribers should also consider the severity of BD when weighing the risk and benefits of continued therapy in this population. They should recognize, too, that many pregnancies in individuals with BD are unintended; (139) therefore, they should discuss birth control as well as the risks and benefits of continued therapy in the broader population of individuals of child-bearing potential who are stabilized on lithium.

When continuing lithium therapy in pregnant individuals, several risk management strategies can reduce the risk of harm to the developing fetus or newborn infant. First, FDA labeling indicates that lithium should be prescribed in the lowest effective dose, especially during the first trimester, and temporarily decreased or discontinued 48–72 hours before delivery because these periods are associated with the greatest harm to the fetus and newborn infant.(140) However, recent studies (not included in the evidence base nor impacting the strength of the recommendation) have found no association between neonatal lithium blood concentrations and neonatal outcomes and suggest that lithium doses may not need to be lowered or discontinued during the perinatal period.(141, 142) Furthermore, FDA labeling suggests that more frequent serum lithium concentration monitoring is required in this population because of pregnancy-related physiological changes that might necessitate frequent upward dosage adjustments. Lastly, the FDA recommends that providers consider fetal echocardiography between 16–20 weeks gestation in individuals with first-trimester lithium exposure because of the potential increased risk of fetal cardiac malformations.(140)

Patient preferences vary largely regarding this treatment. The patient focus group noted that lithium can be especially effective in treating bipolar symptoms. However, many individuals are unfamiliar with or have heard negative things about lithium. Further, large variation in patient preferences is likely to occur regarding prioritizing the benefits of lithium to the individual while weighing the risks to the developing fetus or newborn infant because BD relapse can also be dangerous to the pregnant individual, developing fetus, and newborn infant. Psychoeducation to ensure that individuals and, where appropriate, their families are aware of the benefits and the risks of continued treatment with lithium is important, and treatment planning should follow a process of shared decision making. In formulating this recommendation, the Work Group acknowledged that psychoeducation and shared decision making can be time-intensive for the individual and the health care team, but also recognized that these processes are necessary.

The Work Group systematically reviewed evidence related to this recommendation. (137, 138) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence was limited on data for the treatment of acute episodes, lithium exposures to the newborn infant during breastfeeding, and how to model processes for decision making that include prior treatment responses as well as additional risks related to pregnancy.(137, 138) This fact mostly reflects how little controlled, high-quality research has been undertaken with this population. The benefits of stable lithium therapy slightly outweighed the potential harms from lithium discontinuation (e.g., recurrence of manic symptoms) and risks to the fetus from continuing lithium (e.g., serious, but rare, teratogenic effects). Patient values and preferences varied largely because of different attitudes toward lithium treatment and opinions on whether decision making should prioritize the benefits to the individual and fetus of maintaining a stable mood versus concern about potential risks to the safety of the developing fetus or newborn infant from continuing lithium. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)**

Discussion

There is currently insufficient evidence demonstrating the superiority of valproate, carbamazepine, or topiramate over other medications with proven benefits in the treatment of BD to support their use in individuals of child-bearing potential despite evidence for increased risks of teratogenicity. Studies show that these agents are inferior or equivalent to other medications used for BD, including lithium and quetiapine.(89, 143-145) However, these agents are associated with an important risk of fetal harm in pregnancy.(138) Although the evidence base did not include studies reporting robust data describing these harms, the Work Group recommends against the use of valproate,(146) carbamazepine,(93) and topiramate,(147) in individuals of childbearing potential.

Information about fetal risks for these medications as summarized in the FDA-approved product labeling is available at https://labels.fda.gov/. For valproate, there is a Black Box warning and statement indicating that "valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following in utero exposure," and "valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications

have failed to provide adequate symptom control or are otherwise unacceptable." For carbamazepine, there is a statement that, "epidemiological data suggest that there might be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida" For topiramate, there is a statement that "topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age."

Because the known harms of these agents outweigh their limited potential benefits in BD, we recommend against their use in individuals of childbearing potential. Further, before the initiation of any medication for this patient population, providers should establish whether the individual is sexually active, pregnant, or might become sexually active or pregnant and discuss the potential risks of specific medications and untreated BD in pregnancy.

Patient preferences vary regarding this recommendation. The patient focus group noted some hesitancy in switching therapies for BD because they want to continue taking treatments that have been effective for them. However, other individuals might be more sensitive to any potential fetal or newborn harm. Following this recommendation is often feasible because there are other evidence-based therapies for BD that do not have the same teratogenic effects as valproate, carbamazepine, or topiramate, though not all individuals tolerate or respond well to these options.

The Work Group systematically reviewed evidence related to this recommendation.(89, 138, 143-145) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including lack of well-designed, large-scale trials assessing the use of these medications in this patient population.(89, 138, 143-145) The harms of potential teratogenic effects outweighed the potential benefit of valproate, carbamazepine, or topiramate for the treatment of BD in individuals of child-bearing potential. Patient values and preferences varied because some patients place high importance on potential fetal harms, although others who are stable on one of these medications for BD might want to maintain their current treatment regimen rather than switch therapies. Thus, the Work Group made the following recommendation: We recommend against valproate, carbamazepine, or topiramate in the treatment of bipolar disorder in individuals of child-bearing potential.

C. Other Somatic Therapies

Recommendation

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)

Discussion

Electroconvulsive therapy 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. Evidence suggests that ECT, in combination with pharmacotherapy, reduces the severity of manic symptoms in individuals with BD 1.(148) Zhang et al. (2021) conducted a meta-analysis of 12 studies evaluating the use of ECT with or without medication for moderately severe to severe manic symptoms. The authors found that ECT in addition to pharmacotherapy was associated with improvements in manic severity scores and absolute manic scores when compared with pharmacotherapy alone.(148) A limitation of this meta-analysis is that 11 of the 12 studies were published in Chinese journals and English translations were unavailable. Zhang et al. (2021) noted that ECT is more commonly used in China than in Western countries, and, thus, more studies are done there.(148) Because English language translations of the Chinese studies were unavailable, the Work Group could not evaluate the adequacy of the research designs or the quality of the data.

Nevertheless, this finding is consistent with the conclusions of earlier reviews of observational studies that included seven prospective studies of ECT (alone or in combination with pharmacotherapy).(149, 150) These reviews were not included in the systematic evidence review carried out as part of this CPG, and they were not considered in developing this recommendation. In addition, the systematic evidence review did not find an SR or RCTs related to the efficacy of ECT in bipolar depression.

Evidence also indicates some level of harm associated with ECT; 1 study within the SR by Zhang et al. (2021) reported significantly greater cognitive and memory impairment in the ECT combined with the pharmacotherapy group as compared with the group receiving pharmacotherapy alone.(148) Providers considering ECT for individuals with BD should recognize and plan for the need for maintenance therapy after patients respond, typically with pharmacotherapy.

Patient preferences vary regarding this treatment. One participant in the patient focus group reported receiving ECT. Some individuals do not want to receive ECT because of stigma or concerns about adverse effects. Further, barriers to ECT include lack of availability in some clinical settings as well as provider discomfort with this treatment option. After a successful course of ECT, medication to prevent recurrent manic and depressive episodes is recommended (see Recommendations 18–22 and Recommendations 23–28).

The Work Group systematically reviewed evidence related to this recommendation.(148) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including lack of pertinent information about the samples (e.g., whether the participants were treatment-resistant) and suggestion of publication

bias. Further, many of the studies included in the SR by Zhang et al. (2021) lacked pertinent details, including the number of total ECT sessions, session frequency, and method of ECT administration.(148) Most studies did not provide specific information about medications and dosages used. Eleven of the 12 included studies were from China and unavailable in English; therefore, the Work Group could obtain no information not reported in the Zhang et al. (2021) SR. The benefits of ECT in combination with pharmacotherapy, considering an improvement in mania symptom severity, slightly outweighed the potential harm of effects on cognition and memory. Patient values and preferences varied because some individuals do not want ECT. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

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 individuals with bipolar depression.(151) An SR and meta-analysis by Lam et al. (2020) included seven RCTs (n=259) evaluating the use of light therapy for individuals with BD. It reviewed one study that included bipolar seasonal affective disorder (SAD) and six studies that excluded bipolar SAD.(151) Lam et al. (2020) found that treatment with light therapy was associated with a significant improvement in depressive symptoms using the Hamilton Depression Rating Scale (HAM-D).(151) In a secondary endpoint, the authors also demonstrated that light therapy was associated with a significant difference in rates of clinical response; however, a subgroup analysis showed that significant improvements in depression and clinical response were seen in studies that measured effects over two weeks in duration but not in studies that were three weeks in duration. There was also no difference in the rate of clinical remission. The SR included a mixed population of individuals with BD 1 and BD 2.

Light therapy appears to be well tolerated and low risk. No differences were found in discontinuation rates or affective switch rates compared with control conditions.(151) There were, however, mild activating symptoms of agitation, anxiety, and arousal during bright light treatment. These symptoms were resolved on reducing the duration of light exposure, so the authors noted that individuals should be actively monitored for overstimulation and hypomanic symptoms that might require light dosage adjustment.

No study evaluating maintenance efficacy of light treatment, which is a strong priority of this CPG in the selection of treatments, was identified in the systematic evidence

review. How often and how many treatments are needed to maintain an initial benefit is unclear.

Patient preferences vary largely regarding light therapy because the treatment might be burdensome as a result of the amount of time involved and the need for active monitoring. Additionally, some equity concerns exist because light therapy might be unavailable to some individuals because of time constraints and active monitoring requirements.

The Work Group systematically reviewed evidence related to this recommendation.(151) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low for outcomes of depression and clinical response and very low for clinical remission and affective switch rates. The body of evidence had some limitations including uncertainty on allocation concealment and blinding of the clinical team, incomplete information on dropouts, and imprecision. The Work Group determined that the potential benefits of light therapy for improving bipolar depression and clinical response slightly outweighed the potential harm. Patient values and preferences varied largely because light therapy can be burdensome in terms of time commitment and active monitoring requirements. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)**

Discussion

Repetitive transcranial magnetic stimulation involves administering an induced magnetic field to a specific area of the brain, resulting in neuronal activation in the targeted cortical area. The FDA has cleared rTMS for use in treatment-resistant depression. An SR by Tee et al. (2020) found that rTMS improves depressive symptoms and remission rates in individuals with BD 1 and BD 2.(152) This SR and meta-analysis identified 11 RCTs of rTMS with sham control, 7 of which recruited participants with bipolar depression, 1 of which recruited participants with either bipolar depression or unipolar depression, and 3 that included participants with mania. Metanalysis of outcomes for the participants with bipolar depression (n=257) found that treatment with rTMS was associated with small but significant improvements in depression scores (SMD: 0.302; 95% CI: 0.055–0.548; p=0.016). The risk difference for remission in individuals with bipolar depression treated with rTMS as compared with participants receiving sham treatment was 0.104 ± 0.044; in other words, the remission rate for those treated with rTMS was 10.4% greater than the remission rate for sham-treated participants. In 3

studies of individuals experiencing an episode of bipolar mania (n=86), manic symptoms decreased in 1 study, but not in the 2 others.(152) The follow-up interval for the studies included in the SR ranged from 2–10 weeks. The studies thus did not address maintenance treatment following a course of rTMS, including choices of maintenance therapies, nor did they study the effectiveness and safety of repeated courses of rTMS.

Two RCTs identified by the systematic evidence review were published after the SR by Tee et al. (2020).(153, 154) Mak et al. (2021) (n=54) conducted a single-blind, randomized, sham-controlled trial in individuals with bipolar depression who had not responded to antidepressant treatment and found no differences in response or remission rates.(153) McGirr et al. (2021) (n=37) assessed the effectiveness of intermittent theta burst stimulation, a form of rTMS that has some evidence of efficacy in unipolar depression and requires less time to administer.(154) This RCT studied rTMS using the intermittent theta burst stimulation (iTBS) protocol in individuals with BD 1 or BD 2 who were experiencing a major depressive episode and found no significant differences between iTBS, rTMS, and sham rTMS regarding depressive symptom change.

In the SR, 6 of the studies of bipolar depression included individuals with either BD 1 or BD 2.(152) Another study included only individuals with bipolar 2 depression. Yet another study did not specify one of these diagnoses; instead, the study just indicated that participants had a diagnosis of bipolar depression. The SR did not mention any comparison of response rates for study participants with BD 1 versus BD 2 for these studies. Mak et al. (2021) did not present differences in response to rTMS by bipolar diagnosis type in a sample that consisted mostly of individuals with BD 2.(153) McGirr et al. (2021), in their negative study of iTBS, found no differential effect of the treatment among relatively small samples of individuals with the two disorders.(154)

None of the studies included in the systematic evidence review carried out as part of the development of this CPG found significant differences in adverse effects, including emergence of mania during the rTMS or sham treatment period.

Patient preferences vary regarding this treatment. Patients might appreciate therapeutic options other than pharmacotherapy. However, rTMS requires multiple visits to a health care facility (e.g., five visits per week for four weeks) and cannot be done virtually. Therefore, an equity issue occurs for individuals who reside in rural areas and those who otherwise face transportation barriers. In addition, a feasibility issue occurs because rTMS is unavailable at some facilities and clinics. Consequently, providers might not routinely discuss rTMS with patients as a treatment option.

The Work Group systematically reviewed evidence related to this recommendation. (152-154) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence for rTMS treatment in bipolar depression had some limitations; one of the studies that carried the most weight in the meta-analysis by Tee et al. (2020) did not provide a clear description

of allocation concealment and the blinding process and also did not control for confounders (e.g., medication doses and treatment resistance).(152) The number of sessions and method of rTMS administration varied across the studies. Further, some of the studies enrolled individuals with bipolar depression who had not responded to pharmacotherapy. Although variability occurred in the samples of the studies reviewed, this recommendation specifies the use of rTMS as an adjunctive treatment for individuals with partial or no response to pharmacotherapy because more evidence for the effectiveness of pharmacotherapy exists. The benefits of rTMS (e.g., improved depression symptoms, greater remission rate) slightly outweighed potential harm or burden because the benefits were small (and nothing is known about maintenance procedures), although potential patient burden is associated with rTMS. Patient values and preferences varied because although many individuals prefer non-invasive treatments, rTMS requires multiple visits over multiple weeks. Thus, the Work Group made the following recommendation: 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.

D. Psychosocial and Recovery-Oriented Therapy

a. Psychotherapy

Recommendation

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)

Discussion

Evidence suggests that manual-based psychotherapies (e.g., cognitive behavioral therapy [CBT], family or conjoint therapy, interpersonal and social rhythm therapy [IPSRT], non-brief psychoeducation), when provided as augmentations to appropriate psychopharmacological treatment, are effective at improving outcomes for individuals with BD when compared with psychopharmacology alone.(155) These improvements can be seen in the form of reduced illness recurrence along with decreased mania and depression severity at follow-up (typically assessed 6–12 months after treatment completion).

For example, a total of 24 studies included in an SR by Miklowitz et al. (2021) included various comparisons between psychotherapies and TAU.(155) The SR demonstrated that the manualized psychotherapies as a class were associated with lower recurrence rates than control treatments (OR: 0.56; 95% CI: 0.43-0.74). However, findings for individual treatments varied from therapy to therapy. Studies included in this SR indicated that CBT was associated with reductions in mood episode recurrence,(156,

157) decreased mania severity at follow-up,(156) and decreased depression severity at follow-up (158) when compared with TAU. Additionally, family or conjoint therapy was associated with reductions in mood episode recurrence (159, 160) and decreased mania severity at follow-up (161) when compared with TAU. IPSRT was associated with decreased depression severity at follow-up compared with TAU, although this finding did not reach statistical significance.(155) Psychoeducation lasting at least six treatment sessions was associated with reductions in mood episode recurrence when compared with TAU,(162) with some aggregate evidence suggesting that group-based psychoeducation might be particularly effective.(155) In each of these cases, TAU included concurrent psychopharmacological treatment. Many types of psychoeducation involve a mix of didactic information, skills training, and discussion, so for this CPG the Work Group considered psychoeducation to be a type of psychotherapy. However, the Work Group acknowledges that psychoeducation might involve different emphases than other psychotherapy approaches.

In each case, other studies within the same SR found that the listed treatments (CBT, family or conjoint therapy, IPSRT, and psychoeducation) did not result in greater improvements in mood episode recurrence, mania severity at follow-up, or depression severity at follow-up when compared with TAU. However, the aggregate ORs for outcomes (comparing these treatments with TAU) remained significant, although many of these null studies were small (e.g., featuring treatment and control groups of between 20 and 30 individuals each) (163) and likely underpowered to detect modest treatment effects.

Patient preferences varied regarding these treatments. The patient focus group valued psychotherapy treatments as an augmentation to medications, and many of the RCTs described above had reasonably high retention rates in the active treatment groups. Several feasibility and subgroup issues should be considered, however. First, these trials typically did not recruit individuals who were acutely manic. Stabilizing manic symptoms might be crucial for individuals with BD to effectively use these psychotherapies. Further, family or conjoint therapy might be less effective for people who are unable to enlist the help of a significant other or family member in treatment. Across these treatments, periodic training might be required to sustain a workforce with the required expertise to deliver them to individuals with BD.

A host of other psychotherapies and related approaches 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, might draw heavily from the principles underlying one or more of the psychotherapies described above (e.g., Life Goals Collaborative Care [LGCC], which incorporates elements of psychoeducation and behavioral therapy across seven or more treatment sessions).(164) Based on the studies retrieved in the systematic evidence review, the Work Group cannot conclusively determine whether other psychotherapies might perform similarly to the ones listed above for individuals with BD.

The Work Group systematically reviewed evidence related to this recommendation.(155, 161) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes, heterogeneity in specifics of treatment delivery (e.g., group versus individual psychoeducation), and variable follow-up periods. The benefit of these psychotherapy approaches slightly outweighed the potential harms, the latter of which primarily consisted of the time and opportunity costs to participation. Patient values and preferences varied because of variable interest in psychotherapies, in particular psychotherapies that are manualized and involve predetermined structures and topics. Thus, the Work Group made the following recommendation: 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).

Recommendation

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)

Discussion

As described in Recommendation 34, evidence suggests that certain psychotherapies represent effective augmentations to psychopharmacology for the treatment of BD (e.g., CBT, family or conjoint therapy, IPSRT, and psychoeducation lasting at least six sessions).(155) Only a small number of studies in an SR by Miklowitz et al. (2021) included head-to-head comparisons to determine whether one or more of these psychotherapies were more effective than others for preventing illness recurrence, reducing manic symptoms at follow-up (typically 6–12 months post-treatment), or reducing depressive symptoms at follow-up. In general, these head-to-head comparisons did not indicate statistically significant differences in the outcomes among the listed psychotherapies. Comparisons included CBT versus psychoeducation,(165, 166) and family or conjoint therapy versus psychoeducation lasting at least six sessions.(167) Given the relative paucity of head-to-head trials, Miklowitz et al. (2021) compared effect sizes versus TAU for these psychotherapies in an SR and network meta-analysis, finding little evidence for consistent differences in effectiveness among individuals with BD.(155)

Although the patient focus group suggested appreciation for psychotherapies in general, The Work Group members believe some variation in patient preferences exists among specific psychotherapies. For example, some individuals with BD might prefer group versus individual delivery formats, in-person versus virtual delivery methods,

manualized versus more fluid approaches to care, and variable emphasis on different aspects of BD (e.g., periodic mood charting, psychoeducation, behavior change planning, cognitive restructuring, daily rhythms, family dynamics). Furthermore, finding practitioners familiar with these specific treatments might be difficult, and periodic training might be required to sustain a workforce with the required expertise to deliver them to individuals with BD. Other psychotherapeutic approaches might also perform comparably to these listed treatments (e.g., LGCC),(164) but the systematic evidence review provided insufficient data for us to draw firm conclusions in these cases.

The Work Group systematically reviewed evidence related to this recommendation. (155) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes, heterogeneity in psychotherapy delivery, and few head-to-head comparisons.(155) The benefits of these psychotherapies were balanced with the potential burdens, which typically consist of the time and effort needed to participate in structured psychotherapy sessions. Patient values and preferences varied because of a diversity of individual perspectives and preferences regarding psychotherapy in general as well as specific aspects of particular psychotherapies. Thus, the Work Group made the following recommendation: 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. We emphasize that this does not mean that we recommend neither for nor against psychotherapy as an augmentation to psychopharmacology for BD, but rather that we found insufficient evidence to recommend for or against any particular approach to psychotherapy in this context.

b. Complementary and Integrative Health and Supplements

Recommendation

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)

Discussion

In general, there is very limited evidence comparing different types of complementary and integrative health interventions (e.g., acupuncture, art therapy, dance therapy, mindfulness, music therapy, relaxation, yoga, and tai chi) for individuals with BD 2.

The literature reviewed did not study patients diagnosed with BD 1. Some evidence, however, demonstrates that meditation is beneficial for individuals diagnosed with BD 2. A large RCT (n=311) conducted in eight African and Asian cities showed some improvement in depressive symptoms for individuals who were offered meditation only

compared with those who were offered group CBT only as what the investigators considered to be a control condition.(168) At the two-year follow-up, individuals practicing meditation demonstrated improvement in depressive symptoms compared to the CBT control group; the author noted reductions in guilt and feelings of helplessness and hopelessness. However, the study included neither Veterans nor Service members.

Symptom severity was measured with the Bipolar Depression Rating Scale (BDRS). Symptom severity was lower for men in Asian cities who were Hindu or Buddhist, middle class, and married. In addition, symptom severity was lower for individuals who attended all the scheduled meditation sessions and then continued to self-practice.

Large variation in patient values and preferences occurred because some individuals might not embrace this treatment modality. This study was conducted in Africa and Asia, where meditation might be more mainstream than in the U.S. There are subgroup considerations because whether Veterans, active-duty Service members, Reserve, and National Guard members would be open to meditation as an intervention for BD 2 is unclear. In addition, acceptability and feasibility concerns exist. Although training for meditation and mindfulness-based practices is increasing within VA, providers might lack confidence in suggesting this treatment. Also, some smaller and more rural areas might have insufficient staffing to offer this modality.

The Work Group systematically reviewed evidence related to this recommendation.(168) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including concerns with generalizability because the study was conducted only in urban areas in Africa and Asia.(168) Veterans and Service members were not included in the study. The benefits of meditation outweighed the potential harms because depressive symptoms decreased with no harm noted. Patient values and preferences varied largely because some individuals might not prefer this treatment modality. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)**

Discussion

Evidence was reviewed for nutritional supplements and their impact on BD. The systematic evidence review identified two SRs and five RCTs that, in all, evaluated omega-3 polyunsaturated fatty acids (PUFA), magnesium, probiotics,

S-adenosylmethionine (SAMe), vitamin B6, and vitamin D. These studies suggest the following.

Magnesium

Evidence from one very small RCT in one SR (169) reported no difference between magnesium and placebo for improving depressive symptoms in individuals with BD. The Work Group's confidence in the quality of the evidence was very low because of the small sample size and imprecision.

Omega-3 polyunsaturated fatty acids

Evidence from six RCTs within two SRs (169, 170) reported that most studies found no difference between omega-3 PUFAs and placebo for improving manic or depressive symptoms in individuals with BD at 3–24 weeks follow-up.

One additional RCT with a 15-month follow-up also reported no difference between omega-3 PUFAs and placebo for improving most measures of mania or overall bipolar symptoms.(171) PUFAs were associated with manic symptom improvement measured by the Young Mania Rating Scale (YMRS) at 12 months but not at 15 months.

No difference in functional status occurred between high eicosapentaenoic acid and docosahexaenoic acid plus low omega-6 versus the control diet (172) as well as no difference in cognitive functional status between docosahexaenoic acid versus placebo.(173) Additionally, no difference in adverse events was found between omega-3 PUFAs and placebo.(169, 171)

The Work Group's confidence in the quality of the evidence was very low because of small sample sizes, inconsistency, and imprecision.

Probiotics

Evidence from a small RCT (174) within one SR (169) and an additional RCT (175), reported no difference between probiotics and placebo for improving manic or depressive symptoms in individuals with BD. However, the small RCT (174) within the SR (169) did demonstrate a lower number of rehospitalizations in the treatment group. The Work Group's confidence in the quality of the evidence was low because of small sample sizes and imprecision. In addition, there was no significant difference in adverse effects between placebo and probiotics.(169)

S-adenosylmethionine

Evidence from a small RCT within one SR (170) found no difference between SAMe and placebo for improving manic or depressive symptoms in individuals with BD. The Work Group's confidence in the quality of the evidence was very low because of the small sample size and imprecision.

Vitamin B6

Evidence from one RCT found no difference between vitamin B6 and placebo for improving mania symptoms in individuals with BD who were taking lithium.(176) The Work Group's confidence in the quality of the evidence was low because of imprecision.

Vitamin B9 (folic acid)

Evidence from three RCTs within two SRs suggested that folic acid as an adjunctive treatment might improve manic symptoms but not depressive symptoms in individuals with BD.(169, 170) The SR by Ashton et al. (2021)(170) included two RCTs. A small RCT showed a significant improvement in manic symptoms in individuals taking sodium valproate who were prescribed 3 mg per day of folic acid versus placebo. A second RCT within the same SR demonstrated no difference in depressive symptoms from adding 500 mcg per day of folic acid versus placebo in individuals taking quetiapine and lamotrigine. Finally, a third RCT within a second SR (169) demonstrated no difference in the improvement of depression symptoms by adding folic acid versus placebo.(169) The Work Group's confidence in the quality of the evidence was low because of small sample sizes and imprecision. In addition, concurrent folic acid might reduce the effectiveness of lamotrigine.(108)

Vitamin D

Evidence from two RCTs within two SRs found no difference between vitamin D and placebo for improving manic or depressive symptoms in individuals with BD.(169, 170) The Work Group's confidence in the quality of the evidence was very low because of small sample sizes and imprecision.

The Work Group systematically reviewed evidence related to this recommendation.(108, 169-173, 175, 176) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence ranged from low to very low depending on the supplement. The body of evidence had some limitations, including small sample sizes, inconsistency, and imprecision, as detailed above. Any potential benefit was felt to be balanced with potential harms because no significant adverse events were noted for the treatment groups. Patient values and preferences related to taking supplements varied because some patients prefer taking them although others do not. The Work Group also noted concerns about potentially high out-of-pocket expenses of some supplements without benefit. Thus, the Work Group made the following recommendation: 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.

c. Technology-based Care

Recommendation

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)

Discussion

Evidence from a large meta-analysis suggests that varied smartphone-based interventions accompanied by psychoeducation improve depressive and manic symptoms in individuals with BD.(177) However, although evidence from varied smartphone-based interventions did show differences, web-based applications showed no difference in mood-based symptoms in individuals with BD.

Among the evidence examined, the effect of virtual interventions for symptom monitoring, recurrence of mood episodes, cognition, and community function, among other outcomes, was studied for various computer- or web-based interventions and smartphone-based monitoring and interventions (e.g., mobile applications, SMS text messaging).(177-186) Participants in the intervention and comparator groups across all studies received TAU, which typically included medication, psychological therapy, clinical visits, or any combination of these three. Of the 10 studies, 7 were conducted in non-U.S. settings.

No studies met the inclusion criteria for the systematic evidence review that specifically addressed hybrid telehealth and in-person, telephone, or video-call encounters.

Evidence from one independent RCT in Scandinavia of individuals diagnosed with BD (179) and six RCTs in one SR (177) showed improvement in manic symptoms with a smartphone intervention. It should be noted that the objective of these applications varied widely, from a focus on monitoring of symptoms to interventions including positive psychology and psychosocial intervention. For depressive symptomatology, eight RCTs in the same SR (177) found an improvement in the smartphone intervention arm, and one RCT (179) showed no difference in depressive symptoms with a smartphone-based intervention. However, these applications varied widely, and no head-to-head comparison of similar applications was found. Evidence from a smaller RCT (n=60) in Iran in individuals with BD 1 and BD 2 also suggested that manic, anxiety, and depressive symptoms improved in a study group provided with a mobile application focused on psychoeducation, when compared with TAU.(178) This variation in the focus of applications leads to an inconclusive determination and summary at this time, given the wide ranging research in this area.

No evidence to indicate any level of harm associated with smartphone-based applications was found.

Despite the range in applications studied, significant considerations were reviewed in three RCTs from one SR that summarized a subgroup analysis.(177) In this data, depressive symptoms improved in the smartphone-based interventions with psychoeducation group when compared with the control group (e.g., usual care, paper and pencil monitoring, other unspecified conditions) at 1–12 months follow-up. This follow-up time, especially for mental health studies, was found to represent a significant finding compared with prior research.

Evidence from five RCTs in one SR (177) indicated that in a subgroup analysis, depressive symptoms did not differ between smartphone-based interventions without psychoeducation versus control (e.g., usual care, paper and pencil monitoring, other unspecified conditions) at 1–12 months follow-up. Further data from two RCTs in the same SR demonstrated that in a subgroup analysis, depressive symptoms improved in the group receiving smartphone-based interventions with phone call instructions compared with the control group at 1–12 months follow-up.(177) Lastly, evidence from six RCTs in this same SR suggested that in a subgroup analysis, depressive symptoms did not differ between the smartphone-based interventions without phone call instructions group versus control group at 1–12 months follow-up.(177)

These attempts at determining which elements of the applications impacted BD symptoms positively revealed that despite the wide range of the types of applications, positive effects were noted when the application was paired with psychoeducation.

Six individual RCTs included in the evidence base compared web-based interventions with another virtual intervention or TAU.(180-185) No studies met the inclusion criteria for the systematic evidence review that specifically addressed hybrid telehealth and in-person, telephone, or video-call encounters. Participants in the intervention and comparator groups across all studies received TAU, which typically included medication, psychological therapy, clinical visits, or any combination of the three.

When looking at these modalities in total, one SR including nine RCTs compared virtual interventions (smartphone-based interventions or monitoring, mobile applications, and computer- or web-based interventions) with another virtual intervention or TAU.(177)

Evidence from one RCT of individuals with BD in England showed improvement in depressive symptoms with a web-based application, “Living with Bipolar,” that offers a recovery-based program to patients, including peer support.(181) The study did not differentiate between BD subtypes in the study population. In individuals diagnosed with BD, an Australian study reviewed the effect of online psychoeducation versus online psychoeducation and peer support versus control.(180) The results showed increased perceptions of control, decreased perceptions of stigmatization, and significant improvements in levels of anxiety and depression from pre- to post-intervention across all groups, although the study was unable to show a significant difference on outcome

measures. Of note, adherence to the treatment program was significantly higher in the supported intervention group than in the unsupported group.

One RCT with a 70-hour web-based program focused on cognitive remediation in individuals with BD with psychosis.(184) This intervention did show improvement in cognition, but not in community function, compared with routine care, and notable high dropout occurred in both groups (approximately 50%). Thus, findings were recommended to be considered preliminary by the primary authors. Another study, in individuals with BD 1 and BD 2, evaluated the use of two web-based programs, Mood Swings (psychoeducation) and Mood Swings Plus (psychoeducation plus CBT), aimed at decreasing mood symptoms and recurrence.(182) Although decreased mood symptoms were noted in both groups, there was no control arm and, again, notable high attrition across groups (approximately 80%), limiting any conclusions.(182) Additionally, no difference in anxiety symptoms was found in an internationally recruited patient population of individuals with BD 1, BD 2, or not otherwise specified, when apps focused on brief mindfulness interventions via the web.(183) One Australian study of individuals with BD 1 or BD 2 examined symptom thresholds for time-to-recurrence for a hypo/manic, depressive, or BD episode with a web-based psychoeducational and CBT program compared with TAU and also showed no difference.(185) No evidence to indicate any level of harm associated with computer- or web-based applications was found.

Some variation in patient and provider preferences regarding both treatment modalities is expected. The Work Group considered concerns around the use of technology in care (e.g., related to privacy and data security as well as provider and patient proficiency) and age-based variations in provider and patient use. Patient values and preferences would be expected to vary because of the assessed patient's comfort with technology and its availability, yet the breadth of international studies in this section lends itself to universal appeal. For example, although older patients might dislike mobile apps overall, an expectation exists that less age-based variation will exist as the population becomes more technologically literate.

In the area of telehealth, a recent survey by the American Psychiatric Association noted that providers were encouraged to find alternatives to synchronous telehealth modalities (simultaneous video and audio), if needed, for patients with either poor access to technology or broadband, poor cognitive ability to use video platforms, or both.(187) The Work Group determined that this recommendation was in line with that intent, although emphasizing that providers should ask patients about their preferences rather than making assumptions based on age or other demographic characteristics.

Other concerns around equity were based on the ideas that some patients might lack the agility and information technology literacy to use mobile apps, less access might exist in rural areas (to both devices and adequate WiFi), and local and regional variations in bandwidth might impact availability of synchronous communication. Additionally, some of the concerns listed above could extend to providers and to clinical

or administrative staff or both who might require training in technology use. Therefore, these interventions could be resource intensive for some providers and staff.

The Work Group systematically reviewed evidence related this recommendation.(177-186) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The methodological quality of the RCTs included in the SR (177) was rated by the authors of the review as good to fair using USPSTF criteria, with most studies receiving good ratings. RCTs rated as fair quality had concerns around lack of or inadequate blinding of participants and personnel as well as some concerns around attrition. The methodological quality of the nine individual RCTs was rated fair to poor, primarily because of the lack of blinding of patients, study personnel, assessors, or any combination of the three; concerns around baseline group comparability; high attrition (14–81%); and lack of intention-to-treat analysis in four studies.(178, 180-182) The benefits of specific smartphone apps could be noted only when combined with psychoeducation. The little evidence of benefit for computer- or web-based interventions slightly outweighed potential harms, which were determined to be of low burden to the patient. Patient values and preferences varied because acceptance of these interventions might vary with age and availability. Thus, the Work Group made the following recommendation: For individuals with bipolar disorder, there is insufficient evidence to recommend for or against any particular phone application or computer- or web-based intervention.

E. Supportive Care/Models of Care

a. Supportive Care

Recommendation

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)

Discussion

Supported housing interventions provide varying levels of resources and support, to include immediate shelter and stability, followed by wraparound services to address other psychosocial needs. In an RCT conducted by Tinland et al. (2020), the authors studied the implementation of one such model in France, known as Housing First, for individuals experiencing housing insecurity.(188) This study was large (n=703) with a 24-month follow-up period.

Little evidence was found demonstrating that the Housing First model was beneficial for this population of individuals. It led to increases in housing stability, but no notable differences were observed in emergency department visits, hospital admissions, length of stay, or medication adherence for individuals receiving Housing First compared with those receiving TAU. However, the intervention led to decreases in inpatient days, and

improvements in reports of wellbeing. No harm occurs in providing safe, stable, and affordable housing to individuals struggling with severe mental illnesses.

However, very few studies focused specifically on individuals with BD. The study by Tinland et al. (2020) was conducted outside the U.S. and had only a small proportion of individuals with BD.(188) It is possible that the two-year follow-up period was too short to see improved results, or that France's robust social security system meant the TAU condition performed better than the social safety net might be expected to perform in other countries. Also, notably, study results were self-reported through interviews, which could pose challenges when assessing symptoms.

Unfortunately, no other studies on Housing First met the criteria for inclusion in the systematic evidence review, which leaves the Work Group with one RCT in which only 30% of the individuals in the study met criteria for a diagnosis of BD. Despite the limited evidence of benefit, the Work Group believes there is little to no harm in providing affordable (income-based) housing to individuals who are experiencing homelessness or who are precariously housed.

The Work Group is interested in seeing more research on supportive housing models with a specific focus on individuals in the U.S. with BD. The Work Group notes that because of a dearth of studies focusing on BD and supportive housing models, they decided to develop a *Neither for nor against* recommendation. The Work Group reiterates that providing safe and affordable housing to persons diagnosed with BD involves little to no harm. Because this study was conducted in urban settings, whether the results could be different in more rural populations is unclear.

The Work Group systematically reviewed evidence related to this recommendation. (188) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including that the length of follow-up time could have been longer, the study was conducted outside the U.S., and the proportion of individuals with diagnoses of BD was low.(188) The benefits of Housing First outweighed the potential harm because no evidence of harms was identified. Patient values and preferences varied because some individuals do not prefer to live in traditional housing. Finally, regarding resource use and equity concerns, a dearth of low-income housing occurs across the country, but especially in more rural areas. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with bipolar disorder experiencing housing insecurity.

Recommendation

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)

Discussion

Individual Placement Support (IPS) is a model that helps individuals with mental illnesses and other disabilities find and keep meaningful employment. Because there are no requirements for prevocational training, individuals receiving IPS usually find work quickly. Support continues after they find a job to help them maintain their job. IPS Enhanced refers to IPS, but with additional services, such as cognitive, psychosocial skills, and illness management training.

Two RCTs focused specifically on individuals with bipolar disorder, which the Work Group reviewed and considered when developing this recommendation.(189, 190) Although the confidence in the quality of evidence was low for all outcomes related to functional status, enough evidence exists to suggest that individuals receiving IPS and IPS Enhanced intervention have increased hours of employment or schooling compared with those receiving usual care. These individuals were also able to obtain employment or education more quickly than those receiving usual care. However, Killackey et al. (2019) found that although IPS was superior to usual care in rates of employment over six months, this rate was not sustained at the 12- and 18-month follow-up marks.(189) Further, both studies were conducted outside the U.S., so results might be inapplicable to individuals receiving IPS or IPS Enhanced in the U.S., and benefits of IPS might be not sustained.

The Work Group systematically reviewed evidence related to this recommendation. (189, 190) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The benefits of IPS and IPS Enhanced outweighed the potential harms because few downsides are associated with helping individuals secure employment or education. However, the benefits appear to be limited to a small subset of individuals and seem to fade over a long period of time. Patient values and preferences varied because some individuals might be uninterested in programs like IPS. Feasibility, resource use, and equity issues are associated with this program because travel to programs might be difficult and employment opportunities might be limited for individuals in rural or remote areas. Thus, the Work Group made the following recommendation: For individuals with bipolar disorder who require vocational or educational support, we suggest Individual Placement and Support or Individual Placement and Support Enhanced.

b. Models of Care/Care Delivery

Recommendation

41. For individuals with bipolar disorder, we suggest caregiver support programs to improve mental health outcomes.
(Weak for | Reviewed, New-added)

Discussion

This recommendation was based on the KQ on the effectiveness of using a team-based multidisciplinary or interdisciplinary model of care, which included caregiver support programs as an intervention of interest. The critical outcome for this KQ was bipolar symptom change with an important outcome of QoL. Evidence suggests that caregiver support programs improve health and mental health outcomes in both caregivers and individuals with BD. An RCT by Perlick et al. (2018) evaluated the effectiveness of the Family-Focused Treatment-Health-Promoting Intervention (FFT-HPI) on the physical and mental health of persons over age 18 who were the primary caregivers of individuals with BD 1 and BD 2.(161) These caregivers were identified as having current problems with physical or mental health behaviors. In addition to the effects of FFT-HPI on the caregiver's mental health, this study also evaluated whether the intervention had an impact on the patient's bipolar symptoms. The results of the intervention were compared with the results of standard health education for caregivers. At the six-month follow-up, caregivers' scores on the Center for Epidemiological Studies for Depression Scale and the 36-Item Short Form Survey favored the use of FFT-HPI.(161) The patients' scores on the HAM-D and the YMRS also favored the use of FFT-HPI with caregivers. This study suggests that caregiver treatment with FFT-HPI is associated with improved outcomes in individuals with BD.

In an RCT by Madigan et al. (2012), authors investigated BD caregivers' psychological health, where caregivers were over age 18, were living in the community, had a minimum IQ of 80, and were fluent in English.(191) This study compared two interventions, multifamily group psychoeducation and solution-focused group psychotherapy, with TAU. They found an improvement in caregivers' knowledge and reduced overall burden and psychological distress of the caregiver at one- and two-year follow-ups. An improvement in caregiver QoL was found for individuals treated with either of the two interventions. However, this study did not consider the impact of the intervention in patient outcomes.

Limited evidence is available for assessing the efficacy of caregiver support programs, and the quality of the two studies reviewed was low. Evidence suggests that this intervention demonstrates improved mental health outcomes for both the individual with BD 1 and 2 and the individual's caregiver. The benefits of the intervention slightly outweigh the potential harm of caregiver burnout. Preventing caregiver burnout is important for QoL of both the individual with BD and the caregiver. The importance of this fact was noted by the focus group.

Patient preferences vary regarding caregiver support programs. Caregiver interventions require the consent of both the individual and the caregiver as well as a significant time commitment. Often, individuals with BD experience variations in their relationships with family and friends, as noted in the patient focus group. This experience could impact their desire to have family and friends involved in their treatment. Findings from the patient focus group noted a benefit of peer support programs with a desire to involve others in the management of their disorder. Despite this benefit, the time intensive demands of caregiver support programs should be considered when recommending such programs. Interventions in both the Perlick et al. (2018) and Madigan et al. (2012) studies took a minimum of 45 minutes per week, for up to 12 weeks, of the caregiver and BD patient's time.(161, 191) Neither study accounted for variations in medication regimens in patients or caregivers and did not mention the potential impact of other interventions already in use with the patient. The feasibility of this intervention in DoD is limited because of the structure and nature of the standard mental health setting, but VA has found a positive impact in similarly existing programs.

The Work Group systematically reviewed evidence related to this recommendation. (161, 191) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample sizes and high attrition rates,(161, 191) low racial and ethnic diversity,(161) and English language requirements.(191) The benefits of caregiver support programs improving outcomes for patients and their caregivers slightly outweighed the potential harms of caregiver burnout. Patient values and preferences varied because both patients and caregivers must consent to the intervention and be willing to commit significant time. Additionally, the relationship that individuals with BD have with family and friends varies significantly, and they might not want family or friends involved in their care. Thus, the Work Group made the following recommendation: For individuals with bipolar disorder, we suggest caregiver support programs to improve mental health outcomes.

Recommendation

42. For individuals with bipolar disorder, we suggest that clinical management should be based on the collaborative care model.
(Weak for | Reviewed, New-added)

Discussion

The evidence review conducted to inform this CPG included four RCTs evaluating the impact of interventions based on collaborative care models, also known as collaborative chronic care models.(192-195) Together, the findings suggest that clinical management based on this model led to lower levels of manic or depressive symptoms.

As discussed in an SR by Woltmann et al. (2012) (196) (not included in the evidence base nor impacting the strength of the recommendation), interventions can be considered to fit the collaborative (or collaborative chronic care) model when they

include at least three elements from among the following: patient self-management support, clinical information systems use, delivery system redesign, provider decision support, community resource linkage, and health care organization support. For each of the clinical trials for BD, operationalizing these elements included the delivery of measurement-based care.(197, 198) This process consisted of care managers collaborating with patients in an ongoing basis to monitor symptoms using standardized methods, sharing this information with the treatment team, and using it to support decision making about modifying treatments, when appropriate. Although these clinical trials all fit the model, they differed in the discipline of the providers who served as care managers; they included social workers,(192) unspecified masters-level health specialists,(193) nurses,(194) and clinical pharmacy practitioners.(195) The value of including social workers and nurses as members of mental health treatment teams with direct contact with patients is well established; however, evidence for inclusion of clinical pharmacy practitioners is more recent. Evidence for benefits of direct contact with pharmacists was strengthened by other studies suggesting that interventions focused on education provided by pharmacists rather than the collaborative care model can improve medication adherence.(199, 200)

Of the four clinical trials evaluating the collaborative care model for BD, three found benefits. Van der Voort et al. (2015) found low quality evidence for benefits based on reduced depressive symptoms; Kilbourne et al. (2013) found very low quality evidence for depressive symptoms; and Salazar-Ospina et al. (2017) found very low quality evidence for manic symptoms.(193-195) In contrast, Kilbourne et al. (2012) found no benefits for collaborative care for either manic or depressive symptoms.(192) Of note, however, Kilbourne et al. (2012) was a small-scale pilot study designed to obtain preliminary data on enhancements to the chronic care model, addressing cardiovascular risks as well as symptoms of BD.(192) It informed development of the intervention tested in Kilbourne et al. (2013),(193) but it did not, by itself, have adequate power to detect moderate or small effects.

Findings from the clinical trials included in the systematic evidence review are aligned with findings from two earlier large-scale clinical trials demonstrating the effectiveness of collaborative care for BD.(201-205) They also align with findings from an SR and meta-analysis that included studies of BD and demonstrated benefits for the intervention across a range of mental health conditions.(196) Note that these publications were considered to be outside the scope of the systematic evidence review because they were published before the start of the timeframe considered for the systematic evidence review. Further, the systematic evidence review did not provide findings stratified by diagnosis. Together, these publications define the state of knowledge about collaborative care before the start of the systematic evidence review; however, they were not considered in developing the current recommendation.

One of the key elements defining collaborative care is patient self-management support. It is well aligned with patient values and preferences. The benefits with respect to

symptoms of mania and depression are not offset by adverse effects or harms to individuals with BD, except, possibly, for what some might consider increased burdens associated with the additional time spent in contact with providers. Nevertheless, it is important to recognize that the resources required for implementing collaborative care might be substantial. Moreover, implementation of collaborative care might be infeasible for solo practitioners or practical for small clinics. However, VA has had experience in providing collaborative care for BD remotely, by telehealth (13,14).(164, 206) In principle, telehealth could serve as a strategy for overcoming many of the barriers that have limited its availability.

The Work Group systematically reviewed evidence related to this recommendation. (192-195, 199, 200) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The Work Group recognized that collaborative care is well aligned with patient values and preferences and determined that the benefits for reducing symptoms of mania and depression slightly outweighed the burdens (e.g., possible burdens to individuals with BD, including extra time spent participating in care; burdens to health care organization, including the extra resources required). Thus, the Work Group made the following recommendation: For individuals with bipolar disorder, we suggest that clinical management should be based on the collaborative care model.

F. Co-occurring Conditions

Considering the frequent, common co-occurring conditions accompanying BD, it is imperative that providers evaluating patients for BD work to identify each condition and address core clinical features in a systematic manner. The available evidence for each discrete mental health condition should guide treatment choice while balancing treatment burdens or side effects on BD (e.g., metabolic side effects, antidepressants, stimulants). In addition, good clinical practice dictates use of shared decision-making in treatment planning and caution when making additional diagnoses where symptoms might be better explained by BD. Patients can experience a considerable burden when mental health conditions are added to a problem list without careful validation and an application of illness criteria and treatments.

Recommendation

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)

Discussion

Smoking-related illnesses and related mortality are markedly elevated in people with BD, so efforts to address tobacco use with people with BD is important. Broadly speaking, tobacco cessation involves a combination of education and counseling in

conjunction with medical interventions. Evidence suggests offering varenicline for tobacco cessation because it may be a tolerable and effective cessation treatment for nicotine users diagnosed with BD. Heffner et al. (2019) performed a subgroup analysis from the larger Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) (207) and found that, across individuals with BD cohorts, varenicline seems to have an effect on abstinence based on the seven-day point prevalence abstinence (PPA) at the week 12 secondary endpoint (OR: 2.93; 95% CI: 1.15–7.51).(208) Heffner et al. (2019) also determined that varenicline was superior to bupropion (OR: 2.19; 95% CI: 1.00–4.78) and nicotine replacement therapy (NRT) using a transdermal nicotine patch (OR: 3.14; 95% CI: 1.23–8.02) for PPA at week 12.(208) However, there was no significant effect on the primary outcome, continuous abstinence, from weeks 9–12. Heffner et al. (2019) found continuous abstinence rates did not differ significantly with the use of varenicline compared with placebo at 9–12 weeks or 9–24 weeks.(208) No differences were found between the use of NRT or bupropion compared with placebo in smoking cessation rates at 12–24 weeks.

The subgroup analysis performed by Heffner et al. (2019) found that varenicline efficacy with BD 1 and BD 2 and tobacco use was very similar to the efficacy noted in the full sample of individuals with neuropsychiatric conditions in the EAGLES trial by Anthenelli et al. (2016).(207, 208) The EAGLES trial (not included in the evidence base nor impacting the strength of the recommendation), included 8,000 individuals divided into two groups (4,000 with only nicotine use disorder and 4,000 with other mental health conditions including BD).(207) The study found that varenicline was effective and that no difference in adverse events, side effects, or both between groups occurred with neuropsychiatric conditions treated with varenicline, bupropion, nicotine patch, or placebo. Following the review of the findings of this study, the FDA removed a Black Box warning about serious mental health side effects.(209) Anthenelli et al. (2016) suggest that suicidal ideation, when it occurs, might be related to nicotine withdrawal, not varenicline, and that tapering nicotine use to alleviate symptoms might be helpful.(207) The benefits of offering varenicline slightly outweigh the harms and burdens because the effect size was large and side effects were insignificant.

Other studies provided very low quality evidence on other outcomes with the use of varenicline or NRT compared with placebo in individuals with both BD 1 and 2. Two studies found increased smoking cessation at 12 weeks with the use of varenicline compared with placebo but no between-group differences at 24 weeks.(208, 210)

Patient preferences vary regarding this treatment. Convincing individuals diagnosed with BD who use nicotine to participate in tobacco use disorder treatment can prove challenging. Additionally, some might be unready to stop smoking, and smoking cessation rates for people with BD are small. However, that providers engage individuals with BD who smoke in discussions about their smoking is important. Further, subgroup considerations might exist for individuals with untreated, serious depressive symptoms because the EAGLES trial participants had stable symptoms for six months.

Nevertheless, smoking-related illnesses and related mortality are elevated in people with BD, so efforts to help them reduce the harms from tobacco use remain important.

The Work Group systematically reviewed evidence related to this recommendation. (208, 210). Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes and a post hoc subgroup analysis.(208, 210) The benefits of offering varenicline for tobacco cessation for individuals with BD 1 or BD 2 and tobacco use disorder slightly outweighed the potential harms, burdens, or both. The associated risks are short lived because treatment is intended for up to12 weeks. Patient values and preferences varied because individuals who use tobacco might struggle to quit using it. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

About one-third of individuals with BD in the community may also struggle with a co-occurring SUD,(211) with even higher rates of co-occurrence in clinical populations.(212) In developing this recommendation, the Work Group considered evidence related to various medication and psychotherapy treatments for SUD in this population, with an emphasis on possible improvement in SUD outcomes specifically.

One SR (213) and one RCT (214) investigated pharmacotherapy for co-occurring BD and SUD, but the results focused primarily on symptoms related to BD and psychosis rather than on SUD outcomes.

Multiple studies investigated psychotherapy for co-occurring BD and SUD. An SR by Crowe et al. (2019) included two small RCTs that demonstrated varying impacts of integrated group therapy on SUD outcomes among individuals with BD.(215) In one of these studies, 20 weeks of integrated group therapy was associated with greater improvements in some measures of SUD symptoms than 20 weeks of group drug counseling.(216) In the other study, 12 weeks of integrated group therapy was not associated with statistically significant improvements in SUD symptoms when compared with group drug counseling.(217) Two other small RCTs compared treatments rooted in cognitive therapy principles to TAU for co-occurring BD and SUD.(218, 219) Jones et al. (2019) found that integrated motivational interviewing and CBT did not outperform TAU

in addressing alcohol use,(218) while Wenze et al. (2015) found that the CBT-based Integrated Treatment Adherence Program did not outperform enhanced assessment and monitoring in terms of SUD outcomes.(219)

Patient preferences vary regarding treatment for SUD that might co-occur with BD. Individual-level fluctuations in motivation to discontinue using substances, accompanied by ambivalence toward SUD treatment, should never be taken as an excuse on the part of health systems to withhold these treatments. Instead, providers might need to discuss these issues openly with individuals with BD who hesitate to participate in SUD treatment.

The Work Group systematically reviewed evidence related to this recommendation. (213-215, 218, 219) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample sizes and a limited number of studies assessing substance use outcomes.(214) The benefits of specific SUD treatments for this population were balanced against their respective burdens, which consisted primarily of the time required to complete the listed treatments. Patient values and preferences varied because of varying levels of interest in SUD treatments. Thus, the Work Group made the following recommendation: 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.

We emphasize, however, that the systematic evidence review carried out as part of this CPG focused specifically on individuals with co-occurring BD and SUD. Much larger bodies of literature addressing SUD treatments in the general population or among people with co-occurring SUD and other mental health conditions were not included. Therefore, the Work Group did not review studies evaluating evidence-based treatments in other populations (e.g., medication-assisted treatment for opioid use disorder [OUD]) (220) or consider these studies in the development of this recommendation. It is important to note that this recommendation does not mean that the Work Group is neither for nor against providing SUD treatment to individuals with co-occurring BD and SUD, but rather that sufficient evidence was unavailable to recommend one particular SUD treatment over another for this population specifically. For example, no evidence exists to suggest that the use of buprenorphine, methadone, or naltrexone for the treatment of opiate use disorder is less effective in individuals with co-occurring BD, and the provision of medications for opiate use disorder, because they are lifesaving, should remain a high priority to be delivered to individuals with BD. A diagnosis of BD should not at this time exclude individuals from receiving SUD treatment. Thus, please refer to the VA/DoD SUD

CPG[c] for evidence-based approaches to managing SUD and for managing SUD and co-occurring mental health conditions.

Recommendation

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)

Discussion

Evidence suggests that CBT is effective for individuals with fully or partially remitted BD 1 or BD 2 with residual anxiety symptoms. An SR by Seeberg et al. (2021), which included 10 RCTs (n=29 to 160), suggested a reduction in residual anxiety in individuals in the psychotherapy group compared with those in the control group after treatment completion.(221) It also suggested a possible within-group reduction in anxiety for those in the psychotherapy and control group; however, two studies had unclear statistical methods for within-group evaluation. For non-mindfulness CBT specifically, two of five RCTs included in the SR suggested a reduction in anxiety symptoms in the psychotherapy group compared with the control group. For mindfulness-based cognitive therapy (MBCT) specifically, two of three RCTs included in the SR showed that individuals with BD who received MBCT experienced a reduction in anxiety symptoms when compared with control. The third RCT found within-group reduction in anxiety but no between-group difference. In earlier recommendation narratives, the Work Group also discussed evidence suggesting that the benefits of quetiapine may include reductions in comorbid anxiety.(100, 122) However, the Work Group determined that the strength of the evidence was not sufficient to include a suggestion for pharmacotherapy with quetiapine for comorbid anxiety.

There is variation in patient preferences regarding this treatment. Participation in CBT, which requires individuals to meet with a provider regularly, can be time consuming. Additionally, CBT treatment often requires time to rehearse interventions and complete readings and worksheets between appointments. CBT might also pose feasibility issues because providers might need specialized training to work specifically with individuals with BD experiencing anxiety symptoms.

The Work Group systematically reviewed evidence related to this recommendation. (221) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations. Concerns related to RCTs within the Seeberg et al. (2021) SR included, for example, small sample sizes, unclear allocation procedures, and lack of blinding. The benefits of CBT for individuals with fully or partially remitted BD 1 or BD 2 outweighed the potential harm. Patient values and preferences varied because some individuals do

[c] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: https://www.healthquality.va.gov/.

not want to participate in therapy because of the time commitment. Thus, the Work Group made the following recommendation: For individuals with fully or partially remitted bipolar disorder and with residual anxiety symptoms, we suggest cognitive behavioral therapy.

X. Research Priorities

During the development of this CPG, the Work Group identified areas in which well-designed studies, preferably in the populations of interest (active duty military and Veteran), are needed. Most of the RCTs of pharmacological treatments for BD that make up the data in this CPG are industry sponsored with the goal of obtaining regulatory approval for marketing, rather than with the goal of understanding which treatments are most helpful for patients. Therefore, a need exists to complement these studies with additional research into the effectiveness of treatments not funded by organizations with a financial interest in the outcomes of those studies. More studies are needed on BD, especially on depression in BD, because much of the research focuses on MDD. BD is understudied relative to other psychiatric illnesses, including MDD, PTSD, and psychotic disorders such as schizophrenia. Needed studies encompass areas requiring stronger evidence to support current recommendations as well as research exploring new ideas to guide future CPGs. After assessing the currently available evidence, the Work Group identified the following important topics for future research.

A. Screening and Evaluation

- Studies assessing costs and benefits of screening for BD in the general population and various clinical settings, including study of the use of BD screening instruments in underrepresented populations, including individuals with childbearing potential, individuals of color, and those with histories of trauma
- Studies assessing what specific scales are valid and reliable for monitoring symptoms in BD
- Studies of the effectiveness of measurement-based care for BD, connecting clinical outcomes, outcome measures, and the best frequency of measurements to improve patient outcomes regarding BD
- Studies evaluating the impact of other interventions for self-monitoring, structured monitoring, and in- and outside-office measurement on BD symptoms, to include studies among Veteran and active-duty populations

B. Pharmacotherapy

a. Acute Mania

- Studies that help determine whether tracking blood levels is useful to inform decision making about dosing of medications in different phases of illness, including for lithium, valproate, and lamotrigine

b. Acute Bipolar Depression

- More well-designed clinical trials on treatments for bipolar depression to determine whether there is a difference in efficacy for BD 1 versus BD 2 depression
- More well-designed clinical trials on the use of standard antidepressants in BD (They are among the medications used most commonly by providers for individuals with BD, yet little is known about their safety and efficacy in BD, and specifically in BD 2.)
- Studies assessing the use of rapid acting therapeutics, such as ketamine and esketamine, in large clinical trials, including subjects with BD 1 and BD 2

c. Prevention of Recurrence of Mania and Depression

- Maintenance trials of recently approved medications for the acute treatment of bipolar depression to determine which medications might be preferably initiated acutely (Depression in BD tends to be both long lasting and recurrent. The efficacy of maintenance treatments in BD 2 are understudied, and there are no FDA-approved maintenance treatments for this condition.)
- Studies assessing the long-term effects of medications on morbidity and mortality, considering the differences in metabolic effects of drugs
- Studies of lithium, with the same rigor of study design as for drugs studied by commercial entities, without the bias of study design intended to benefit the commercial compounds

d. Other Priorities

- Studies of deprescribing of polypharmacy in BD (Polypharmacy is common, with a high number of drugs used concurrently without systematic evidence that it is effective or safe.)
- Treatment studies conducted in older populations with bipolar disorder

C. Somatic Therapy

- Research to determine the specific stimulation methods most effective in treating BD and preventing recurrences

D. Psychosocial and Recovery-Oriented Therapy

a. Psychotherapy

- More research on interventions to improve motivation and engagement in BD treatment
- More mood-phase specific psychotherapies in BD
- Research to further delineate the relative benefits of group versus individual formats for BD psychotherapies (Group settings, particularly for psychoeducation, might be more cost effective than one-on-one formats.)

- More research to guide real world implementation of these psychotherapies in busy clinics

b. Technology-Based Care

- Research on technology-assisted care and assessment in individuals with BD
- Studies on the effectiveness of mobile applications to improve treatment outcomes in BD
- Research on possible gender or other demographic differences in the use of mobile applications among individuals with BD
- Research on duration and frequency of mobile application use among individuals with BD
- Research on the impact of language differences and barriers in subpopulations on the use of mobile applications among individuals with BD

E. Supportive Care and Models of Care

a. Supportive Care

- More studies on peer support among individuals with BD, especially in the U.S. (This research could investigate literature on “circles of support” in Canada.)

b. Models of Care and Care Delivery

- More research on resource burden and relationship between the load on the health system and on the caregiver helping individuals with BD
- Research examining the mechanisms by which collaborative care might impact clinical outcomes for individuals with BD (This research might include examining the ideal frequency of patient and provider contact in the context of collaborative models of care.)

F. Co-occurring Conditions

- Research assessing safety as it pertains to suicide risk for varenicline for smoking cessation among individuals with BD, especially in people who are at high risk for suicide at baseline
- Studies assessing behavioral health interventions for smoking cessation among individuals with BD, with and without pharmacotherapies or somatic treatments
- Research to determine whether individuals with BD and co-occurring SUDs can receive and respond to the same treatments used for SUD alone (Do the drugs treating BD have the same efficacy and safety if the patient has SUDs?)
- Studies on the safety of stimulants for co-occurring attention-deficit/hyperactivity disorder (ADHD) with regard to the risk of mania or increased episode cycling in individuals with BD or schizoaffective disorder

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 20 key questions (KQ) on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 lists and describes the PICOTS elements.

Table A-1. PICOTS (222)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition or conditions, populations or sub-populations, disease severity or stage, co-occurring conditions and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic or screening test or both used with the patient or population.
Comparator	Treatment or treatments (e.g., placebo, different drugs) or approach or approaches (e.g., different dose, different frequency, standard of care) being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting; QoL: quality of life

Because of resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 20 highest priority KQs for inclusion in the systematic evidence review (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1–9 scale (7–9, critical for decision making; 4–6, important, but not critical, for decision making; and 1–3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Populations

- Key Question 1
    - Including: Adults being screened for BD, adults who screened positive being assessed for a BD diagnosis

- Key Question 2
  - Including: Adults treated with antidepressants for MDD
- Key Questions 3–8, 10, 16, 17, 19, 20
  - Including: Adults (age 18 and older) treated with any diagnosis covered within “bipolar and related disorders” of the DSM-5
- Key Question 9
  - Including: Pregnant adults and adults of childbearing potential, postpartum, or lactating from the standard population
- Key Question 11
  - Including: Adults with a co-occurring condition from the standard population
    - Chronic insomnia not part of other co-occurring conditions
    - ADHD
    - Borderline personality disorder
    - SUD (AUDs, OUDs, stimulant use disorders, other drug use disorders, recreational or medical use of cannabis, use of hallucinogens)
    - OCD
    - PTSD
    - Anxiety disorders
    - TBI
- Key Question 12
  - Including: Adults with SUDs from the standard population
    - AUDs
    - OUDs
    - Stimulant use disorders
    - Other drug use disorders
    - Cannabis and hallucinogens recreational use
    - Tobacco use disorder
- Key Question 13
  - Including: Adults with ADHD from the standard population
- Key Question 14
  - Including: Adults with anxiety disorders from the standard population

- Key Question 15
  - Including: Individuals on pharmacotherapy or considering pharmacotherapy from the standard population
- Key Question 18
  - Including: Adults with chronic insomnia from the standard population

b. Interventions

- Key Questions 1 and 2
  - Rapid Mood Screener (6 items)
  - Altman Self Rating Mania Scale (5 items)
  - Bech-Rafaelsen Mania Rating Scale
  - Bipolar Inventory of Symptoms Scale
  - BSDS
  - Clinical Monitoring Form
  - Clinically Useful Depression Outcome Scale with questions for the DSM-5 mixed features specifier (CUDOS-M)
  - HAM-D (5 items)
  - HCL-32 (Hypomania Checklist)
  - HCL-33 (Hypomania Checklist)
  - ISS
  - MDQ
  - Mini-International Neuropsychiatric Interview
  - Montgomery-Asberg Depression Rating Scale
  - Patient Health Questionnaire-2 (PHQ-2)
  - PHQ-9
  - Patient Mania Questionnaire
  - Quick Inventory of Depressive Symptoms
  - Scale for the Assessment of Episodes in BD
  - Structured clinical interview for DSM
  - YMRS
- Key Question 3
  - Measurement-based care
    - In-office measurement
    - Self-monitoring

        - Structured monitoring
    - List of assessments that would inform patient care
        - 12-Item Short Form Survey
        - 36-Item Short Form Survey
        - ISS
        - Veterans RAND 12-Item Health Survey
- Key Question 4
    - Synchronous or asynchronous technology-based interventions
        - Computer- or web-based interventions
        - Hybrid telehealth and in-person
        - Mobile apps (to include apps related to sleep)
        - Telephone interventions
        - Use of apps or technological approaches (without clinical monitoring)
        - Video call interventions
- Key Question 5
    - Models of medical care/care systems
        - ACT
        - Care management model
        - Caregiver support program
        - Collaborative care model, chronic care model, collaborative chronic care model
        - Coordinated specialty care
        - Health coaching
        - Integrated care
        - Intensive Community Mental Health Recovery (ICMHR) - formerly known as Mental Health Intensive Case Management
        - Patient-Aligned Care Team
        - Patient-Centered Medical Home
        - Personalized case management services
        - Whole health approach

- Key Questions 6, 8, and 15
  - Drug classes
    - Anticonvulsants/antiepileptics
    - Antidepressants (including SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRI], TCAs)
    - Antipsychotics
    - Calcium channel blockers
    - Cannabinoids
    - LAIs
    - Mood stabilizers/antimanic agents
    - Tranquilizers/antipsychotic agents (neuroleptic agents)
  - Specific agents
    - Amfebutamone
    - Amitriptyline
    - Amoxapine
    - Aripiprazole
    - Asenapine
    - Brexpiprazole
    - Bupropion
    - Carbamazepine
    - Cariprazine
    - Chlorpromazine
    - Citalopram
    - Clomipramine
    - Clonazepam
    - Clozapine
    - Desipramine
    - Desvenlafaxine
    - Diazepam
    - Doxepin
    - Duloxetine
    - Escitalopram
    - Fluoxetine

- Fluphenazine
- Fluvoxamine
- Gabapentin
- Haloperidol
- Iloperidone
- Imipramine
- Isradipine
- Ketamine
- Lamotrigine
- Levomilnacipran
- Lithium
- Lorazepam
- Loxapine
- Lumateperone
- Lurasidone
- Milnacipran
- Mirtazapine
- Molindone
- Nimodipine
- Nortriptyline
- Olanzapine
- Olanzapine and fluoxetine
- Olanzapine and samidorphan
- Oxcarbazepine
- Paliperidone
- Paroxetine
- Perphenazine
- Pimozide
- Pregabalin
- Protriptyline
- Psilocybin
- Quetiapine

        - Risperidone
        - Samidorphan
        - Sertraline
        - Tetrahydrocannabinol
        - Thioridazine
        - Thiothixene
        - Trifluoperazine
        - Trimipramine
        - Valproate
        - Valproic acid
        - Venlafaxine
        - Verapamil
        - Ziprasidone
- Key Question 7
    - Same list as in KQ 6, with the following additional drugs
        - Treatments for ADHD: dexamphetamine, dexmethylphenidate, dextroamphetamine and amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate
        - Treatments for narcolepsy: amphetamine, armodafinil, modafinil, oxybate sodium, pitolisant, sodium oxybate, solriamfetol
        - Amphetamine and related products
        - Antiparkinson agents
        - Atomoxetine
        - Dopamine agonists
        - Isocarboxazid
        - Maprotiline
        - Methylphenidate and related products
        - Moclobemide
        - Nefazodone
        - Phenelzine
        - Selegiline
        - Tranylcypromine
        - Trazodone

        - Vilazodone
        - Vortioxetine
- Key Question 9
    - Pharmacotherapies (same list as in KQ 6)
    - Somatic therapies (same list as in KQ 10)
- Key Question 10
    - Pharmacotherapy (same list as in KQ 6) plus somatic interventions
        - Bright light therapy
        - Deep brain stimulation
        - ECT
        - Transcranial magnetic stimulation
        - Vagus nerve stimulation
- Key Question 11
    - Evidence-based psychotherapy, psychosocial interventions, and pharmacotherapy for BD (see earlier KQs)
- Key Question 12
    - Psychotherapies for SUD (same list as in KQ 16)
        - Participation in 12-step programs
        - Seeking Safety for comorbid PTSD and SUD
    - Integrated care
    - AUD
        - Acamprosate
        - Carbamazepine
        - Disulfiram
        - Divalproex sodium
        - Gabapentin
        - Lamotrigine
        - Naltrexone
        - Topiramate
    - OUD
        - Buprenorphine
        - Methadone
        - Naltrexone

    - Stimulant use disorder
        - Citicoline
        - Disulfiram
        - Naltrexone/bupropion
        - Topiramate
    - Tobacco use disorder
        - Bupropion
        - E-cigarettes
        - NRT
        - Varenicline
- Key Question 13
    - Psychotherapies for ADHD (same list as in KQ 16)
    - Pharmacotherapies:
        - Amphetamines
        - Atomoxetine
        - Bupropion
        - Clonidine
        - Dexmethylphenidate
        - Dextroamphetamine
        - Dextroamphetamine and amphetamine
        - Guanfacine
        - Lisdexamfetamine
        - Methylphenidate
        - Nortriptyline
        - Venlafaxine
- Key Question 14
    - Psychotherapies for anxiety disorders (same list as in KQ 16)
    - Pharmacotherapies
        - Alprazolam
        - Buspirone
        - Citalopram
        - Clomipramine

    - Clonazepam
    - Diazepam
    - Duloxetine
    - Escitalopram
    - Fluoxetine
    - Fluvoxamine
    - Gabapentin
    - Hydroxyzine
    - Imipramine
    - Lorazepam
    - Mirtazapine
    - Paroxetine
    - Phenelzine
    - Pregabalin
    - Quetiapine
    - Sertraline
    - Venlafaxine
    - Ziprasidone
- Key Question 16
    - Combination psychotherapy and pharmacotherapy (see KQ 6 for list of pharmacotherapies)
    - Psychotherapies
        - Acceptance and Commitment Therapy
        - Adaptive strategies
        - Brief CBT
        - CBT
        - Cognitive remediation
        - Eye Movement Desensitization and Reprocessing
        - Family psychotherapy
        - Illness Management and Recovery
        - IPSRT
        - Jungian analysis
        - LGCC

        - Mindfulness-based therapy
        - Motivational interviewing
        - Psychodynamic psychotherapy
        - Psychoeducation
        - Social Skills Training
        - Supportive therapy
- Key Question 17
    - Community care
    - Compensated Work Therapy
    - Crisis support
    - Housing and Urban Development/Veterans Affairs Supported Housing
    - Multisystem treatment
    - Peer support programs
    - Supported employment
    - Supported housing
- Key Question 18
    - Treatment for sleep problem
        - Auricular acupuncture with seed and pellet
        - Brief behavioral treatment of insomnia
        - CBT for insomnia
        - Pharmacotherapy
            - Agomelatine
            - Diphenhydramine
            - Doxepin
            - Eszopiclone
            - Melatonin
            - Quetiapine
            - Ramelteon
            - Tasimelteon
            - Zaleplon
            - Zolpidem

- Key Question 19
  - Usual care plus
    - Acupuncture
    - Art therapy
    - Dance therapy
    - Meditation
    - Mindfulness
    - Music therapy
    - Relaxation
    - Stress management
    - Yoga/tai chi
- Key Question 20
  - Nutritional interventions
    - Anti-inflammatory diet
    - B vitamins (1, 6, and 12)
    - Fish oil
    - Folate
    - Grapefruit juice
    - Ketogenic diet
    - Magnesium
    - Mediterranean diet
    - Nutrient-rich versus nutrient-poor diet
    - PUFAs
    - Probiotics
    - SAMe
    - Specific foods to eat or avoid
    - Vitamin C
    - Vitamin D
    - Zinc

c. Comparators

- Key Question 1
  - Other screening tools/clinical assessment

- Key Question 2
  - Usual care or alternative monitoring/screening approach
- Key Question 3
  - Usual care
- Key Question 4
  - TAU, with or without professional peer support or coaching
  - Other virtual intervention
- Key Question 5
  - Usual care
  - Other models of care
- Key Question 6
  - Other pharmacotherapy, usual care, or placebo
- Key Question 7
  - Other pharmacotherapy, usual care, or placebo
- Key Question 8
  - Maintenance medication management
  - Alternative maintenance medication regimen
- Key Question 9
  - Other pharmacotherapy, usual care, or placebo
- Key Question 10
  - Pharmacotherapy alone
  - Pharmacotherapy plus sham intervention
  - Sham alone (i.e., sans pharmacotherapy)
- Key Question 11
  - Evidence-based psychotherapy, psychosocial interventions, and pharmacotherapy for BD (see earlier KQs) in the standard population without the co-occurring conditions of interest
- Key Question 12
  - Other treatments
  - TAU
- Key Question 13
  - Other treatments
  - TAU

- Key Question 14
  - Other treatments
  - TAU
- Key Question 15
  - Usual care
- Key Question 16
  - Single pharmacotherapy
  - Single psychotherapy
  - Combination
- Key Question 17
  - Usual care/no supported care intervention
- Key Question 18
  - Other treatments
  - TAU
- Key Question 19
  - Same usual care plus
    - Placebo, sham intervention, or both (if appropriate)
    - Active control
- Key Question 20
  - Usual care without nutritional intervention

d. Outcomes

- Key Question 1
  - Critical outcome
    - Diagnostic accuracy
  - Important outcomes
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - QoL/wellbeing
    - Functional status: vocational, social

        - Early treatment discontinuation for any reason (including medication adherence)
- Key Question 2
    - Critical outcomes
        - Diagnostic accuracy
        - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Important outcomes
        - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
        - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
        - QoL/wellbeing
        - Functional status: vocational, social
        - Early treatment discontinuation for any reason (including medication adherence)
- Key Questions 3, 4, 7, 8, 11, 16, and 20
    - Critical outcome
        - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Important outcomes
        - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
        - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
        - QoL/wellbeing
        - Functional status: vocational, social
        - Early treatment discontinuation for any reason (including medication adherence)
- Key Question 5
    - Critical outcome
        - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)

- Important outcomes
  - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
  - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
  - QoL/wellbeing
  - Early treatment discontinuation for any reason (including medication adherence)
  - Functional status: vocational, social
  - Adherence to USPTF or The Centers for Disease Control and Prevention (CDC) immunization recommendations

- Key Question 6
  - Critical outcome
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
  - Important outcomes
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - Other adverse events (e.g., excessive sedation, weight gain, diabetes, metabolic syndrome)
    - QoL/wellbeing
    - Functional status: vocational, social
    - Early treatment discontinuation for any reason (including medication adherence)

- Key Question 9
  - Critical outcomes
    - Pregnancy outcomes (e.g., teratogenicity, premature birth, abnormal birth weight, normal infant development, fetus health, childbirth, pregnancy, complications, congenital disorders)
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)

- Important outcomes
  - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
  - QoL/wellbeing
  - Functional status: vocational, social
  - Early treatment discontinuation for any reason (including medication adherence)

- Key Question 10
  - Critical outcomes
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
  - Important outcomes
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - QoL/wellbeing
    - Functional status: vocational, social
    - Early treatment discontinuation for any reason (including medication adherence)

- Key Question 12
  - Critical outcome
    - Changes in substance use
  - Important outcomes
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - Early treatment discontinuation for any reason (including medication adherence)
    - Functional status: vocational, social
    - QoL/wellbeing

- Key Question 13
  - Critical outcome
    - ADHD symptom change
  - Important outcomes
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Functional status: vocational, social
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - QoL/wellbeing
    - Early treatment discontinuation for any reason (including medication adherence)
- Key Question 14
  - Critical outcome
    - Anxiety disorders symptom change
  - Important outcome
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Functional status: vocational, social
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - QoL/wellbeing
    - Early treatment discontinuation for any reason (including medication adherence)
- Key Question 15
  - Critical outcomes
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)

    - Important outcomes
        - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
        - Early treatment discontinuation for any reason (including medication adherence)
        - Functional status: vocational, social
        - QoL/wellbeing
- Key Question 17
    - Critical outcome
        - Functional status: vocational, social
    - Important outcomes
        - QoL/wellbeing
        - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
        - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
        - Early treatment discontinuation for any reason (including medication adherence)
        - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
- Key Question 18
    - Critical outcome
        - Changes in sleep
    - Important outcomes
        - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
        - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
        - QoL/wellbeing
        - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)
        - Functional status: vocational, social
        - Early treatment discontinuation for any reason (including medication adherence)

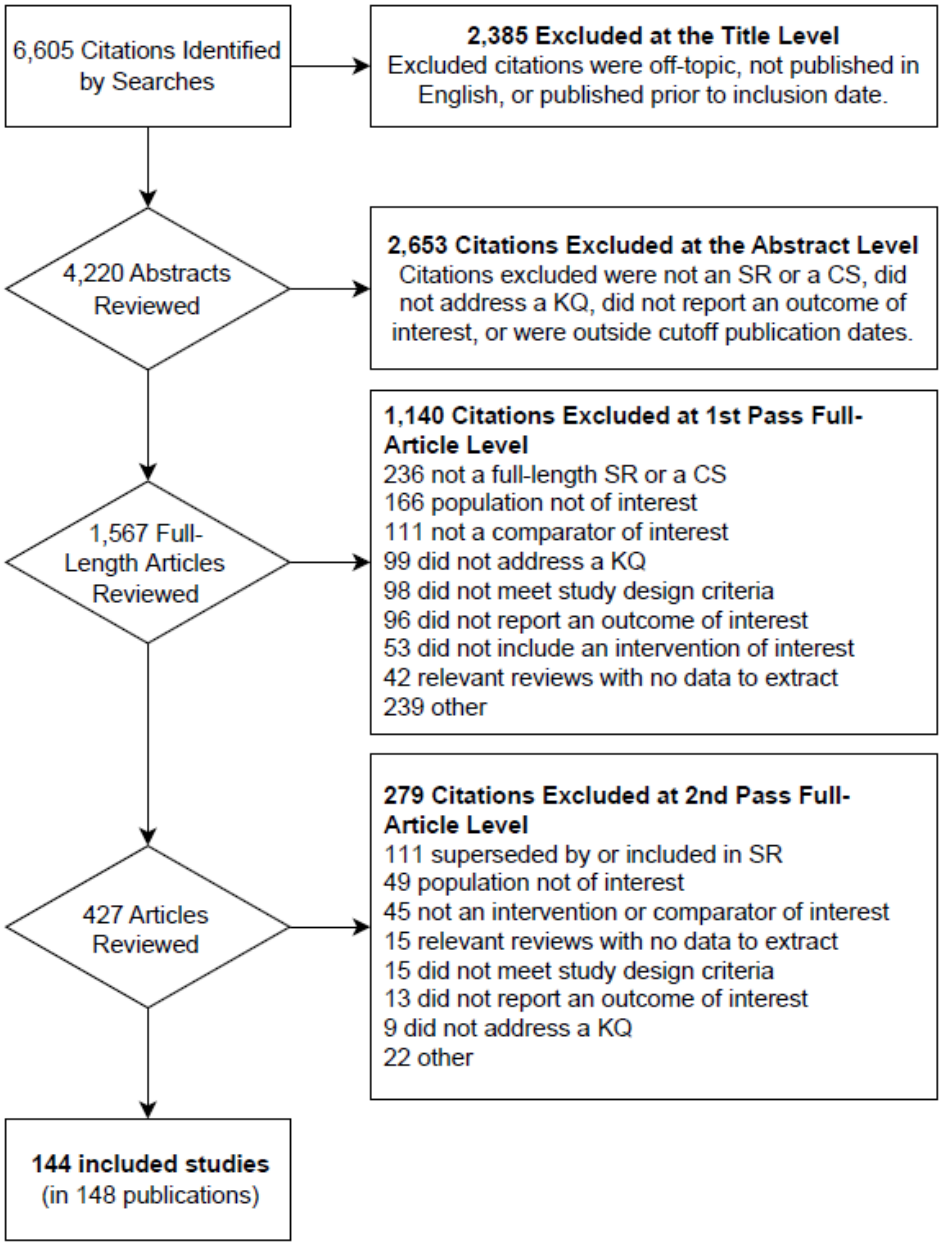
- Key Question 19
  - Critical outcome
    - QoL/wellbeing
  - Important outcomes
    - Bipolar symptom change (including manic and depressive episodes, mixed features specifier, recurrence, and remission)
    - Changes in self-harm (including suicide) and pretreatment levels of suicidal behaviors/ideations
    - Early treatment discontinuation for any reason (including medication adherence)
    - Functional status: vocational, social
    - Treatment-related serious adverse events (e.g., cardiac events, stroke, mortality, hospitalization)

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 6,605 citations identified by searches
    a. Right to Box 2: 2,385 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to the inclusion date.
    b. Down to Box 3
2. Box 3: 4,220 abstracts reviewed
    a. Right to Box 4: 2,653 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or a CS, did not address a KQ, did not report an outcome of interest, or were outside cutoff publication dates.
    b. Down to Box 5
3. Box 5: 1,567 full-length articles reviewed
    a. Right to Box 6: 1,140 citations excluded at 1st pass full-article level
        i. 236 not a full-length SR or a CS
        ii. 166 population not of interest
        iii. 111 not a comparator of interest
        iv. 99 did not address a KQ
        v. 98 did not meet study design criteria
        vi. 96 did not report an outcome of interest
        vii. 53 did not include an intervention of interest
        viii. 42 relevant reviews with no data to extract
        ix. 239 other
    b. Down to Box 7
4. Box 7: 427 articles reviewed
    a. Right to Box 8: 279 citations excluded at 2nd pass full-article level
        i. 111 superseded by or included in SR
        ii. 49 population not of interest
        iii. 45 not an intervention or comparator of interest
        iv. 15 relevant reviews with no data to extract
        v. 15 did not meet study design criteria
        vi. 13 did not report an outcome of interest
        vii. 9 did not address a KQ
        viii. 22 other

b. Down to Box 9

5. Box 9: 144 included studies (in 148 publications)

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	Who should be screened for BD, and what is the comparative effectiveness, accuracy, and clinical impact of available tools for screening for BD and for evaluating those who screen positive to establish a diagnosis?	4 SRs, 23 diagnostic cohort studies
2	For adults treated with antidepressants for major depressive disorder (MDD), is there evidence supporting specific screening and monitoring approaches to identify first episodes of mania/hypomania?	4 diagnostic cohort studies
3	For adults with BD or schizoaffective disorder, how does the use of treatment outcome measures affect treatment and patient outcomes? a) Which measures are most effective? b) What is the best frequency of measurements?	1 RCT
4	For adults with BD or schizoaffective disorder, what is the effectiveness, comparative effectiveness, and safety of virtual interventions, both synchronous or asynchronous (e.g., telephonic, video, or computer-based apps)?	1 SR, 9 RCTs
5	For adults with BD or schizoaffective disorder, what is the effectiveness, comparative effectiveness, and safety of team-based multi/interdisciplinary models of medical care/care systems for the management of BD and/or for providing general medical care?	10 RCTs (in 11 publications)
6	For adults with BD or schizoaffective disorder, what is the effectiveness, comparative effectiveness, and safety of pharmacotherapy (monotherapies and combination treatments) on patient outcomes for the management of acute manic or depressive episodes, and mixed features?	5 NMAs, 15 SRs, 15 RCTs (1 RCT appeared in 2 publications)
7	What is the risk and comparative risk of medications triggering a switch to manic episode, mixed features, and depressive episodes for a) BD 1, b) BD 2, c) other BDs, and d) schizoaffective disorder?	3 SRs, 3 RCTs
8	What is the effectiveness, comparative effectiveness, and safety of maintenance pharmacotherapy for preventing breakthrough manic or depressive episodes for adults with a) BD 1, b) BD 2, c) other BDs and d) schizoaffective disorder?	1 NMA, 4 SRs, 4 RCTs (the RCTs appeared in 7 publications)
9	During pregnancy, childbearing potential, postpartum, or lactation, what clinical and pregnancy outcomes are associated with pharmacotherapies and other somatic therapies for BD?	2 SRs
10	For adults with BD or schizoaffective disorder, what is the effectiveness, comparative effectiveness, and safety of specific somatic treatments either as monotherapy or as augmentation to pharmacotherapy?	3 SRs, 2 RCTs
11	For adults with BD or schizoaffective disorder, what is the impact of co-occurring conditions on the treatment outcomes for BD?	4 RCTs, 2 prospective cohort studies
12	For adults with BD or schizoaffective disorder and substance use disorder (SUD), what is the effectiveness, comparative effectiveness, and safety of treatments and treatment strategies for SUD?	3 SRs, 5 RCTs

KQ Number	KQ	Number and Study Type
13	For adults with BD or schizoaffective disorder and attention-deficit/hyperactivity disorder (ADHD), what is the effectiveness, comparative effectiveness, and safety of treatments and treatment strategies for ADHD?	0 studies
14	For adults with BD or schizoaffective disorder and anxiety disorders, what is the effectiveness, comparative effectiveness, and safety of treatments and treatment strategies for anxiety disorders?	2 SRs
15	For adults with BD or schizoaffective disorder, what is the effectiveness and safety of tracking blood levels to guide decision-making about dosing of medications?	0 studies
16	For adults with BD or schizoaffective disorder, what is the comparative effectiveness of pharmacotherapy alone, psychotherapy alone, and pharmacotherapy in combination with various forms of psychotherapy?	1 SR, 2 RCTs
17	For adults with BD or schizoaffective disorder, what is the effectiveness and safety of recovery-based rehabilitation and supported care programs?	4 RCTs
18	For adults with BD or schizoaffective disorder and chronic insomnia, what is the effectiveness, comparative effectiveness, and safety of treatments and treatment strategies for sleep problems not related to other co-occurring conditions?	2 SRs
19	For adults with BD or schizoaffective disorder, what is the effectiveness, comparative effectiveness, and safety of specific complementary and integrative health and other non-pharmacologic interventions?	3 RCTs
20	For adults with BD or schizoaffective disorder, what is the therapeutic benefit of various nutritional interventions in the prevention of manic and depressive episodes?	2 SRs, 5 RCTs
	Total Evidence Base	**144 studies (in 148 publications)**

Abbreviations: ADHD: attention deficit/hyperactivity disorder; BD: bipolar disorder; RCT: randomized controlled trial; SR: systematic review; SUD: substance use disorder

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs published on or after January 1, 2012, to December 31, 2021. If multiple SRs address a KQ, the most recent or comprehensive review or both were selected. SRs were supplemented with RCTs published subsequent to the SR.
- Studies must be published in English.
- Only full clinical studies or SRs were included; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- SRs must have searched MEDLINE or Excerpta Medica Database (EMBASE) for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such

as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the AHRQ). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. An existing review was not used as evidence if it was impossible to assess the overall quality of the evidence in the review.

- For all KQs except KQs 1 and 2, a prospective, RCT with an independent control group was required. Crossover trials were not included unless they reported data for the first phase of the study separately.
- In addition to RCTs and SRs, KQ 1 included observational diagnostic study designs that compared different assessment methods, tools, or both and their accuracy for screening and diagnosis of BD. KQ 2 included observational diagnostic study designs that compared different assessment methods for identifying first episodes of mania and hypomania in patients being treated with antidepressants for MDD.
- Studies must have enrolled at least 20 patients (10 per study group for treatment studies, 20 total patients for diagnostic or prognostic studies). Small sample size is associated with increased risk of bias, and small studies were downgraded in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm.
- Newer Cochrane reviews already take into account small sample size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, those data were not downgraded a second time.
- Studies must have enrolled at least 85% of patients who meet the study population criteria: adults (age 18 years and older) treated with any diagnosis covered within “bipolar and related disorders” of the DSM-5. For studies examining mixed patient populations, studies must enroll at least 85% of patients with the relevant condition.
- Studies must have reported at least one outcome of interest.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform, provider, or both can be found in Table A-3. See Appendix L for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform or Provider
Bibliographic Databases	EMBASE (Excerpta Medica) and MEDLINE	January 1, 2012, through December 31, 2021	Elsevier
	PsycINFO (for selected KQs)	January 1, 2012, through December 31, 2021	Ovid
	PubMed (in-process and Publisher records)	January 1, 2012, through December 31, 2021	NLM
Grey Literature	Agency for Healthcare Research and Quality (AHRQ)	January 1, 2012, through December 31, 2021	AHRQ
	U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	January 1, 2012, through December 31, 2021	VA

c. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(223)

Next, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, Defense Health Agency, the Lewin Team convened a four-day in-person recommendation development meeting from July 19–22, 2022, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains.(52) Information on each domain, questions to consider, and the resulting judgment can be found in Table A-4.

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include: *High*, *Moderate*, *Low*, or *Very Low*. These four ratings are a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(54, 55)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very Low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(52)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they might apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include *similar values*, *some variation*, or *large variation*. For instance, there might be *some variation* in patient values and preferences for a recommendation on the use of acupuncture because some patients might dislike needles. When patient values seem homogeneous, this domain might increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain might decrease a recommendation's strength. As part of this domain, the

Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix I).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain, for example, include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population might be geographically remote from an intervention (e.g., complex radiological equipment); a drug might be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	• Among the designated critical outcomes, what is the lowest quality of relevant evidence? • How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very Low
Balance of desirable and undesirable outcomes	• What is the magnitude of the anticipated desirable outcomes? • What is the magnitude of the anticipated undesirable outcomes? • Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	• Benefits outweigh harms/burdens • Benefits slightly outweigh harms/burdens • Benefits and harms/burdens are balanced • Harms/burdens slightly outweigh benefits • Harms/burdens outweigh benefits
Patient values and preferences	• What are the patients' values and preferences? • Are values and preferences similar across the target population? • Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• What are the costs per resource unit? • Is this intervention generally available? • What is the variability in resource requirements across the target population and settings? • Are the resources worth the expected net benefit from the recommendation? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 4. For this new CPG, all recommendations were categorized as *Reviewed, New-added* (see Recommendations). *Reviewed*, *New-added* recommendations are original, new recommendations based entirely on evidence included in the systematic evidence review.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG, as appropriate, to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, quick reference guide, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in May 2023.

Appendix B: Recovery Approach in an Outpatient Medical Setting

Before recovery-focused conversations begin in an outpatient medical setting, an individual seeking care might have other concerns that become barriers on the road to recovery. Identifying cultural concerns and dealing with stigma are components of barrier reduction.(224) Much of the literature related to recovery considers a more heterogenous population versus specifying BD.

A. Setting the Stage for Recovery

Building recovery into mental health care begins with observing the language used to identify a Service member or Veteran. The use of the term "patient" can denote the older medical model of care where the focus was on symptom management versus the whole person and the person's journey of recovery. Awareness of potentially stigmatizing experiences early in service can be a challenge Service members or Veterans face as they seek care in recovery. The context related to stigma in the military is especially unique.(225) Cultural needs related to mental health can exist within and outside military service.

B. Stigma in the Military

According to one study, almost 25% of non-deployed U.S. Army personnel met the criteria for a mental disorder.(225) Another report indicated that nearly 60% of Service members suffering from mental health problems do not seek help.(226) BD 1 (and BD 2 on a case-by-case basis) is considered a disqualifying medical condition that could impact military diagnosis and discharge.(35) For many Service members, identity and purpose are connected to their time in the military. Loss of connection because of the military-related medical discharge can bring about both shame and distress related to grief. Recognizing and addressing the emotional impact of a diagnosis should be supported both while in care and while transitioning out. Efforts to remove stigma and encourage Service members to seek care have been developed in the military. Encouraging Service members to continue needed care on discharge might also include discussions about their mission transitioning from the service and potential barriers they will encounter. Programs such as InTransition offer a supportive connection between the military and the next provider of mental health care.[a]

C. Hope Inspiring Settings and Relationships

Veterans and Service members recovering from mental health symptoms are likely to seek help from people and settings least likely to foster stigma. Psychoeducation about a diagnosis can provide Veterans and Service members with the opportunity to express concerns and ask questions. Service members have shared concerns about how they are identified as needing assistance, whether seeking care will impact their career, and how they are seen by their command and others. Peer specialists have been used in

[a] See information on InTransition Program, available at: https://veteran.com/intransition-program/.

recovery models in both VA and the community and can be seen in the transition from the start of care to completion of care. Peer specialists might be a part of the outreach that feeds the recovery process because speaking with a peer might be more comfortable than speaking to a professional (e.g., provider, therapist).

Feedback from Veterans regarding their choice to see a mental health specialist indicates that their choice most often involves recommendations from their PCP and sometimes from peers and family members. Occasionally, Veterans voice discomfort if the building they attend for mental health care displays the words “behavioral health” or “behavioral medicine” on its sign. The arrangement of the building lobby also makes a difference to a Veteran’s comfort level (e.g., allowing for seating where a Veteran’s back is not to a window or other individuals). For many Veterans, being able to check in for their appointment and having short wait times also adds to their comfort. Integrated primary care and behavioral health programs might produce less perceived stigma as mental health is treated as “part of” an individual’s whole health. During the appointment, a provider should use recovery language because it is more collaborative than patriarchal. The VHA’s group of mental health providers developed a language statement as part of a fluid and living document to address recovery in language.(227) It is important that providers ask the Veteran or Service member what the individual’s treatment goals are at the onset of mental health care and also throughout subsequent sessions. If possible, others identified as potential support systems should be included in the first visit to the mental health provider with the permission of the individual. Integration of whole health services and spiritual supports can help when the focus in care also includes overall wellbeing and meaning in life. SAMHSA has recognized housing as an element of recovery; therefore, identified resources for housing might be needed.(42)

D. Development of a Recovery Plan

Development of a person-centered recovery plan should center on goals identified by the individual being served. It is necessary, within a recovery-oriented framework, to return to the “organic whole of the person” and the individual’s ongoing life. Identifying the individual’s strengths, supportive community (e.g., family, friends, spiritual, leisure), and internal purpose, values, and mission can put the focus back on the individual managing their life, with mental health care as an adjunct to offering assistance. Immediate involvement of families or other supports also can enhance outcomes. Frequency of care is a balance between what is necessary to provide clinical assistance and the individual’s availability. Frequency of care should be addressed in a recovery plan with the individual being served. Timeliness of care is reported to have been a determinative factor in the engagement of services. Models of care supporting the development of structure in life for individuals in recovery might also consider whole health activities to nurture balance. Adherence enhancement customized for the individual, such as the use of customized adherence engagement (CAE), might be helpful for individuals struggling with medication adherence. Individuals engaged in CAE might use this tool to stay on medication and remain in open communication with the

medication provider. Prevention planning with an individual acknowledges that, in dealing with BD, times might occur when the balance between a healthy life and mental illness is lost. Addressing risk can be as much a part of the planning process as it is during the diagnostic process. Risk for individuals with BD is frequently considered as suicide risk or accidental self-harm through drug or alcohol use. Additional risks include changes in relationships, loss of housing or a job, significant decline in health, adversarial relationships with the legal system, or any perceived risks by the individual.

Individuals with BD might choose to use non-traditional approaches to care, including avoidance of synthetic medications, dietary changes, use of supplements, or homeopathic remedies. The individual in recovery is the true owner of their recovery plan, and it is up to their discretion who is involved in their recovery and the approach that they choose to follow. SAMHSA identified 14 domains of recovery subsequently adapted to PRRC outcome measures in VA. Although not specific to BD, the domains are connected to recovery.(228) Consideration should be given to the documentation of recovery in a Service member's or Veteran's medical chart. Difficulties should be noted with the availability of diagnostic or coding changes to reflect accomplishment of the Service member's or Veteran's gains.

Appendix C: Additional Educational Materials and Resources

Table C-1. Reference Guide for Providers, Veterans, and Families: Accessing Mental Health Services for Bipolar Disorder

Category	Questions or Mental Health Need	Mental Health Reference Materials and Websites to Learn More
Education	Do I need help?	Determine how BD symptoms impact daily living https://www.nimh.nih.gov/health/publications/my-mental-health-do-i-need-help?utm_campaign=shareNIMH&utm_medium=Portal&utm_source=NIMHwebsite
	Diagnosis and Treatment Can Help	Overview of BD: diagnosis, symptoms, risk factors, and treatments https://www.nimh.nih.gov/health/topics/bipolar-disorder?utm_campaign=shareNIMH&utm_medium=Portal&utm_source=NIMHwebsite
	Coping with BD	Help yourself manage BD and provide information for family and friends https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder/Support
	Veterans Seeking Help with BD: Overview and Treatments	Information about BD and seeking care at VA https://www.mentalhealth.va.gov/mentalhealth/bipolar/index.asp
	VA VISN 5 MIRECC	Mission is to maximize the recovery and community functioning of Veterans with SMIs https://www.mirecc.va.gov/visn5/
	VA VISN 22 MIRECC	Improve the long-term functional outcome of Veterans with psychotic mental disorders https://www.mirecc.va.gov/visn22/
Treatments	Treatments for BD	BD psychotherapy and medications https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder/Treatment
	Evidence-Based Treatments for BD	Treatments for BD and seeking care in VA https://www.mentalhealth.va.gov/bipolar/treatment.asp
	Find a TRICARE Provider or Treatment Facility	Finding treatment options for Service members https://tricare.mil/ https://www.tricare.mil/mtf/
Screening Tools	Online BD Screening Tools	Take a BD test https://screening.mhanational.org/screening-tools/bipolar/?ref

Category	Questions or Mental Health Need	Mental Health Reference Materials and Websites to Learn More
Support Groups and Online Help	Online Support Groups for BD	Help locate an online support group https://www.dbsalliance.org/support/chapters-and-support-groups/online-support-groups/ https://www.dbsalliance.org/support/chapters-and-support-groups/find-a-support-group/
	Parent Support Community	Online support community for parents and caregivers of those with BD https://community.dbsalliance.org/
	Ask a Doc about BD	Ask a mental health provider your questions online https://www.dbsalliance.org/education/ask-the-doc/?filter=bipolar-disorder
	Free, Online Problem-Solving Therapy	Online treatment to help with problem solving https://www.veterantraining.va.gov/movingforward/
Hotline	Military/Veteran Crisis Line	Acute care for Veterans, Service members, and civilians Veterans' Crisis Line (988 or 1-800-273-8255, option 1; text 838255; online chat: https://www.veteranscrisisline.net/get-help-now/chat/) National Suicide Prevention Lifeline (988 or 1-800-273-8255) https://mhanational.org/crisisresources

Abbreviations: BD: bipolar disorder; MIRECC: Mental Illness Research, Education, and Clinical Center; SMI: serious mental illness; VA: Department of Veterans Affairs; VISN: Veterans Integrated Services Network

Appendix D: Strategies that Promote Engagement of Family and Other Support

Rationale for Including Family Members in Treatment. Mental illness affects the whole family. Family services teach families to work together toward recovery. With family service interventions, families attend educational sessions where they learn basic facts about mental illness, coping skills, communication skills, problem-solving skills, and ways to work with one another toward recovery. Individuals who participate in family interventions experience fewer psychiatric symptoms and relapses, improved treatment adherence, and improved family functioning. Family members also benefit and report feeling more satisfied with their relationship and less burden.

When to Consider Involving Family Members. Providers should consider involving family members in care for any Veteran or Service member who relapses frequently, is at risk for relapse, experiences persistently exacerbated symptoms, or is at a transitional point in life and needs social support. Family involvement should also be considered for any family member who needs education or support or who makes frequent contact with treatment teams because of concerns about the Veteran or Service member. Contraindications to family involvement might include abuse, trauma, divorce, custody, inheritance, and financial support. Individual circumstances surrounding sensitive clinical and legal issues should be carefully explored to avoid potential damage to, or exploitation of, the Veteran or Service member.

When collaborating with family members, consider the following target areas.

1. **Understanding the patient's psychiatric diagnosis.** For many family members, this experience might be their first exposure to their loved one's diagnosis. Taking the time to explain the individual's diagnosis and address any false ideas or beliefs about both the diagnosis and mental health, in general, can be beneficial in encouraging family members' engagement.
2. **Setting realistic goals.** It is imperative that the individual, loved ones, and clinical team are on the same page regarding treatment outcomes. Setting realistic goals about what is achievable through treatment is essential for ensuring collaboration among all parties. It can also help assess both the individual's and the family's understanding of the diagnosis.
3. **Supporting recovery.** One of the most common questions family members have when caring for someone with a mental illness is, "What can I do to help support my loved one?" Although this question is often directed at the provider, it is essential to involve the individual in recovery in this conversation, as well, to ensure buy-in from all parties.
4. **Preparing for a crisis.** Unfortunately, most psychiatric illnesses follow a relapsing and remitting course. Although the goal of treatment is to work toward long-term stability, the reality is that many individuals experience an exacerbation

of symptoms requiring acute intervention. Preparing for these situations is crucial and should be a fundamental part of the treatment discussion with family members. We recommend the following.

a. **Learning to recognize the early symptoms and potential triggers (e.g., substance use, poor sleep, mood changes).**

b. **Developing a Wellness Recovery Action Plan.** This planning can include phone numbers of health care providers, a record of the individual's relevant medical and psychiatric history, and a list of current medications. Further recommendations for developing such a plan can be found here: https://www.wellnessrecoveryactionplan.com/.

c. **Considering a psychiatric advanced directive or conservatorship.** Psychiatric advanced directives, although recognized in only 25 states, can provide individuals with autonomy in dictating their preferences for future mental health treatment. Additional information about developing psychiatric advanced directives can be found here: https://nrc-pad.org/getting-started/. Additionally, for individuals who have difficulty caring for themselves or managing their affairs because of a serious mental health condition, family members might consider petitioning for a mental health conservatorship. Laws regarding conservatorship vary by state, though information can typically be found through the state's Department of Mental Health.

d. **Calling 911 during a mental health emergency.** Many family members are concerned for both their safety and the safety of their loved ones should the police be needed for an acute mental health emergency. The National Alliance on Mental Illness (NAMI) provides tips and information about how to communicate with emergency responders should their loved ones be in crisis: https://www.nami.org/Your-Journey/Family-Members-and-Caregivers/Calling-911-and-Talking-with-Police.

5. **Supporting family member wellness.** To ensure quality support from family members, it is crucial that family members take care of themselves, as well. Discussing the concept of caregiver fatigue can help normalize what family members might experience while caring for their loved ones. Encouraging family members to develop their own support systems (to include family, friends, and support groups) and to address their own physical and mental health concerns are of utmost importance.

Important to note that not all Veterans or Service members will have family support or will be comfortable with the treatment team coordinating with their family. In these cases, the provider should work with the individual to determine whether there are other sources of support (e.g., friends, caregivers, guardians) who could be included in these discussions. There might still be benefit to providing basic psychoeducation to support persons if the individual chooses not to share personal medical information with them.

Range of Family Services. A range of family programs is available to fit the specific needs of each family. Some families benefit from just a few sessions, although more intensive services are especially helpful for families experiencing high levels of stress and tension and for individuals who are chronically symptomatic or prone to relapse. Providers are encouraged to consider a continuum of care in deciding how family members can be integrated into treatment.

Engaging family members in care begins with the Veteran or Service member. Motivational interviewing techniques can be used to engage Veteran and Service members in family services by exploring the role they want their family to play in their recovery and their preferences regarding family participation. This engagement handout was designed to engage Veterans in Behavioral Family Therapy (BFT), but it can be used to engage Veterans in any type of family service: https://www.mirecc.va.gov/visn22/familyconsultation_veteran_engagement.pdf.

Veteran-Centered Brief Family Consultation (VCBFC) is a brief intervention designed to integrate the Veteran's family, chosen supports, or both into their recovery process. The intervention is typically 1–3 sessions with a maximum of 5 sessions. Family Consultation can also be used as the first step in assessment or treatment planning when considering more intensive family therapies, such as BFT. Resources to implement VCBFC into clinical practice, including assessment, education, skills training, and other intervention handouts, can be found at https://www.mirecc.va.gov/visn22/Veteran_Centered_Brief_Family_Consultation.asp.

Training in VCBFC is available on the Talent Management System (Course #37314) and is approved for four continuing education units for most licensed mental health professionals. Those who do not need continuing education units can request an instructional DVD/CD set at https://www.mirecc.va.gov/visn22/Veteran_Centered_Family_Consultation_DVD.asp.

Behavioral Family Therapy is for families with greater needs. Sessions are focused on family education, communication skills training, and problem-solving skills training. BFT generally lasts 6–9 months and can be conducted in single-family or multi-family formats. An instructional DVD/CD set is available at https://www.mirecc.va.gov/visn22/Behavioral_Family_Therapy_DVD.asp.

Coaching into Care is a free service for families and friends of Veterans. Responders will briefly assess concerns and provide appropriate resources and referrals. Through 10–30-minute calls, licensed psychologists and social workers offer guidance and help for starting conversations with a Veteran about their mental health or substance use and motivating them to seek treatment if it is needed. Family and friends can call 888-823-7458. More information is available at https://www.mirecc.va.gov/coaching/.

NAMI Family-to-Family is a free, 8-session educational program for families, significant others, and friends of individuals with mental health conditions. Led by a NAMI-trained

family member, sessions include presentations, discussions, and exercises pertinent to managing a psychiatric illness successfully. More information is available at https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Family-to-Family.

NAMI Homefront is a free, 6-session educational program for families, caregivers, and friends of military Service members and Veterans with mental health conditions. It is based on the NAMI Family-to-Family program but is designed to address the unique needs of families, caregivers, and friends of those who have served or are currently serving. More information is available at https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Homefront.

Support and Family Education Model (SAFE) is a 10-session family education program for people who care about someone living with mental illness or PTSD. The treatment manual and implementation tools are available at https://www.ouhsc.edu/safeprogram/.

SAMHSA Family Psychoeducation Evidence-Based Practices Toolkit offers evidence-based practices to help public officials develop family psychoeducation mental health programs. The kit can be found at https://store.samhsa.gov/product/Family-Psychoeducation-Evidence-Based-Practices-EBP-KIT/SMA09-4422.

Appendix E: Pharmacotherapy

Table E-1. Medications for Bipolar Disorder, Oral Dosing and Dosage Forms (229-234)

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Aripiprazole	T: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg ODT: 10 mg, 15 mg S: 1mg/ml LAI (Maintena): 300 mg, 400 mg	Acute mania treatment: 15 mg once daily	30 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	Dose adjustment warranted in patients who are CYP2D6 poor metabolizers or taking medications that inhibit or induce CYP3A4. Lacks evidence for acute bipolar depression and preventing recurrence of mania and bipolar depression.
Asenapine	ST: 2.5 mg 5 mg 10 mg TD: 3.8 mg/24 hours, 5.7 mg/24 hours, 7.6 mg/24 hours	Acute mania and maintenance treatment: 5–10 mg twice daily (ST)	10 mg twice daily (ST)	No adjustment necessary	No adjustment necessary	No adjustment necessary (Child-Pugh A or B) Contraindicated (Child-Pugh C)	Patients may not eat or drink for 10 minutes following sublingual administration. Lacks evidence for acute bipolar depression and preventing recurrence of mania and depression.
Carbamazepine	CR: 100 mg, 200 mg, 300 mg SU: 100 mg/5 ml T: 200 mg ET: 100 mg, 200 mg, 400 mg CT: 100 mg	Acute mania: 100–400 mg/day in 2–4 divided doses	1.6 g/day	Initiate at lower end of dosing range.	No adjustment necessary	Use caution; consider dose reduction.	Lacks evidence for acute bipolar depression and preventing recurrence of mania and depression.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Cariprazine	CA: 1.5 mg, 3 mg, 4.5 mg, 6 mg	Acute mania and depression: 1.5 mg once daily	Acute mania: 6 mg/day Depression: 3 mg once daily	Initiate at lower end of dosing range.	No adjustment necessary (CrCl. ≥30 ml/min) Not recommended (CrCl <30 ml/min)	No adjustment necessary (Child-Pugh A or B) Not recommended (Child-Pugh C)	Lacks evidence for preventing recurrence of mania and bipolar depression.
Divalproex Sodium	CA: 250 mg CS: 125 mg S: 250 mg/5 ml IV: 100 mg/ml TDR: 125 mg, 250 mg, 500 mg ET: 250 mg, 500 mg	Acute mania: 750 mg/day in divided doses	60 mg/kg/day	Initiate at lower end of dosing range.	No adjustment necessary	Not recommended (Child-Pugh A or B) Contraindicated (Child-Pugh C)	Lacks evidence for acute bipolar depression and preventing recurrence of mania and depression. Serum levels may help guide dosing, dosed to a clinical response with a trough plasma concentration between 50 and 125 mcg/mL for acute mania.
Haloperidol	T: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg CO: 2 mg/mL I (short acting): 5 mg/mL LAI: 50 mg/mL, 100 mg/mL	Acute mania: 2–15 mg/day in 1–2 divided doses	20 mg/day	Initiate at 0.5 to 2 mg 2–3 times daily.	No adjustment necessary	Use caution	Lacks evidence for preventing recurrence of mania and depression.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Lamotrigine	T: 25 mg, 100 mg, 150 mg, 200 mg ET: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg CDT: 5 mg, 10 mg, 25 mg ODT: 25 mg, 50 mg, 100 mg, 200 mg	Bipolar depression: 25 mg every other day –50 mg/day depending on concomitant medications	400 mg/day	Initiate at lower end of dosing range.	No adjustment necessary	No dosage adjustment (Child-Pugh A) Reduce initial and maintenance dose by 25% (Child-Pugh B and C) without ascites. Reduce initial and maintenance dose by 50% (Child-Pugh B and C) with ascites.	Not beneficial for acute mania or acute bipolar depression. Effective in preventing recurrences of bipolar depression.
Lithium	T: 300 mg CA: 150 mg, 300 mg, 600 mg ET: 300 mg, 450 mg S: 8mEq (300 mg)/5 ml	Acute mania: 600–900 mg in 2–3 divided doses, then switch to once daily at bedtime	1,800 mg/day	Refer to adult dosing; usually require lower doses because of age-related reduction in GFR	No adjustment for CrCl ≥60 ml/min; initiate lower dose for CrCl 30-<60 ml/min; avoid for CrCl <30 ml/min.	No adjustment necessary	Beneficial in preventing recurrence of manic and depressed episodes. Use serum levels to guide dosing; optimal maintenance dose is 0.6–0.8 mEq/L. Acute treatment may go higher, but levels over 1.0 mEq/L are associated with higher risk of eventual kidney harm and should be avoided, if possible. Serum levels should be obtained 11–14 hours after last dose.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Lumateperone	CA: 10.5 mg, 21 mg, 42 mg	Bipolar depression: 10.5–42 mg once daily, depending on concomitant medications	42 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary (Child-Pugh A) Avoid use (Child-Pugh B and C)	Avoid concomitant use with CYP3A4 inducers. Lacks evidence for preventing recurrence of bipolar depression.
Lurasidone	T: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg	Bipolar depression: 20 mg once daily	120 mg/day	No adjustment necessary	No adjustment necessary for CrCl ≥50 ml/min) 20 mg once daily (CrCl <50 ml/min)	No adjustment necessary (Child-Pugh A) 20 mg daily initial, 80 mg max (Child-Pugh B or C)	Take within 30 minutes of food (>350 calories). Lacks evidence for preventing recurrence of bipolar depression.
Olanzapine	T: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg ODT: 5 mg, 10 mg, 15 mg, 20 mg I (short acting): 5 mg/mL each vial contains 10 mg LAI: 210 mg, 300 mg, 405 mg	Acute mania and depression: 5–15 mg once daily	20 mg/day	No adjustment necessary	No adjustment necessary	No adjustment necessary	Use of parenteral benzodiazepines with short-acting IM olanzapine is not recommended. Long-acting dosage form associated with post-injection delirium/sedation syndrome. Beneficial in preventing recurrence of both manic and depressive episodes.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Paliperidone	ET: 1.5 mg, 3 mg, 6 mg, 9 mg 1-Month Injection (PP1M): 39 mg, 78 mg, 117 mg, 156 mg, 234 mg 3-Month Injection (PP3M): 273 mg, 410 mg, 546 mg, 819 mg 6-Month Injection (PP6M): 1,092 mg, 1,560 mg	Acute mania: 6 mg once daily	12 mg/day	No adjustment necessary (normal renal function) 3 mg max for CrCl 10-<50ml/min	3 mg once daily initial, 6 mg max for CrCl 50–79 ml/min; 1.5 mg initial, 3 mg max for CrCl 10–49 ml/min; not recommended for CrCl <10 ml/min. PP1M and PP3M: not recommended (CrCl < 50 mL/min); PP6M: not recommended (CrCl <90 mL/min)	No adjustment necessary	Beneficial in preventing recurrence of manic episodes.
Quetiapine	T: 25mg, 50mg, 100mg, 150mg, 200mg, 300 mg, 400 mg ET: 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	Acute mania: 50 mg twice daily (T), 300 mg once daily (ET) Acute depression: 50 mg once daily at bedtime (T, ET)	800 mg	Consider a lower starting dose (50 mg/day [T, ET]), slower titration, and careful monitoring during initial dosing.	No adjustment necessary	25 mg/day (T) initial, increase based on response and tolerability 50mg/day (ET) initial, increase based on response and tolerability	Beneficial in preventing recurrence of both manic and depressive episodes.

Medication	Dosage Form or Forms	Initial Dose	Maximum Dose/Day	Geriatric	Renal	Hepatic	Clinical Considerations
Risperidone	T: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg ODT: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg S: 1 mg/mL-30 mL bottle LAI (Consta, Rykindo): 12.5 mg vial/kit, 25 mg vial/kit, 37.5 mg vial/kit, 50 mg vial/kit	Acute mania: 1–3 mg/day once daily or in 2 divided doses	6 mg/day	0.5 mg twice daily initial, titrate carefully	No adjustment necessary for CrCl >60 ml/min; 50–75% of usual dose for CrCl 30–60 ml/min; 50% of usual dose for CrCl 10 to <30 ml/min	No adjustment necessary (Child-Pugh A or B) 0.5 mg twice daily initial (Child-Pugh C)	Beneficial in preventing recurrence of manic episodes. When co-administered with enzyme inducers, such as carbamazepine, the dose should be doubled and decreased if the enzyme inducer is discontinued. When co-administered with fluoxetine or paroxetine, the dose should be reduced.
Ziprasidone	CA: 20 mg, 40 mg, 60 mg, 80 mg I: 20 mg/mL	Acute mania: 40 mg twice daily with a meal	80 mg twice daily	No adjustment necessary	No adjustment necessary	Use caution.	Administer with a meal (≥500 calories). Lacks evidence for preventing recurrence of mania and depression. Avoid with drugs known to prolong the QTc interval or if QTc > 500msec.

Abbreviations: CA: capsule; CDT: chewable dispersible tablet; CO: concentrate; CR: extended-release capsule; CrCl: creatinine clearance; CS: capsule, sprinkle; CT: chewable tablet; E: elixir; ET: extended-release tablet; GFR: glomerular filtration rate; I: injection; IV: intravenous; kg: kilogram; LAI: long-acting injectable; mEq: milliequivalent; ml: milliliter; ml/min: milliliters/minute; ODT: oral disintegrating tablet; QTc: QT corrected for heart rate; S: solution; SGA: second-generation antipsychotic; ST: sublingual tablet; SU: suspension; T: tablet; TD: transdermal; TDR: tablet, delayed release; TS: tablet with sensor

Table E-2. Antipsychotic Adverse Event Profiles (229-234)

Medication	EPS	Sedation	Weight Gain	Metabolic	Orthostasis	AcH	QTc
Aripiprazole	++	+	+	+	+	0	+
Asenapine	++	+	+	+	+	0	+
Cariprazine	++	+	+	+	+	0	+
Haloperidol	+++	+	+	+	+	0	++
Lumateperone	+	+	+	+	+	+	+
Lurasidone	++	+	+	+	+	0	+
Olanzapine	+	+++	+++	+++	++	++	+
Paliperidone	+++	+	++	+	+	+	++
Quetiapine	+	+++	++	++	++	+	++
Risperidone	+++	++	++	++	++	0	++
Ziprasidone	++	+	+	+	++	0	+++

Key: +++ = strong effect, ++ = moderate effect, + = minimal effect, 0 = no effect

Abbreviations: AcH: anticholinergic effects; EPS: extrapyramidal symptoms; Metabolic: diabetes, dyslipidemia, increased waist circumference; QTc: QT corrected for heart rate

Table E-3. Antipsychotic Metabolic Monitoring (235)

	Baseline	1 Month	2 Months	3 Months	6 Months	Annually
Body Mass Index	X	X	X	X	X	X
HbA1c	X			X		X
Fasting Plasma Glucose	X			X		X
Fasting Lipid panel	X			X		X

Table E-4. Antipsychotic Long-Acting Injectable (229-232, 234)

Medication	Injection site	Initial Dose	Maintenance dose	Maximum Dose	Oral Overlap**
Aripiprazole monohydrate (Maintena)	Deltoid or gluteal	400 mg per month 300 mg per month (known CYP2D6 poor metabolizer)	400 mg per month 300 mg per month (known CYP2D6 poor metabolizer) 200 mg per month (CYP2D6 poor metabolizers taking concomitant CYP3A4 inhibitors	400 mg per month 300 mg per month (known CYP2D6 poor metabolizer)	14 consecutive days of concurrent oral aripiprazole
Paliperidone palmitate (PP1M)	Initial: deltoid Maintenance: deltoid or gluteal	234 mg followed by 156 mg one week later (+/- 4 days)	39mg–234mg every month Dose conversion: 12 mg oral = 234 mg/month 9 mg oral = 156 mg/month 6 mg oral = 117 mg/month 3 mg oral = 39–78 mg/month	234 mg/month	Not required Studied and approved only for schizoaffective disorder
Paliperidone palmitate Q3 MO (PP3M)	Deltoid or gluteal	Only to be used after paliperidone palmitate (PP1M) has been established as adequate treatment for at least 4 months, with last 2 doses being the same strength 78mg PP1M = 273mg 117mg PP1M = 410mg 156mg PP1M = 546mg 234mg PP1M = 819mg	273 mg–819 mg every 3 months	819 mg every 3 months	Not required Use only after the patient has been adequately treated with PP1M for at least four months. Only approved for schizophrenia

Medication	Injection site	Initial Dose	Maintenance dose	Maximum Dose	Oral Overlap**
Paliperidone palmitate Q6 MO (PP6M)	Gluteal	To be used only after paliperidone palmitate (PP1M) has been established as adequate treatment for at least 4 months, or PP3M for at least one 3-month cycle. 156 mg PP1M = 1,092 mg 234 mg PP1M = 1,560 mg 546 mg PP3M = 1,092 mg 819 mg PP3M = 1,560 mg	1,092 mg–1,560 mg every 6 months	1,560 mg every 6 months	Not required Use only after the patient has been adequately treated with PP1M for at least four months OR PP3M for at least one three-month cycle. Only approved for schizophrenia
Risperidone long-acting injection	Deltoid or gluteal	25mg every 2 weeks	25–50 mg every 2 weeks 1–3 mg po = 25 mg 4–5 mg po = 37.5 mg ≥6 mg po = 50 mg Consider 12.5 mg for history of poor tolerability or renal/hepatic impairment	50 mg every 2 weeks	Oral overlap with risperidone or another antipsychotic should occur for at least 21 days after the first injection.

** Oral overlap refers to the need to continue treatment with the oral antipsychotic while awaiting the long-acting injectable's effects.

Table E-5. 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.

[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 E-6. 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.

Appendix F: Primary Care Management

Primary care managers (PCM) must be equipped to recognize key features of BD and be prepared to take appropriate clinical action to mitigate disability attributable to BD because evidence suggests that positive screens for BD range between 7.6–9.8% of individuals presenting to primary care. Using structured clinical exams, rates of BD diagnoses range from 0.5–4.5% among individuals managed in primary care.(70) Key factors identified by PCMs include elevated scores on depression and anxiety screens (e.g., Patient Health Questionnaire (PHQ)/Generalized Anxiety Disorder Scale), high rates of reported housing instability (53%), and lack of identifiable social support person or persons.(236) Some studies demonstrate that only 26% of BD illnesses are referred to mental health specialty care, and undetected BD is believed to contribute to higher rates of morbidity and mortality because of BD illness-associated injuries and medical comorbidity.(237) Adapting strategies for early detection, initial treatment planning, and mental health referral is key to preventing the higher rates of functional impairment and reduction in QoL because of BD. This section will serve as a guide to inform the PCM on managing practice resources to improve the detection and initial management of suspected BD in primary care. This section also addresses key PCM considerations for maintaining continuity of care for individuals with diagnosed BD.

A. Screening

Studies demonstrate delays between clinical presentation and a BD diagnosis ranging up to 14.5 years.(238) Considering the amount of time between the onset of symptoms and a BD diagnosis, we advise against routine screening by PCMs for symptoms suspicious of BD. However, many individuals with BD initially present to a PCM in a clinical setting for symptoms of depressed mood or anxiety. When an individual is being treated with an antidepressant and suspicion of mania/hypomania on clinical interaction occurs, we recommend the following formal screening approaches.

1. Symptoms of depression, anxiety, and psychosis or a history suggestive of mania should prompt discussion of a possible BD illness. If psychotic or manic symptoms are absent, family history might reveal a predilection for BD, notably if cyclical mood disorders, a history of suicide, or psychotic symptoms are present in first-degree relatives.
2. Patients with a history of a peripartum mood disorder, particularly if the individual experienced psychotic symptoms, should prompt discussion and examination.
3. Evidence of concerning, poorly planned decisions (e.g., impulsively planned long trips) outside established patterns of behavior or evidence of social supports raising concerns for aberrant behaviors should be closely examined for symptoms reflective of mania. For example, new patterns of insomnia, increased substance use, multiple job or housing changes, multiple sexually transmitted infections, infidelity when in established relationships, and unanticipated legal or financial issues often represent emerging mania.

4. Mental status changes indicating rapid or disinhibited speech or both, elevated or expansive mood, labile mood, significant psychomotor agitation (e.g., fidgeting, moving throughout the room, difficulty sitting down), significant distractibility or tangentiality, reports of starting new projects or ventures and never finishing them, spending sprees, or any evidence of psychosis should prompt BD illness consideration.

Evaluating the following is, generally, considered important.

1. Determining whether there is a significant change in sleep or energy levels. Notably, does the individual sleep far less without a significant drop in energy level or notice an energy level rise that interferes with the need or desire to sleep?

2. Do close social supports make notable comments reflecting increases in the pace of speech, engagement in activities inconsistent with established patterns of behavior (i.e., drug use, risky sexual encounters), or notable increases in irritability? If irritability is reported, determine what provokes the irritability: in mania, it is usually that the individual wants to do things or buy things that others (e.g., spouse, boss) consider unwise or impossible. PTSD is a common cause of irritability also, and the "triggers" for it are usually events or memories that remind the individual of traumas experienced and that provoke an agitated "fight or flight" response.

BD screening questionnaires might be useful in the primary care setting when applied in clinical situations with reasonable pretest probability. For example, application of these screening instruments on a PCM's recognition of BD symptoms increases the accuracy of making a diagnosis of BD and can be useful to include in the mental health referral. A commonly used validated screening tool is the MDQ, which can be accessed as a PDF file for free online. Another screening tool that may be used is the HCL.

B. Initial Work Up and Treatment

A 2015 study by Malowney et al. revealed that wait times for referral of a new patient to mental health care from a PCM were as long as 93 days, with an average of 25 days.(239) As such, it is imperative for PCMs to have some understanding of the initial workup, appropriate triaging, and preliminary treatment of suspected BD. As a result of these study findings, VA has implemented several national policies aimed to mitigate wait times for new consults to mental health and has tasked each VA facility to establish clinic staffing models enabling same day access to mental health.

If a PCM suspects BD, additional information should be obtained to help clarify the diagnosis. A specific timeline of current and past mood episodes can be of utility and will be of interest to future mental health providers should a referral be indicated. A thorough substance use history (including cannabis, which worsens mood swings in BD, caffeine, and supplement use) should also be obtained with a urine drug screen as clinically indicated. Other laboratory workup should include a complete blood count,

complete metabolic panel, urinalysis, pregnancy test (in addition to discussion about the patient's intention to become pregnant and current status of contraception use), thyroid function tests, and medication levels (if applicable). In many instances, obtaining collateral information from a close social support is useful for identifying mental status findings or behaviors suggestive of hypomania and mania because often individuals are not fully aware of mental status changes observable by others. This information can also be useful in assessing safety concerns. Addressing areas of lethality toward self or others is important to identify, as well as access to firearms and changes in self-care or work and family productivity.

Based on this screening information, the PCM must decide the appropriate level of care. Concerns for mania, psychosis, or safety of the patient (as well as the safety of others if the patient expresses thoughts or intent of harming another individual) should all prompt immediate referral to an emergency room for acute evaluation by a mental health provider. If these conditions are absent, continuing to see the individual in the primary care setting would be reasonable, though perhaps at an increased frequency to allow for close monitoring of mental status changes while the patient awaits intake with a mental health provider. Consider including telephonic and nurse follow-ups with a frequency range of weekly to quarterly or longer, depending on the stability of the individual's clinical status, treatment regimen, and psychosocial circumstances. During this waiting period, PCMs can do a few things to begin the initial treatment.

1. Taper and discontinue medications or substances that might be contributing to symptoms and impairments. For individuals with mania or hypomania, this step can include nearly all addictive drugs used nonmedically (does not include medications being used in the treatment of SUDs), supplements[a] (in particular, caffeinated workout supplements or supplements containing St. John's Wort), and prescribed medications (including SSRIs, SNRIs, monoamine oxidase inhibitors, atypical antidepressants, and stimulants).
2. Aim treatment interventions toward improving sleep, which can include teaching the individual about basic sleep hygiene, relaxation techniques, and judicious use of starting sleep medications.
3. If the individual was previously seen by a mental health professional, consider consulting the professional (with the individual's permission) and restarting previously effective medications.

A word of caution for PCMs managing individuals with a suspected diagnosis of BD (who has NOT been diagnosed by a mental health provider): This diagnosis (in addition to many other psychiatric diagnoses) can have serious implications for future treatment decisions, readiness, screening for special assignments, and retainability. The Work Group strongly recommends against coding for a psychiatric diagnosis of which one is

[a] See Uniformed Services University of the Health Sciences' (USUHS) Consortium for Health and Military Performance's supplement checker, available at: https://www.opss.org/.

unsure and, consequently, encourages all PCMs to use a general psychiatric diagnosis (e.g., Unspecified Mood [Affective] Disorder or Unspecified Depressive Disorder) in these situations.

C. Caring for Patients with a Known Diagnosis of Bipolar Disorder in a Primary Care Setting

At some point during their career, most PCMs will care for an individual with a SMI. When treating these patients, maintaining contact with their mental health provider is paramount because their treatments are often complex and easily disrupted by any number of primary care interventions. Additionally, PCMs might also be the first to notice changes in psychiatric symptoms and be able to share valuable information regarding treatment adherence and social support. PCMs should feel welcome to consult with their patient's mental health providers, both to share information and to ask questions that arise about the management of the individual's medical conditions. For specific information on potential medication side effects and monitoring of medications, please see other CPG sections (e.g., Recommendation 6, Recommendation 18, Table E-2. Antipsychotic Adverse Event Profiles).

Appendix G: Support Programs

Program Name	Description	Available in VA or DoD?
Art Therapies	Contains a list of various organizations providing art therapy services, to include comedy, theater, visual arts, and creative writing, open to Veterans and active duty Service members. https://www.operationwearehere.com/arttherapy.html	Both
ACT or ICMHR	Varies by state. General information can be found here: https://henrico.va.networkofcare.org/mh/library/article.aspx?id=311	Both
Caregiver Support	Military OneSource: https://www.militaryonesource.mil/confidential-help/interactive-tools-services/caregiver-support-services/	DoD
Clinical Trials	https://www.clinicaltrials.gov/	Both
Connection Program	Assists Veterans in establishing mental health treatment. https://www.maketheconnection.net/	VA
Crisis Resources	Suicide Hotline: 1-800-273-TALK (8255) Veterans Crisis Line: 1-800-273-8255, press 1	Both
Educational and Employment Support	https://warriorcare.dodlive.mil/Care-Coordination/Education-Employment-Initiative/ https://warriorcare.dodlive.mil/Care-Coordination/Operation-Warfighter/ https://www.operationwearehere.com/WoundedWarriorEducationEmployment.html https://www.veterantraining.va.gov/success/index.asp Military OneSource: https://www.militaryonesource.mil/confidential-help/specialty-consultations/education/	Both
Family and Marital Therapy	https://saluteheroes.org/get-help/other-programs/ https://www.ourmilitarykids.org/ Fleet and Family Support Center (available on most naval bases, see base details for more info) Military OneSource: https://www.militaryonesource.mil/confidential-help/specialty-consultations/building-healthy-relationships/	Both
Family Support and Education	https://warriorcare.dodlive.mil/caregiver-resources/ https://www.veterantraining.va.gov/parenting/index.asp	Both
General Resources	https://health.mil/Military-Health-Topics/Centers-of-Excellence/Psychological-Health-Center-of-Excellence/Psychological-Health-Resource-Center National Helpline (treatment referrals and information): 1-800-662-HELP (4357) Disaster Distress Hotline: 1-800-9858 DHA Warrior Care Recovery Coordination Program: https://nrd.gov/ National Veterans Foundation: http://nvf.org/	Both
Health Coaching	https://www.veterantraining.va.gov/movingforward/index.asp	VA
Individual Resiliency Training	https://www.veterantraining.va.gov/recovery/index.asp https://www.veterantraining.va.gov/movingforward/index.asp	Both

Program Name	Description	Available in VA or DoD?
Individualized Case Management Services and assistance with establishing mental health care	inTransition: https://health.mil/Military-Health-Topics/Centers-of-Excellence/Psychological-Health-Center-of-Excellence/inTransition Psychological Health Resource Center: 1-866-966-1020	Both
Medical Management	Primary Care or Psychiatry clinics	Both
NAVIGATE	Psychiatric Transition Program at Naval Medical Center San Diego and Continuing Psychiatric Care Program at Naval Medical Center Portsmouth	DoD
Peer Support	https://www.nami.org/Support-Education/Support-Groups Depression and Bipolar Support Alliance: https://www.dbsalliance.org/support/ Military OneSource (https://www.militaryonesource.mil/confidential-help/specialty-consultations/peer-to-peer/): 1-800-342-9647	Both
Transitions of Care	https://health.mil/Military-Health-Topics/Centers-of-Excellence/Psychological-Health-Center-of-Excellence/inTransition Vet Center Call Center (to assist with transitions of care): 1-877-927-8387 inTransition: https://health.mil/Military-Health-Topics/Centers-of-Excellence/Psychological-Health-Center-of-Excellence/inTransition Military OneSource: https://www.militaryonesource.mil/confidential-help/specialty-consultations/transitioning-veterans/	Both
Vocational Rehab	https://www.veterantraining.va.gov/	VA
Wellness Coaching	Military OneSource: https://www.militaryonesource.mil/confidential-help/specialty-consultations/health-wellness-coaching/	DoD

Abbreviations: ACT: Assertive community treatment; ICMHR: Intensive Community Mental Health Recovery; DoD: Department of Defense; VA: Department of Veterans Affairs

Appendix H: Consensus on Balancing Ethical Principles of Respect for Autonomy and Beneficence

In working to develop recommendations for the care that should be provided to individuals with BD, the Work Group came to consensus that the principles underlying the approaches to care specified in this CPG should be supplemented by a statement on the need to balance the ethical principles of respect to autonomy and beneficence while providing care for individuals with BD and others with SMIs.

The emphases on patient-centered care and shared decision making in the Approach to Care in Department of Veterans Affairs and Department of Defense section reflects the commitment of VA and DoD to provide mental health care based on the ethical principle of respect for autonomy that helps individuals with mental health conditions lead the kind of lives they prefer, despite diagnoses, symptoms, and impairments. However, it is important to recognize that mania and severe depression, with or without psychosis, can be associated with impairments in judgment, decision making capacity, and impulse control that can lead to suicide, self-harm, self-neglect, or danger to others. When these episodes occur, too great an emphasis on respect for autonomy can place lives at risk, and providers are obligated to prioritize actions to prevent harm, including involuntary hospitalization, when needed, based on the principle of beneficence, that is, on doing what is right for the individual with a mental health condition, even when they disagree.

Although health care providers in VA and DoD practice within federal facilities, state law defines the indications and procedures for involuntary hospitalization and treatment for mental health conditions in VA and community-based acute mental health inpatient services. These indications and procedures differ from state to state, and they are evolving. The policies for federal military treatment facilities are distinct. At the time of writing of this CPG, involuntary hospitalization in these facilities requires that an active duty Service member has, or likely has, a severe mental disorder or poses imminent or potential danger to self or others, and placement in a less restrictive level of care would result in inadequate medical care; procedures are detailed in DoD instructions and must be consistent with applicable CPGs.(240) Providers must be aware of these laws and policies and must be prepared to act on them when necessary.

Even when it is necessary, prioritization of beneficence over autonomy to prevent harm must be limited to times when risks and relevant symptoms or impairments continue to be present and to specific elements of care covered by state law or, for military treatment facilities, federal policy. Outside these limits, care should remain patient-centered and based on principles of recovery and respect for autonomy.

Treatment planning for individuals with BD should include a focus on enhancing autonomy and preventing dangerous degrees of deterioration through ongoing attention to the treatment alliance and engagement in maintenance treatment. Additionally, providers should consider the use of behavioral health advance directives (241) that

allow individuals with mental health conditions to proactively document their preferences for future treatment in the event of impairments that limit autonomy or using Wellness Recovery Action Plans that provide proactive help with self-management for individuals with mental health conditions and assist providers with promoting autonomy.(242)

Appendix I: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited three participants for the focus group, with support from the Champions and other Work Group members, as needed. Although participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses. The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed, and the Work Group approved a patient focus group guide covering these topics. The focus group facilitator led the discussion used the guide to elicit patient perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Participants noted that bipolar disorder impacts many aspects of their lives, including their employment, social relationships, and functioning. Participants stated that support from family/friends, online communities, peer support, and group therapy helps manage their bipolar disorder.

- Participants expressed that their BD has negatively impacted various facets of their lives, such as relationships with friends and family, social functioning, daily functioning, and employment. One participant also described the positive, high functioning aspects of BD, such as enhanced creativity and drive.
- Participants reported having comorbid mental health disorders, such as PTSD and SUD (i.e., alcoholism). Two participants shared that they have periodic suicidal ideation and have used suicide prevention services. Of these two participants, one has survived a suicide attempt and has contacted the suicide hotline twice.
- Participants recognized the importance of family and peer support. These social connections help them manage their BD.

b. Participants felt that an accurate diagnosis of bipolar disorder improved their treatment.

- Participants expressed that the buildup of multiple social, environmental, and employment factors contributed to their BD diagnosis.
- Some participants reported being misdiagnosed during their care and noted that separating depression versus BD is difficult.
- One participant noted being grateful for his diagnosis of BD, although another felt this diagnosis was inaccurate.

c. Participants explained that they commonly use pharmacologic treatments (e.g., lithium, SSRIs) to manage their bipolar symptoms and have found these treatments to be effective.

- Participants noted they found medications to be useful in treating and managing their BD. All participants reported use of lithium and indicated it was effective.
- Participants recognized the value in communicating about treatment with their providers.

d. Participants also indicated they engage in non-pharmacologic treatments and self-management. Participants noted they have received various non-pharmacologic therapies (e.g., ECT, CBT).

- One participant recognized the usefulness of the VA Bipolar Disorder Workbook Program. Another participant listed ECT, pharmacologic treatment, and both inpatient and outpatient treatment as previous mechanisms of management for his BD.
- Two participants felt that providers were dismissive of their suggestions regarding care preferences and indicated a lack of acceptance by providers for alternative explanations, treatments, and management approaches (e.g., Jungian analysis, shamanism).

Appendix J: Evidence Table

Table J-1. Evidence Table[a,b,c]

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
1.	We suggest against routine screening for bipolar disorder in a general medical population.	(69, 71, 77, 81) **Additional references** (70, 72-76, 78-80)	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.	(69, 71, 82) **Additional references** (10, 72, 76)	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.	(83-86)	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.	(87) **Additional reference** (88)	Neither for nor against	Reviewed, New-added

[a] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the development of this CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation, but which were not identified through the systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[b] Strength of Recommendation column: The VA/DoD BD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Determining Recommendation Strength and Direction section for more information.

[c] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process, the categories, and their definitions.

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
5.	We suggest lithium or quetiapine as monotherapy for acute mania.	(89, 90) **Additional references** (91, 92)	Weak for	Reviewed, New-added
6.	If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania.	(89, 90)	Weak for	Reviewed, New-added
7.	If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preferences and characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania.	(89, 90) **Additional references** (93, 94)	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.	(95) **Additional reference** (96)	Weak for	Reviewed, New-added
9.	We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania.	(89)	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.	(95)	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.	(89, 95, 97)	Neither for nor against	Reviewed, New-added
12.	We recommend quetiapine as monotherapy for acute bipolar depression.	(97, 98, 100) **Additional reference** (99)	Strong for	Reviewed, New-added
13.	If quetiapine is not selected based on patient preferences and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression.	(97, 101-104)	Weak for	Reviewed, New-added

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
14.	There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression.	(97, 105)	Neither for nor against	Reviewed, New-added
15.	We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression.	(106, 108) **Additional reference** (107)	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.	(106, 109, 113) **Additional references** (110-112)	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.	(97, 105, 106, 114, 115, 117) **Additional reference** (116)	Neither for nor against	Reviewed, New-added
18.	We recommend lithium or quetiapine for the prevention of recurrence of mania.	(89, 90, 118, 120) **Additional references** (92, 119, 121-126)	Strong for	Reviewed, New-added
19.	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.	(89, 90, 129) **Additional references** (127, 128, 130)	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).	(90, 118) **Additional reference** (131)	Neither for nor against	Reviewed, New-added
21.	We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania.	(90, 120) **Additional reference** (132)	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.	(89, 90, 133-135)	Weak for	Reviewed, New-added
23.	We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes.	(89, 120)	Strong for	Reviewed, New-added

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
24.	We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.	(90, 98, 136)	Weak for	Reviewed, New-added
25.	If lithium or quetiapine is not selected based on patient preferences and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.	(90, 98, 136)	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.	(89, 90, 134)	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.	(90)	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.	(90)	Neither for nor against	Reviewed, New-added
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.	(137, 138) **Additional references** (139-142)	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.	(89, 138, 143-145) **Additional references** (93, 146, 147)	Strong against	Reviewed, New-added
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.	(148) **Additional references** (149, 150)	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.	(151)	Weak for	Reviewed, New-added

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
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.	(152-154)	Weak for	Reviewed, New-added
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).	(155, 161) **Additional references** (156-160, 162-164)	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.	(155) **Additional references** (164-167)	Neither for nor against	Reviewed, New-added
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.	(168)	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.	(108, 169-173, 175, 176) **Additional reference** (174)	Neither for nor against	Reviewed, New-added
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.	(177-186) **Additional reference** (187)	Neither for nor against	Reviewed, New-added
39.	There is insufficient evidence to recommend any specific supported housing intervention over another for individuals with bipolar disorder experiencing housing insecurity.	(188)	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.	(189, 190)	Weak for	Reviewed, New-added

#	Recommendation	Evidence	2023 Strength of Recommendation	Recommendation Category
41.	For individuals with bipolar disorder, we suggest caregiver support programs to improve mental health outcomes.	(161, 191)	Weak for	Reviewed, New-added
42.	For individuals with bipolar disorder, we suggest that clinical management should be based on the collaborative care model.	(192-195, 199, 200) **Additional references** (164, 196-198, 201-206)	Weak for	Reviewed, New-added
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.	(208, 210) **Additional references** (207, 209)	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.	(213-215, 218, 219) **Additional references** (211, 212, 216, 217, 220)	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.	(221) **Additional references** (100, 122)	Weak for	Reviewed, New-added

Appendix K: Participant List

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Appendix L: Literature Review Search Terms and Strategy

Table L-1. EMBASE and MEDLINE in EMBASE.com Syntax (all KQs)

KQ	Set #	Concept	Strategy
KQs 1 and 2	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Adults with MDD taking antidepressants	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	#3	First episodes of mania/hypomania	'bipolar mania'/mj OR hypomania/mj OR 'mania'/mj OR 'manic psychosis'/mj OR 'mixed mania and depression'/mj OR (hypomani* OR mania OR manias OR manic):ti
	#4	Combine population sets	#1 OR (#2 AND #3)
	#5	6-item Rapid Mood Screener	(rapid NEXT/2 mood NEXT/2 screen*):ti,ab,kw
	#6	Altman Self Rating Mania Scale (5 items)	'altman self rating mania scale'/mj OR ((altman NEXT/2 self*) AND scale*):ti,ab,kw
	#7	Bech-Rafaelsen Mania Rating Scale	'bech-rafaelsen mania scale'/mj OR (('bech rafaelsen' NEXT/2 mania) AND scale*):ti,ab,kw
	#8	Bipolar Inventory of Symptoms Scale	'bipolar inventory of symptoms scale'/mj OR (bipolar NEXT/2 inventor* NEXT/2 symptom*):ti,ab,kw
	#9	Bipolar Spectrum Diagnostic Scale	'bipolar spectrum diagnostic scalescale'/mj OR ((bipolar NEXT/2 spectrum NEXT/2 diagnostic) AND scale*):ti,ab,kw
	#10	Clinical Monitoring Form	'clinical monitoring form':ti,ab,kw,de
	#11	Clinically Useful Depression Outcome Scale with questions for the DSM-5 mixed features specifier (CUDOS-M)	'clinically useful depression outcome scale'/mj OR ('clinically useful depression outcome scale' OR cudos OR 'cudos m' OR cudosm):ti,ab,kw
	#12	Hamilton Depression Rating Scale-5 (5 items)	'hamilton depression rating scale'/mj OR ((hamilton NEAR/5 scale*) AND depression):ti,ab,kw
	#13	HCL-32 OR HCL-33 (Hypomania Checklist)	'hypomania checklist 32'/mj OR ('hypomania check*' OR 'hcl 32*' OR 'hcl 33*'):ti,ab,kw
	#14	Internal State Scale	'internal state scale'/mj OR (internal NEXT/2 state NEXT/2 scale*):ti,ab,kw
	#15	Mini-International Neuropsychiatric Interview	'mini international neuropsychiatric interview'/mj OR ('mini international neuropsychiatric' OR mini):ti,ab,kw
	#16	Montgomery-Asberg Depression Rating Scale	'montgomery asberg depression rating scale'/mj OR ((montgomery NEXT/2 asberg) OR MADRS):ti,ab,kw

KQ	Set #	Concept	Strategy
KQs 1 and 2 (cont.)	#17	Mood Disorder Questionnaire (MDQ)	'mood disorder questionnaire'/mj OR (mood NEXT/2 disorder* NEXT/2 questionnaire*):ti,ab,kw
	#18	Patient Health Questionnaire 2/9 (PHQ 2/9)	'patient health questionnaire'/exp/mj OR ('patient health questionnaire' OR PHQ*):ti,ab,kw)
	#19	Patient Mania Questionnaire	('patient mania questionnaire*' OR 'pmq 9' OR 'pmq9'):ti,ab,kw,de
	#20	Quick Inventory of Depressive Symptoms	'quick inventory of depressive symptomatology'/mj OR 'quick inventory of depressive symptom'/mj OR 'quick inventory of depressive symptomatology clinician rated'/mj OR 'quick inventory of depressive symptomatology self rated'/mj OR 'quick inventory of depressive symptomatology self report'/mj OR 'quick inventory of depressive symptoms'/mj OR (quick NEXT/2 inventor* NEXT/2 depress* NEXT/2 symptom*):ti,ab,kw
	#21	Scale for the Assessment of Episodes in BD	('scale for the assessment of episodes in bipolar disorderdisorder' OR saebd):ti,ab,kw,de
	#22	Structured clinical interview for DSM	'structured clinical interview for dsm disorders'/mj OR ('structured clinical interview' OR (scid* AND interview)):ti,ab,kw
	#23	Young Mania Rating Scale	'young mania rating scale'/mj OR (YMR* OR 'young mani* rating'):ti,ab,kw
	#24	Combine population and intervention sets	#4 AND (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
	#25	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#26	Limit to systematic reviews, meta-analyses, randomized controlled trials, and diagnostic accuracy/cohort studies	See study-type filters at the end of this table
KQ 3	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Measurement Based Care (specific)	'measurement based care'/exp OR ((measurement NEXT/3 based) OR 'routine outcome monitor*' OR (structur* NEAR/3 monitor*)):ti,ab,kw
	#3	Measurement Based Care (general)	'assessment of humans'/exp/mj OR 'depression assessment'/exp/mj OR 'mania assessment'/exp/mj OR 'patient-reported outcome'/mj OR 'psychological rating scale'/exp/mj OR 'questionnaire'/exp/mj OR 'self monitoring'/exp/mj OR (assessment* OR index* OR instrument* OR measure* OR prom OR proms OR questionnaire* OR scale OR scales OR tool*):ti

KQ	Set #	Concept	Strategy
KQ 3 (cont.)	#4	Chronic Care Model	'chronic care model'/de OR ('chronic care model*' OR 'chronic medical care' OR ((ccm OR ccms) AND chronic)):ti,ab,kw
	#5	Collaborative Care Model	'collaborative care model'/de OR (collaborative NEXT/2 (approach* OR care OR model*)):ti,ab,kw
	#6	Internal State Scale	'internal state scale'/mj OR (internal NEXT/2 state NEXT/2 scale*):ti,ab,kw
	#7	Short Form 12 or Short Form 36	'Short Form 12'/de OR ('12 item short form' OR 'short form 12' OR 'sf 12' OR sf12):ti,ab,kw OR 'Short Form 36'/de OR ('36 item short form' OR 'short form 36' OR 'sf 36' OR sf36):ti,ab,kw
	#8	Veterans RAND 12-Item Health Survey	'veterans rand 12 item health survey'/de OR ('vr 12' OR vr12 OR (veteran* NEAR/2 rand)):ti,ab,kw
	#9	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
	#10	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#11	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 4	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Virtual interventions	internet/de OR 'mobile application'/exp OR 'mobile phone'/exp OR 'social media'/de OR 'tablet computer'/de OR teleconsultation/exp OR telehealth/de OR telemedicine/de OR telemonitoring/de OR telephone/de OR telepsychiatry/de OR telepsychology/de OR telepsychotherapy/de OR teletherapy/de OR 'text messaging'/de OR ‘web-based intervention’/de OR 'video consultation'/de OR videoconferencing/de OR (((distance OR remote OR tele OR virtual) NEAR/3 (care OR counseling OR counselor* OR consult* OR health OR medical OR medicine OR monitor* OR psychiatr* OR psycholog* OR psychotherap* OR therapy OR visit*)) OR android* OR app OR apps OR asynchronous* OR automat* OR cellphone* OR 'computer based' OR cyber* OR digital OR 'e health*' OR ehealth* OR facebook OR facetime OR internet OR ipad OR iphone OR 'lap top*' OR laptop* OR 'm health*' OR mhealth* OR ((mobil* OR portab*) NEXT/1 (computer* OR device* OR health OR tablet*)) OR 'on line' OR online OR phone OR phones OR samsung OR 'short messag* service*' OR smartphone* OR ((sms OR text) NEXT/2 messag*) OR (social NEXT/1 (media OR network* OR platform*)) OR software OR synchronous* OR technolog* OR teleconsult* OR telecounsel* OR telehealth* OR telemed* OR telemonitor* OR telephone* OR telepsych* OR teletherapy OR televisit* OR texting* OR video* OR web OR website* OR zoom):ti

KQ	Set #	Concept	Strategy
KQ 4 (cont.)	#3	Combine population and intervention sets	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 5	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Team-based multi/ interdisciplinary models	'care manager'/de OR 'case management'/de OR 'case manager'/de OR coaching/de OR 'collaborative care model'/de OR 'collaborative care team'/de OR 'community mental health service'/exp OR 'coordinated care'/de OR 'coordinated specialty care'/de OR 'health coaching'/de OR 'intensive case management'/de OR 'patient centered medical home'/de OR 'personalized medicine'/de OR 'self care'/exp/mj OR 'self management support'/de OR 'team based care'/de OR ('assertive community' OR (care NEXT/1 (manag* OR model* OR system OR systems)) OR 'case manag*' OR coaching OR (collaborative NEXT/2 (approach* OR care OR model*)) OR (community NEXT/2 'mental health*') OR (coordinated NEXT/2 care) OR 'health coach*' OR ((individual* OR personali*) NEXT/2 (approach* OR intervention* OR management OR therap* OR treatment*)) OR (integrat* NEXT/3 (care OR service*)) OR 'intensive case management' OR 'intensive community' OR (intensive NEXT/2 treatment*) OR 'medical home' OR PACT OR 'patient aligned care team' OR 'patient centered' OR 'patient centred' OR 'personali* case management' OR 'self care' OR 'self management' OR team-based OR 'whole health'):ti,ab,kw OR (coach* OR inter disciplinary OR individuali* OR interdisciplinary OR multi disciplinary OR multidisciplinary OR personalised OR personalized OR team*):ti
	#3	Combine population and intervention sets	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table

KQ	Set #	Concept	Strategy
KQs 6, 7, 8, 9, 15	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	General Pharmacotherapy	'psychopharmacotherapy'/de OR ((medicine* OR medicat* OR drug* OR pharmacologic*) NEAR/3 (manag* OR therap* OR treat*)):ti OR (maintenance OR pharmacotherap*):ti
	#3	Amphetamines (class)	'amphetamine derivative'/exp OR amphetamine*
	#4	Anti-convulsants/Anti-epileptics (class)	'anticonvulsive agent'/exp OR (anticonvuls* OR 'anti convuls*' OR antiepileptic* OR 'anti epileptic*' OR antiepileptiform* OR 'anti epileptiform'):ti,ab,kw
	#5	Anti-depressants (class)	'antidepressant agent'/exp OR (antidepress* OR 'anti depress*' OR thymoanaleptic* OR thymoleptic* OR thymolytic*):ti,ab,kw
	#6	Anti-depressants (sub-headings)	('mao inhibit*' OR 'mono amine oxidase inhibit*' OR 'monoamine oxidase a inhibitor' OR 'monoamine oxidase b inhibitor' OR 'monoamine oxidase inhibit*' OR 'monoaminoxidase inhibit*' OR maoi OR maois OR ((noradrenalin* OR norepinephrine OR serotonin) NEXT/2 (reuptake OR uptake)) OR sdri OR sdris OR snri OR snris OR ((tetracyclic OR tricyclic) NEAR/2 (antidepress* OR 'anti depress*'))):ti,ab,kw
	#7	Anti-narcoleptics (class)	'psychostimulant agent'/exp OR psychostimul*:ti,ab,kw
	#8	Antiparkinson agents (class)	'antiparkinson agent'/exp OR ('anti dyskinesi*' OR antidyskinesi* OR antiparkinson OR antiparkinsonian):ti,ab,kw
	#9	Dopamine agonists (class)	'dopamine receptor stimulating agent'/exp OR dopamine*:ti,ab,kw
	#10	Calcium channel blockers (class)	'calcium channel blocking agent'/exp OR calcium:ti,ab,kw
	#11	Mood stabilizers (class)	'mood stabilizer'/exp OR (antimanic* OR 'mood stabilis*' OR 'mood stabiliz*'):ti,ab,kw
	#12	Tranquilizers & Antipsychotic agents (Class) (neuroleptic agents falls under tranquilizers)	'tranquilizer'/de OR 'neuroleptic agent'/exp OR (antipsychotic* OR 'anti psychotic*' OR ataractic* OR neuroleptic* OR tranquilis* OR tranquiliz* OR tranquillis* OR tranquilliz*):ti,ab,kw
	#13	Antipsychotics, long-acting injectables (class)	'long acting injection'/de OR 'long acting injectable antipsychotic agent'/de OR 'long acting injectable antipsychotic'/de OR ('long act*' NEXT/1 (antipsych* OR 'anti psychotic*' OR inject*)):ti,ab,kw
	#14	Experimental drugs, including cannabinoids	'cannabinoid'/exp OR 'cannabis'/de OR 'medical cannabis'/de OR 'psilocybine'/de OR ((cbd* NEAR/2 oil*) OR bhang* OR cannabi* OR cannador OR charas OR dronabinol OR ganja* OR hashish* OR hemp* OR marihuana OR marijuana OR psilocibin* OR psilocin OR psilocybin*):ti,ab,kw

KQ	Set #	Concept	Strategy
KQs 6, 7, 8, 9, 15 (cont.)	#15	Specific agents named by work group	amfebutamone OR amitriptyline OR amoxapine OR amphetamine OR aripiprazole OR armodafinil OR asenapine OR atomoxetine OR brexpiprazole OR bupropion OR buproprion OR carbamazepine OR cariprazine OR chlorpromazine OR citalopram OR clomipramine OR clonazepam OR clozapine OR desipramine OR desvenlafaxine OR dexamphetamine OR dexmethylphenidate OR dextroamphetamine OR diazepam OR doxepin OR duloxetine OR escitalopram OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR haloperidol OR iloperidone OR imipramine OR isocarboxazid OR isradipine OR ketamine OR lamotrigine OR levomilnacipran OR lisdexamfetamine OR lithium OR lorazepam OR loxapine OR lumateperone OR lurasidone OR maprotiline OR methylphenidate OR milnacipran OR mirtazapine OR moclobemide OR modafinil OR molindone OR nefazodone OR nimodipine OR nortriptyline OR olanzapine OR oxcarbazepine OR 'oxybate sodium' OR paliperidone OR paroxetine OR perphenazine OR phenelzine OR pimozide OR pitolisant OR pregabalin OR protriptyline OR quetiapine OR risperidone OR samidorphan OR selegiline OR sertraline OR 'sodium oxybate' OR solriamfetol OR thioridazine OR thiothixene OR tiotixene OR tranylcypromine OR trazodone OR trifluoperazine OR trimipramine OR valproate OR 'valproic acid' OR venlafaxine OR verapamil OR vilazodone OR vortioxetine OR ziprasidone
	#16	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
	#17	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#18	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 10	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	General neuromodulation therapies	'neuromodulation'/de OR 'neuromodulator'/de OR (neuromodulat* OR 'neuro modulat*'):ti,ab,kw
	#3	Bright light therapy	'bright light therapy'/de OR 'phototherapy'/exp OR (((color OR colour OR illumination OR light OR photoradiation) NEXT/2 (therap* OR treat*)) OR 'bright light' OR phototherap*):ti,ab,kw
	#4	Deep brain stimulation	'brain depth stimulation'/de OR (brain NEXT/3 (excitation OR stimul*)):ti,ab,kw
	#5	Electro-convulsive therapy (ECT)	'electroconvulsive therapy'/de OR 'electrostimulation'/de OR ((electr* NEXT/3 (shock OR stimul* OR therap* OR treat*)) OR ces OR ecs OR ect OR electrotherap*):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 10 (cont.)	#6	Transcranial magnetic stimulation	'transcranial magnetic stimulation'/exp OR 'transcranial magnetic stimulation system'/de OR ((transcranial NEXT/3 (electromagnet* OR 'electro magnet*' OR magnet* OR stimul*)) OR rtms OR tms):ti,ab,kw
	#7	Vagus nerve stimulation (VNS)	'vagus nerve stimulation'/de OR 'vagal nerve stimulator'/de OR (tvns OR vagal* OR vagus* OR vns):ti,ab,kw
	#8	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7)
	#9	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#10	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 11	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Adults with co-occurring borderline personality disorder	'borderline state'/de OR ((borderline NEXT/2 personality) OR 'borderline psychosis' OR 'borderline trait*'):ti,ab,kw
	#3	Adults with co-occurring posttraumatic stress disorder	'posttraumatic stress disorder'/exp OR ((combat NEXT/2 (disorder* OR fatigue OR stress)) OR ((posttrauma* OR trauma*) NEXT/2 (disorder* OR neuros* OR psychos* OR stress OR syndrome*)) OR PTSD OR (sexual NEXT/2 trauma*) OR 'stress disorder*' OR 'war neuros*'):ti,ab,kw
	#4	Adults with co-occurring traumatic brain injury	'acquired brain injury'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ((brain NEXT/1 (damag* OR lesion*)) OR ((brain OR head) NEAR/3 (injur* OR trauma*)) OR mTBI OR 'post concuss*' OR postconcuss* OR TBI):ti,ab,kw
	#5	Combine population sets	#1 AND (#2 OR #3 OR #4)
	#6	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#7	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 12	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 12 (cont.)	#2	Alcohol use disorder	'alcohol abuse'/exp OR 'alcoholism'/exp OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'treatment withdrawal'/exp) AND ('alcohol'/de OR 'alcohol consumption'/de)) OR ((alcohol NEAR/3 (abstain* OR abstinence OR abus* OR addict* OR depend* OR detox* OR discontinu* OR disorder* OR misus* OR use OR uses OR user* OR using OR withdraw*)) OR alcoholi*):ti,ab,kw
	#3	Cannabis use disorder	'cannabis addiction'/exp OR 'cannabis use disorder'/exp OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'treatment withdrawal'/exp) AND ('cannabis'/exp OR 'cannabis use'/exp OR 'medical cannabis'/exp)) OR ((cannabis* OR hashish OR marihuana OR marijuana) NEAR/3 (abstain* OR abstinence OR abus* OR addict* OR depend* OR detox* OR discontinu* OR disorder* OR misus* OR use OR uses OR user* OR using OR withdraw*)):ti,ab,kw
	#4	Hallucinogen use disorder	('psychedelic agent'/exp AND ('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'treatment withdrawal'/exp)) OR ((hallucinogen* OR psychedeli* OR psychodysleptic OR psychomimetic OR 'psychotic drug' OR psychotomimetic) NEAR/3 (abstain* OR abstinence OR abus* OR addict* OR depend* OR detox* OR discontinu* OR disorder* OR misus* OR use OR uses OR user* OR using OR withdraw*)):ti,ab,kw
	#5	Opioid use disorders	'opiate addiction'/de OR 'opioid use disorder'/de OR 'analgesic agent abuse'/de OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'treatment withdrawal'/exp) AND ('narcotic analgesic agent'/exp)) OR ((analgesic* OR codeine OR fentanyl OR heroin OR hydrocodone OR methadone OR morphine OR narcotic* OR opiate* OR opioid* OR opium OR oxycodone OR oxycontin OR percocet) NEAR/3 (abstain* OR abstinence OR abus* OR addict* OR depend* OR detox* OR discontinu* OR disorder* OR misus* OR use OR uses OR user* OR using OR withdraw*)):ti,ab,kw
	#6	Stimulant use disorders	'amphetamine dependence'/de OR 'cocaine dependence'/de OR 'methamphetamine dependence'/de OR (('amphetamine derivative'/exp OR 'central stimulant agent'/exp OR 'psychostimulant agent'/de) AND ('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/exp OR 'treatment withdrawal'/exp)) OR ((adderall OR amphetamine* OR analeptic* OR atomoxetine OR cocaine OR dexamphetamine OR dexedrine OR dexmethylphenidate OR dextroamphetamine OR ecstasy OR lisdexamfetamine OR mdma OR 'meth' OR methamphetamine* OR methylphenidate OR mydayis OR oxymetazoline OR phenylephrine OR pseudoephedrine OR psychostimulant* OR stimulant*) NEAR/3 (abstain* OR abstinence OR abus* OR addict* OR depend* OR detox* OR discontinu* OR disorder* OR misus* OR use OR uses OR user* OR using OR withdraw*)):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 12 (cont.)	#7	Tobacco use	'smoking and smoking related phenomena'/exp OR (('addiction'/exp OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'treatment withdrawal'/exp) AND 'tobacco'/de) OR (cigar* OR nicotine OR pipe OR pipes OR smok* OR tobacco OR vape OR vaping):ti,ab,kw
	#8	Other drug use disorders	'addiction'/mj OR 'drug abuse'/exp OR 'drug dependence'/exp OR 'substance abuse'/de OR 'substance use'/de OR 'withdrawal syndrome'/exp OR (((benzodiazepine* OR drug* OR inhalant* OR recreational OR solvent* OR substance*) NEAR/3 (abstain* OR abstinence* OR abus* OR addict* OR behavi* OR depend* OR disorder* OR habit* OR illegal* OR illicit* OR intoxica* OR misus* OR use OR uses OR user* OR using OR withdraw*)):ti,ab,kw)
	#9	Combine Populations	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
	#10	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#11	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 13	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Adults with attention-deficit/hyperactivity disorder (ADHD)	'attention deficit disorder'/de OR 'conduct disorder'/de OR 'oppositional defiant disorder'/de OR ((addh OR adhd OR 'ad hd' OR 'attention deficit*' OR 'callous unemotional' OR 'conduct disorder*' OR ('disruptive behav*' NEXT/1 disorder*) OR 'opposition* defian* disorder*')):ti,ab,kw
	#3	Combine Populations	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 14	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 14 (cont.)	#2	Adults with anxiety disorders	'anxiety disorder'/exp OR 'anxiety'/de OR ('acute stress disorder*' OR agoraphobi* OR anxiety OR (obsess* NEAR/3 compuls*) OR ((panic OR phobi*) NEAR/3 disorder*) OR ((social OR specific) NEAR/3 phobi*)):ti,ab,kw
	#3	Combine Populations	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 16	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	General psychoeducation	'psychoeducation'/de OR (psychoeducat* OR 'psycho educat*'):ti,ab,kw
	#3	General psychotherapy, including psychodynamic psychotherapy	'psychotherapy'/exp OR psychoanalysis/de OR (psychoanaly* OR psychodynamic OR psychotherap*):ti,ab,kw
	#4	Acceptance and Commitment therapy	'acceptance and commitment therapy'/de OR (accept* NEAR/2 commitment NEAR/2 therap*):ti,ab,kw
	#5	Adaptive strategies	'adaptation'/mj OR 'psychological adjustment'/de OR ((adapt* NEXT/1 strateg*) OR ((emotional OR personal OR psychologic*) NEXT/1 (adapt* OR adjust* OR equilibrium))):ti,ab,kw
	#6	Cognitive behavioral therapy (CBT), including brief CBT	'cognitive behavioral therapy'/exp OR ('cognition therap*' OR (cognitive NEAR/2 (behavior* OR behaviour*) NEAR/2 (therap* OR treatment*)) OR (cognitive NEAR/2 (psychotherap* OR therap*)) OR cbt):ti,ab,kw
	#7	Cognitive remediation	'cognitive remediation therapy'/de OR 'cognitive training'/de OR ('cognitive enhancement therap*' OR 'cognitive rehabilitation' OR 'cognitive remediation' OR 'cognitive training'):ti,ab,kw
	#8	Eye movement desensitization and reprocessing	'eye movement desensitization and reprocessing'/de OR ('eye movement desensiti*' OR emdr):ti,ab,kw
	#9	Family psychotherapy	'family focused therapy'/de OR 'family therapy'/de OR ((family OR vector) NEXT/2 (intervention OR psych* OR therap* OR treat*)):ti,ab,kw
	#10	Illness management	'disease management'/de OR 'disease management program'/de OR ((disease* OR disorder* OR illness* OR medical) NEAR/2 management):ti,ab,kw OR 'illness management and recovery'/de OR 'illness management':ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 16 (cont.)	#11	Interpersonal and social rhythm therapy	'interpersonal and social rhythm therapy'/de OR ((interpersonal NEXT/2 'social rhythm*') OR ipsrt):ti,ab,kw
	#12	Jungian analysis	'Jungian theory'/de OR jungian:ti,ab,kw
	#13	Life Goals CCM	('life goals' OR 'lg cc' OR lgcc OR lgp):ti,ab,de,kw
	#14	Mindfulness-based therapy	'mindfulness'/exp OR (mbct OR mbsr OR mbt OR micbt OR mindful*):ti,ab,kw
	#15	Motivational interviewing	'motivational interviewing'/de OR 'motivational enhancement therapy'/de OR 'motivational intervention'/de OR 'motivational interview'/de OR 'motivational therapy'/de OR (motivational NEAR/2 (intervention* OR interview* OR therap*)):ti,ab,kw
	#16	Social skills training	'social competence'/de OR (social NEXT/2 (skill* OR train*)):ti,ab,kw
	#17	Supported employment	'supported employment'/de OR 'sheltered employment'/de OR ((shelter* OR support*) NEAR/2 employment*):ti,ab,kw
	#18	Supportive therapy	'supportive care'/de OR 'supportive therapy'/de OR (support* NEXT/1 (care OR therap*)):ti,ab,kw
	#19	Vocational rehabilitation	'vocational rehabilitation'/de OR ((occupational OR vocational) NEXT/1 (rehabilit* OR retrain*)):ti,ab,kw
	#20	Combination therapies	'add on therapy'/de OR 'drug combination'/de OR monotherapy/de OR polypharmacy/de OR ((add OR 'add on' OR added OR adding OR additional OR adds OR adjunct* OR augment* OR blend* OR combin* OR incorporat* OR integrat* OR mix*) NEAR/1 (behav* OR cognitive OR counsel* OR drug* OR medicine* OR medication* OR 'mental health' OR pharm* OR psychiatric* OR psychol* OR psychother* OR therap* OR treatment*)):ab,ti,kw OR ('add on' OR adjunct* OR augment* OR combin* OR monotherap* OR polypharm* OR supplement*):ti
	#21	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
	#22	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#23	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 17	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 17 (cont.)	#2	Recovery-based rehabilitation and supported care programs	'community care'/exp OR 'crisis intervention'/de OR employment/exp/mj OR housing/de OR 'peer group'/de OR rehabilitation/exp/mj OR recovery/de OR 'sheltered employment'/de OR 'supported employment'/de OR 'supportive care'/de OR ('community care' OR 'community health* service*' OR 'compensated work therapy' OR (crisis NEXT/1 (intervention* OR support*)) OR 'housing support*' OR 'HUD VASH' OR (('multi system*' OR multisystem*) NEXT/1 (therapy OR treatment)) OR (peer* NEXT/1 (delivered OR facilitat* OR led OR navigat* OR specialist* OR support*)) OR (recovery AND (program* OR rehab*)) OR sheltered OR (support* NEXT/1 (care OR employment OR housing))):ti,ab,kw OR (rehab* OR (recovery NEXT/1 (focused OR oriented))):ti
	#3	Combine population and intervention sets	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 18	#1	Adults with BD, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Adults with chronic insomnia	insomnia/exp OR 'insomnia therapy'/de OR (hypnosomnia* OR insomnia* OR ('sleep initiation' NEAR/3 (disorder* OR dysfunction*)) OR sleepless*):ti,ab,kw
	#3	Combine population strings	#1 AND #2
	#4	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#5	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 19	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	General alternative/integrative medicine regimens	'alternative medicine'/exp OR 'integrative medicine'/de OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR medicine OR modalit* OR therap* OR treat*)):ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 19 (cont.)	#3	Acupuncture	'acupuncture'/exp OR (acupotom* OR acupressure OR acupuncture OR shonishin):ti,ab,kw
	#4	Art therapy	'art therapy'/de OR (art NEXT/1 (therap* OR treatment*)):ti,ab,kw
	#5	Dance therapy	'dance therapy'/de OR danc*:ti,ab,kw
	#6	Meditation	'meditation'/exp OR meditat*:ti,ab,kw
	#7	Mindfulness	'mindfulness'/exp OR mindful*:ti,ab,kw
	#8	Music therapy	'music therapy'/exp OR music:ti,ab,kw
	#9	Relaxation	'relaxation training'/de OR (relaxation NEAR/2 (exercis* OR method* OR technic* OR technique* OR therap* OR training)):ti,ab,kw
	#10	Stress management	'stress management'/de OR (stress NEAR/2 manag*):ti,ab,kw
	#11	Yoga/Tai Chi	'yoga'/exp OR (yoga* OR yogic OR pranayama):ti,ab,kw OR 'tai chi'/de OR ('tai chi' OR 't ai chi' OR taichi OR 'tai ji' OR taiji*):ti,ab,kw
	#12	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
	#13	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#14	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table
KQ 20	#1	Adults with bipolar disorder, including schizoaffective type	'mania'/exp OR ((bipolar NEAR/3 (cycling OR depress* OR disorder* OR illness* OR mania* OR manic OR psychosis)) OR 'bipolar i' OR 'bipolar ii' OR cyclophrenia OR cyclothym* OR ((hypomani* OR mania OR manic) NEAR/3 (behav* OR disorder* OR episode* OR mood)) OR ((mania* OR manic*) NEAR/3 (depress* OR mixed OR psychos*)) OR ('rapid cycling' NEAR/2 (depress* OR disorder*))):ti,ab,kw OR 'schizoaffective psychosis'/de OR ('schizo affective' OR schizoaffective):ti,ab,kw
	#2	Dietary interventions	'nutrition'/exp/mj OR 'polyunsaturated fatty acid'/de OR (diet* OR fat OR fats OR fatty OR 'fish oil*' OR food* OR grapefruit* OR 'grape fruit*' OR nutri* OR meal*):ti,ab,kw
	#3	Probiotics	'probiotic agent'/exp OR probiotic*:ti,ab,kw
	#4	Supplements	'ademetionine'/de OR 'ascorbic acid'/exp OR 'folic acid'/de OR 'magnesium'/de OR 'vitamin b group'/exp OR 'vitamin d'/exp OR 'zinc'/de OR (methionine OR adenosylmethionine OR methioninyladenylate OR 'sam e' OR 'ascorbic acid' OR 'cevitamic acid' OR 'vitamin c' OR ascorbate OR 'folic acid' OR folate OR magnesium OR 'b vitamin*' OR 'vitamin b' OR 'vitamin d' OR zinc):ti,ab,kw
	#5	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4)
	#6	Apply standard exclusions and limits	See filters, exclusions, and limits at the end of this table
	#7	Limit to systematic reviews, meta-analyses, and randomized controlled trials	See study-type filters at the end of this table

KQ	Set #	Concept	Strategy
Standard Exclusions & Limits Applied to Each Search Strategy		Exclude animal and experimental studies	NOT (([animals]/lim NOT [humans]/lim) OR ((animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR sheep* OR swine OR veterinar* OR (vitro NOT vivo)) NOT (human* OR patient*)):ti)
		Exclude studies focusing on children	NOT ((adolescen* OR babies OR baby OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR nurser* OR paediatric* OR pediatric* OR preschool* OR 'school age*' OR schoolchildren* OR teen* OR toddler* OR youth*) NOT (adult* OR men OR women)):ti
		Exclude unwanted publication and study types (e.g., case reports, conferences, editorials)	NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR (book OR chapter OR conference OR editorial OR letter):it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR (abstract OR annual OR conference OR congress OR meeting OR proceedings OR sessions OR symposium):nc OR ((book NOT series) OR 'conference proceeding'):pt OR ('case report' OR comment* OR editorial OR letter OR news):ti OR ((protocol AND (study OR trial)) NOT ('therapy protocol*' OR 'treatment protocol*')):ti)
		Limit to English-language publications	AND [english]/lim
		Limit to results published 2012-2021, and added to the database by December 31, 2021	AND [2012-2021]/py AND ([1-1-1900]/sd NOT [31-12-2021]/sd)
Study-type Filters		Limit to systematic reviews and meta-analyses	AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR (cochrane* OR metaanaly* OR 'meta analy*' OR (search* AND (cinahl* OR databases OR ebsco* OR embase* OR psychinfo* OR psycinfo* OR 'science direct*' OR sciencedirect* OR scopus* OR systematic* OR 'web of knowledge*' OR 'web of science')) OR (systematic* NEAR/3 review*)):ti,ab) NOT ((protocol NEXT/3 review) OR 'review protocol' OR 'scoping review'):ti
		Limit to randomized controlled trials	AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR random*:ti,ab OR RCT:ti,ab)
		Limit to diagnostic accuracy and diagnostic cohort studies	'diagnosis':lnk OR 'cohort analysis'/de OR ‘diagnostic accuracy’/de OR ‘diagnostic test accuracy study’/de OR cohort*:ti,ab OR predict*:ti,ab OR specificit*:ti,ab
Retracted Publications		Remove retracted publications	All results screened and retracted items (and notices of retraction) excluded from final set of citations

Appendix M: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Management of Bipolar Disorder Algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

Module A: Diagnosis and Triage

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: "Adults who present with either suspected or known BD (see **Sidebar 1**)"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Perform safety screening (see **Sidebar 2**)"
3. Box 2 connects to Box 3, in the shape of a hexagon, which asks, "Does the patient need immediate evaluation, hospitalization, or both because of safety concerns (e.g., self-harm)?"
    a. If the answer is "Yes" to Box 3, then Box 4, in the shape of a rectangle: "Exit algorithm; refer to appropriate setting"
    b. If the answer is "No" to Box 3, then Box 5
4. Box 5, in the shape of a hexagon, asks, "Does the patient have established BD?"
    a. If the answer is "Yes" to Box 5, then Box 6, in the shape of a hexagon, asks, "Is the patient reaching treatment goals?"
        i. If the answer is "Yes" to Box 6, then Box 9, in the shape of a rectangle: "Continue maintenance treatment following a plan developed collaboratively by the patient and specialty mental health care providers (see **Sidebar 4**)"
        ii. If the answer is "No" to Box 6, then Box 10, in the shape of a rectangle: "Refer patient to specialty mental health for evaluation"
    b. If the answer is "No" to Box 5, then Box 7, in the shape of a rectangle: "Evaluate presenting symptom or symptoms in primary care (see **Sidebar 3**)"
5. Box 7 connects to Box 8, in the shape of a hexagon, which asks, "Does the patient have suspected BD after being evaluated in primary care?"
    a. If the answer is "Yes" to Box 8, then Box 10, in the shape of a rectangle: "Refer patient to specialty mental health for evaluation"
    b. If the answer is "No" to Box 8, then Box 11, in the shape of a rectangle: "Assess for alternative diagnosis to explain the presenting symptom or symptoms; exit algorithm, as needed"
6. Box 10 connects to Box 12, in the shape of an oval: "Go to **Module B: Specialty Care**"

Module B: Specialty Care

1. The algorithm begins with Box 13, in the shape of a rounded rectangle: “Adults who present with either suspected BD or symptomatic known BD”
2. Box 13 connects to Box 14, in the shape of a rectangle: “Assess for safety (see **Sidebar 2**)”
3. Box 14 connects to Box 15, in the shape of a hexagon, which asks, “Does the patient need immediate evaluation, hospitalization, or both because of safety concerns (e.g., self-harm)?”
    a. If the answer is “Yes” to Box 15, then Box 16, in the shape of a rectangle: “Exit algorithm; refer to appropriate setting”
    b. If the answer is “No” to Box 15, then Box 17
4. Box 17, in the shape of a hexagon, asks, “Does the patient have suspected BD 1?”
    a. If the answer is “Yes” to Box 17, then Box 18, in the shape of a rectangle: “Confirm diagnosis of BD 1 by DSM-5-TR criteria”
        i. Box 18 connects to Box 19, in the shape of a hexagon, which asks, “Does the patient have unstable or acute symptoms?”
            1. If the answer is “Yes” to Box 19, then Box 21
            2. If the answer is “No” to Box 19, then Box 20, in the shape of a rectangle: “Consider maintenance treatment (see **Sidebar 4**)”
    b. If the answer is “No” to Box 17, then Box 25
5. Box 21, in the shape of a hexagon, asks, “Does the patient have acute mania or hypomania with marked impairment?”
    a. If the answer is “Yes” to Box 21, then Box 31, in the shape of a rectangle: “Reassess diagnosis; reconsider BD 1”
    b. If the answer is “No” to Box 21, then Box 22, in the shape of a hexagon, asks, “Does the patient have acute depression?”
        i. If the answer is “Yes” to Box 22, then Box 24, in the shape of an oval: “Go to **Module D: Management of Acute Bipolar Depression**”
        ii. If the answer is “No” to Box 22, then Box 23, in the shape of a rectangle: “Reassess patient for other causes of these symptoms e.g., co-occurring conditions) (see **Sidebar 5**)”

6. Box 25, in the shape of a hexagon, asks, “Does the patient have suspected BD 2?”
    a. If the answer is “Yes” to Box 25, then Box 27, in the shape of a rectangle: “Confirm diagnosis of BD 2 by DSM-5-TR criteria”
    b. If the answer is “No” to Box 25, then Box 26, in the shape of a rectangle: “Reassess (see **Sidebars 3** and **5**)”
7. Box 27 connects to Box 28, in the shape of a hexagon, which asks, “Does the patient have acute depression?”
    a. If the answer is “Yes” to Box 28, then Box 29, in the shape of an oval: “Go to **Module D: Management of Acute Bipolar Depression**”
    b. If the answer is “No” to Box 28, then Box 30
8. Box 30, in the shape of a hexagon, asks, “Does the patient have acute mania or hypomania with marked impairment?”
    a. If the answer is “Yes” to Box 30, then Box 31, in the shape of a rectangle: “Reassess diagnosis; reconsider BD 1”
        i. Box 31 connects to Box 32, in the shape of an oval: “Go to **Module C: Management of Mania/Hypomania**”
    b. If the answer is “No” to Box 30, then Box 33, in the shape of a rectangle: “Rule out hypomania (BD 2)”
9. Box 33 connects to Box 34, in the shape of a hexagon, which asks, “Is the patient stable with no acute symptoms?”
    a. If the answer is “Yes” to Box 34, then Box 35, in the shape of a rectangle: “Consider maintenance treatment (see **Sidebar 4**), or consider non-pharmacological treatment (see **Sidebar 6**) to prevent illness recurrence”
    b. If the answer is “No” to Box 34, then Box 23, in the shape of a rectangle: “Reassess patient for other causes of these symptoms (e.g., co-occurring conditions) (see **Sidebar 5**)”

Module C: Management of Mania/Hypomania

1. The algorithm begins with Box 36, in the shape of a rounded rectangle: “Adults presenting with mania (see **Sidebar 7**)”
2. Box 36 connects to Box 37, in the shape of a hexagon, which asks, “Does the patient have mania with mixed features?”[a]
    a. If the answer is “Yes” to Box 37, then Box 38, in the shape of a rectangle: “Consider initiating quetiapine (600 mg daily or more might be required) or another SGA; or lithium”
    b. If the answer is “No” to Box 37, then Box 39, in the shape of a rectangle: “Initiate lithium”

3. Box 38 connects to Box 40, in the shape of a hexagon, which asks, “Was there a satisfactory response?”
    a. If the answer is “Yes” to Box 40, then Box 42, in the shape of a rectangle: “Consider maintenance treatment (see **Sidebar 4**)”
    b. If the answer is “No” to Box 40, then Box 43, in the shape of a rectangle: “Consider adding valproate or lithium (if the choice above was an SGA)”
        i. Box 43 connects to Box 47
4. Box 39 connects to Box 41, in the shape of a hexagon, which asks, “Was there a satisfactory response?”
    a. If the answer is “Yes” to Box 41, then Box 42, in the shape of a rectangle: “Consider maintenance treatment (see **Sidebar 4**)”
    b. If the answer is “No” to Box 41, then Box 44, in the shape of a rectangle: “Consider adding quetiapine or another SGA”
5. Box 44 connects to Box 45, in the shape of a hexagon, which asks, “Was there a satisfactory response?”
    a. If the answer is “Yes” to Box 45, then Box 42, in the shape of a rectangle: “Consider maintenance treatment (see **Sidebar 4**)”
    b. If the answer is “No” to Box 45, then Box 46, in the shape of a rectangle: “Change to a different SGA; consider valproate or carbamazepine”
6. Box 46 connects to Box 47, in the shape of a rectangle, which contains a bulleted list:
    - Stop ineffective medications in patients with an unsatisfactory response to prevent polypharmacy and avoid giving two antipsychotics simultaneously
    - Consider other contributions to unsatisfactory medication response (see **Sidebar 5**)
    - Choose one of these options if not already used: risperidone, haloperidol, olanzapine, carbamazepine, valproate; or aripiprazole, ziprasidone, asenapine, cariprazine; or clozapine
7. Box 47 connects to Box 48, in the shape of a rectangle, which contains a bulleted list: “If results still unsatisfactory:
    - Remember to stop ineffective medications to prevent polypharmacy
    - Avoid giving two antipsychotics simultaneously
    - Pick another medication from Box 47 or ECT”

Module D: Management of Acute Bipolar Depression

1. The algorithm begins with Box 49, in the shape of a rounded rectangle: “Adults who present with acute bipolar 1 depression”
2. Box 49 connects to Box 50, in the shape of a hexagon, which asks, “Is an urgent indication for ECT present (e.g., severe SI, catatonia, insufficient oral intake)?”
    a. If the answer is “Yes” to Box 50, then Box 51, in the shape of a rectangle: “Consider ECT, as recommended”
    b. If the answer is “No” to Box 50, then Box 52, in the shape of a rectangle: “Consider other non-pharmacological treatment (see **Sidebar 6**)”
3. Box 52 connects to Box 53, in the shape of a rectangle: “Consider ketamine if ECT is unacceptable, unsuccessful, or unavailable”
4. Box 52 and Box 53 connect to Box 54, in the shape of a rectangle: “Determine medications the patient is currently on”
5. Box 54 connects to Box 55, in the shape of a rectangle: “Patient is on lithium”; Box 56, in the shape of a rectangle: “Patient is not on any medications used for BD”; Box 57, in the shape of a rectangle: “Patient is on valproate, carbamazepine, or lamotrigine”; Box 58, in the shape of a rectangle: “Patient is on quetiapine, lumateperone, lurasidone, or cariprazine”; Box 59, in the shape of a rectangle: “Patient is on olanzapine, the combination of olanzapine and fluoxetine, or one or more antidepressants”
6. Box 55 connects to Box 61, in the shape of a rectangle: “Optimize lithium to 0.6–0.8 mEq/L and add lamotrigine or quetiapine; or add lumateperone or lurasidone”
7. Box 61 connects to Box 62, in the shape of a hexagon, which asks, “Did the patient respond?”
    a. If the answer is “Yes” to Box 62, then Box 63, in the shape of a rectangle: “Maintain therapy”
    b. If the answer is “No” to Box 62, then Box 66
8. Box 57 and Box 58 connect to Box 60, in the shape of a rectangle: “Optimize dosage”
    a. Box 60 connects to Box 64
9. Box 59 connects to Box 64, in the shape of a hexagon, which asks, “Has the patient tried quetiapine, lurasidone, cariprazine, lumateperone, or the combination of lithium and lamotrigine?”
    a. If the answer is “Yes” to Box 64, then Box 66
    b. If the answer is “No” to Box 64, then Box 65, in the shape of a rectangle: “Start one of these not previously tried; see text for help in selecting”

10. Box 66, in the shape of a hexagon, asks, “Has there been a trial of one of the other drugs in Box 64?”
    a. If the answer is “Yes” to Box 66, then Box 68, in the shape of a rectangle: “All options have either been tried or are unsuitable (see **Sidebar 5**)”
    b. If the answer is “No” to Box 66, then Box 67, in the shape of a rectangle: “Try another of the five choices not yet tried, or consider ECT”
11. Box 68 connects to Box 69, in the shape of a hexagon, which asks, “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?”
    a. If the answer is “Yes” to Box 69, then Box 70, in the shape of a rectangle: “Continue to avoid antidepressants”
        i. Box 70 connects to Box 72
    b. If the answer is “No” to Box 69, then Box 71
12. Box 71, in the shape of a hexagon, asks, “Has the patient had a trial of adjunctive antidepressants?”
    a. If the answer is “Yes” to Box 71, then Box 72
    b. If the answer is “No” to Box 71, then Box 73, in the shape of a rectangle: “Confirm adequate dose mood stabilizer; add antidepressant (bupropion or an SSRI)”
13. Box 72, in the shape of a hexagon, asks, “Has the patient tried combinations involving lithium, quetiapine, lamotrigine, lurasidone, cariprazine, and lumateperone?”
    a. If the answer is “Yes” to Box 72, then Box 74, in the shape of a rectangle: “Consider ECT or other strategies for refractory bipolar depression”
    b. If the answer is “No” to Box 72, then Box 75, in the shape of a rectangle: “Try one or combinations of these options”

Appendix N: Abbreviations

Abbreviation	Definition
ACT	Assertive Community Treatment
AcH	Anticholinergic effects
ADHD	Attention-deficit/hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
AUC	Area under the curve
AUD	Alcohol use disorder
BD	Bipolar disorder
BD 1	Bipolar 1 disorder
BD 2	Bipolar 2 disorder
BFT	Behavioral Family Therapy
BSDS	Bipolar Spectrum Diagnostic Scale
CAE	Customized adherence engagement
CAMS	Collaborative Assessment and Management of Suicidality
CBT	Cognitive behavioral therapy
CI	Confidence interval
CNS	Central nervous system
COI	Conflict of interest
CPG	Clinical practice guideline
CS	Clinical study
C-SSRS	Columbia-Suicide Severity Rating Scale
CUDOS-M	Clinically Useful Depression Outcome Scale
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation Study
EBPWG	Evidence-Based Practice Work Group
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EMBASE	Excerpta Medica Database
EPS	Extrapyramidal symptoms
FDA	U.S. Food and Drug Administration
FFT-HPI	Family-Focused Treatment-Health-Promoting Intervention
FGA	First-generation antipsychotic
GAD	Generalized anxiety disorder
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAM-D	Hamilton Depression Rating Scale
HCL	Hypomania Checklist

Abbreviation	Definition
HCL-13	13-item Hypomania Checklist
HCL-32	32-item Hypomania Checklist
HCL-33	33-item Hypomania Checklist
HR	Hazard ratio
ICDs	Impulse control disorders
ICMHR	Intensive Community Mental Health Recovery
IPS	Individual Placement Support
IOM	Institute of Medicine
IPSRT	Interpersonal and social rhythm therapy
IR	Incidence rate
ISS	Internal State Scale
iTBS	Intermittent theta burst stimulation
IV	Intravenous
KQ	Key question
LAI	Long-acting injectable
LGCC	Life Goals Collaborative Care
MBCT	Mindfulness-based cognitive therapy
MDD	Major depressive disorder
MDQ	Mood Disorder Questionnaire
MHS	Military Health System
MIRECC	Mental Illness Research, Education, and Clinical Center
MTF	Military treatment facility
NAM	National Academy of Medicine
NAMI	National Alliance on Mental Illness
NICE	National Institute for Health and Care Excellence
NRT	Nicotine replacement therapy
OCD	Obsessive-compulsive disorder
OR	Odds ratio
OUD	Opioid use disorder
PCM	Primary care manager
PCP	Primary care provider
PHQ	Patient Health Questionnaire
PHQ-2	Patient Health Questionnaire-2
PHQ-9	Patient Health Questionnaire-9
PICOTS	Population, intervention, comparison, outcome, timing, and setting
POETIC	Purpose and meaning, optimism and hope, empowerment, tensions, identity, and connectedness
PPA	Point prevalence abstinence
PPV	Positive predictive value
PRRC	Psychosocial Rehabilitation and Recovery Center

Abbreviation	Definition
PTSD	Posttraumatic stress disorder
PUFA	Polyunsaturated fatty acid
PY	Person years
QoL	Quality of life
QTc	QT corrected for heart rate
RCT	Randomized controlled trial
RR	Relative risk
rTMS	Repetitive transcranial magnetic stimulation
SAD	Seasonal affective disorder
SAMe	S-adenosylmethionine
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	Standard deviation
SGA	Second-generation antipsychotic
SJS/TEN	Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
SMD	Standardized mean difference
SMI	Serious mental illness
SNRI	Serotonin-norepinephrine reuptake inhibitor
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TAU	Treatment as usual
TBI	Traumatic brain injury
TCA	Tricyclic antidepressant
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VCBFC	Veteran-Centered Brief Family Consultation
VHA	Veterans Health Administration
VISN	Veterans Integrated Services Network
YLD	Years lost to disability
YMRS	Young Mania Rating Scale

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