Bipolar Disorder Among Older Adults: Newer Evidence to Guide Clinical Practice

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The term *older-age bipolar disorder* (OABD) refers to patients with bipolar disorder who are ages 50 and older. Research findings suggest important differences, including the attenuation of manic symptoms with age and the occurrence of multiple somatic comorbid conditions. Although the pharmacological treatment of OABD is fairly similar, adverse effects, somatic comorbidity, and drug-drug interactions are more common. Lithium is effective in treating OABD and may have the potential to be neuroprotective. Anticonvulsants and second-generation antipsychotics have a growing evidence supporting their use in treating OABD. Behavioral intervention can be a helpful adjunct to pharmacological treatment. Clinicians and health care systems need to be prepared to provide care and services to individuals with bipolar disorder throughout the life span. Although older adults have typically been excluded from bipolar disorder RCTs, emerging efforts organized by global advocates and harnessing teams of clinicians and scientists have the potential to advance care.

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The aging population is increasing, and growth in the proportions of persons ages 60 years and older is occurring in tandem with declines in the proportions of young people under the age of 15, especially in Western and East Asian nations (1). In alignment with this proportional "aging" of the global population, approximately one-quarter of those with bipolar disorder are ages 60 and older (2). Clinicians and health care systems need to be prepared to provide care and services to individuals with bipolar disorder throughout the life span, with particular attention to a growing older population that may have specific care needs.

The term *older-age bipolar disorder* (referred to herein as OABD) refers to patients diagnosed as having bipolar disorder who are ages 50 and older. This age cutoff is recommended by the International Society for Bipolar Disorders (ISBD) Task Force on Older-Age Bipolar Disorder (3) and is motivated by the fact that patients with serious mental illness, such as bipolar disorder, have a reduced life expectancy of 10–20 years (4), and their biological age may precede their chronological age (5).

OABD includes both aging patients whose mood disorder presented earlier in life as well as patients with a first episode after age 40 (6). Although there is no firmly established cutoff for early-onset bipolar disorder versus late-onset bipolar disorder, the ISBD Task Force on Older-Age Bipolar Disorder has suggested a cutoff for late-onset bipolar disorder at 40 years, given the emerging data on age at onset across the life span (3), with a weighted mean age at onset (manic or depressive episode) of 48.0 years (SD=6.4; range=28–65 years) in samples of older adults with bipolar disorder. Historically, the clinical profile of early-onset bipolar disorder has been most often associated with a family history of mood disorder (6). The clinical distinction by age at first mood episode was supposed to guide clinical management with close monitoring of cognitive functioning and anticipating poor treatment response to medication in the late-onset bipolar disorder group. However, a study on bipolar disorder among older adults observed no significant differences in co-occurring medical and psychiatric conditions among patients with early-onset versus late-onset bipolar disorder (7), possibly indicating that clinical profiles cannot be distinguished by age at onset (8). When viewing bipolar disorder in its chronic nature across the life span, the question arises as to whether patients with early-onset versus late-onset bipolar disorder might differ in clinical symptoms and treatment needs. In the Global Aging & Geriatric Experiments in Bipolar Disorder data set with a large proportion of older adults, it was demonstrated that depression, mania, and functioning may not differ between patients with early-onset versus late-onset bipolar disorder (9).

EPIDEMIOLOGY AND CLINICAL COURSE OF OABD

Although OABD does not resolve or "burn out," epidemiologic studies indicate that bipolar disorder affects 0.5%–1.0% of older adults, which is lower than the prevalence of 1.4% reported in patients 18–44 years old (10) (Table 1). The lower prevalence may be due to underreporting by older adults, underrecognition of bipolar disorder symptomatology by clinicians, or premature death caused by co-occurring somatic conditions (11, 12). The prevalence appears to be

higher in clinical populations and settings. OABD accounts for 6% of geriatric psychiatric outpatient visits and 8%–10% of psychiatric hospitalizations (13), with an overall prevalence of late-life mania of 6.0% in older adults with bipolar disorder who are admitted (14). North American studies report a prevalence of 3% for older adults with bipolar disorder in nursing homes and 17% in psychiatric emergency rooms (13).

The clinical course is understudied in OABD. In a lifespan study of 220 patients with bipolar disorder over the course of approximately 40 years, it was shown that the frequency of recurrent mood episodes remained constant up to the age of 70 years and older (15). In a naturalistic study of OABD, with a follow-up of 3 years, 37.5% of patients reported at least one mood episode, mainly depression (16). Life events, somatic illness, and use of lithium were not associated with recurrence during the 3-year follow-up; nor were social, psychological, and cognitive factors (17). However, among older adults with bipolar disorder, those with recurrence were younger, more often female, and less likely to have children.

Predictors for recurrence were studied during COVID-19 measures, as this provided a unique opportunity to study the course of mental health symptoms in individuals with OABD while they experienced a collective negative life event. It was found that not having children, more feelings of loneliness, passive coping style, and neuroticism were associated with more psychiatric symptoms (18). After the initial resilience of older adults with bipolar disorder during the first months of the COVID-19 outbreak, depressive, manic, and anxiety symptoms increased as the pandemic continued (19). It is interesting that sense of mastery was initially protective, but over the course of 6 months, a higher sense of mastery was associated with a greater increase in mood symptoms. This stresses the need to develop psychotherapeutic strategies to prevent recurrence in this vulnerable group.

It is important to note that OABD may present differently from younger adults with bipolar disorder. OABD is associated with a higher comorbidity of physical illness, cognitive dysfunction, prevalence of depressive episodes, secondary mania, and antidepressant use compared with bipolar disorder among younger adults (20). Comparatively, OABD has lower comorbidity of mental illness, personality disorders, severity of depressive episodes, substance use disorders, family history of mood disorders, and attention-deficit hyperactivity disorders (20). In addition to comparing younger adults with older adults, there is also the distinction to be made between early-onset bipolar disorder and late-onset bipolar disorder in older adults (21).

EFFORTS TO BETTER UNDERSTAND OABD

In 2012, the ISBD installed a task force devoted to the study of OABD specifically to facilitate the expansion of our knowledge about OABD, to better understand the evolution of the disorder through the life span, and to determine the impact of current treatment. Notably, this Task Force's work continues a decade later (22). In 2018, the Global Aging & Geriatric Experiments in Bipolar Disorder project was funded by the Bowden Massey Strategic Research Initiative in Bipolar Disorder Award (23), bringing together 14 international investigators, many of which are members of the ISBD Older-Age Bipolar Disorder Task Force, and representing a broad geographic distribution and data on a first "wave" of 1,377 older participants with bipolar disorder (24). Further analyses, including the replication of previous findings, are currently being performed using additional data collected in a second wave from 15 studies and over 1,200 participants and including more international research groups with a focus on aging with bipolar disorders. These efforts, supported by the ISBD, have resulted in several new findings that have potentially far-reaching clinical and scientific implications, as a larger and more diverse pool of data will increase generalizability and impact.

TABLE 1. Prevalence of bipolar disorder among older adults in various settings

Setting and reference	Prevalence (%)
General population (9)	0.5–1.0
Outpatient geriatric clinic (10)	6
Inpatient geriatric clinic (10)	8–10
Nursing home (10)	3
Psychiatric emergency room (10)	17

TREATMENT STRATEGIES AND EVIDENCE

OABD can be a challenge to treat (25). Clinicians must address the issues of polypharmacy, medication adherence, comorbid conditions, and tolerability (25–28). To date, there remains a lack of treatment guidelines mainly because of limited research and clinical trials specifically with older adults (6, 13, 20, 27–29). Awareness of co-occurring conditions and coordination with other care providers are essential for appropriate monitoring, treatment plans, and follow-ups for older adults.

Biological Treatments

Top treatments. Recent literature reviews suggest that treatments for OABD should focus on pharmacological as well as nonpharmacological and psychosocial approaches (20). Pharmacological treatment of OABD is generally fairly similar to adult treatment (6, 30), and the U.S. Food and Drug Administration (FDA) does not currently differentiate bipolar disorder treatments as specific to adults versus older adults. However, the limitation for older adults with bipolar disorder is that these adults have typically been excluded from RCTs of bipolar disorder medications (6, 20, 24), and data specific to this population are sparse.

Lithium is considered the gold-standard treatment for bipolar disorder and is the first and long-term treatment

recommendation (31–34). Lithium is associated with a reduction of suicidality and improvements in depressive episodes, mania, and maintenance (20, 25, 30, 35). Additionally, and perhaps with the greatest relevance for OABD, there is epidemiological and neurophysiological evidence suggesting that lithium may have neuroprotective properties and reduce the risk of subsequently developing dementia (36, 37). The results of neuroimaging studies have suggested that adults with bipolar disorder who were treated with lithium have better preserved cortical gray matter volume (38–40). A five-study meta-analysis evaluating the potential neuroprotective effect of lithium estimated that lithium treatment decreased the risk for dementia by 49% in individuals with bipolar disorder (odds ratio=0.51, 95% confidence interval=0.36–0.72) (41).

The ISBD Older-Age Bipolar Disorder Task Force has published expert-based guidelines on lithium in treating OABD using a Delphi survey approach (42). The expert recommendation for therapeutic blood levels was 0.4–0.8 mmol/L for bipolar disorder among older adults between the ages of 60 and 79 and 0.4–0.7 mmol/L for those ages 80 and older. A cross-sectional study in OABD found lower depression in OABD treated with lithium, as well as better global cognition and functioning performance. A large-scale RCT (the GERI-BD study) of lithium for OABD compared the tolerability and efficacy of lithium with that of divalproex in older adults for acute mania and mixed presentations (43). Both drugs were shown to be effective and well tolerated, although lithium was associated with greater reduction in acute manic symptoms. Lithium users had a higher rate of tremor, which is a leading cause of lithium intolerance (34, 43). The GERI-BD study concluded that treatment guidelines for OABD should suggest the use of lithium because it was effective, was well tolerated, and may have neuroprotective mechanisms and antisuicide effects (43). Additionally, the GERI-BD study authors have suggested less use of antipsychotics because of their adverse effects and potential for premature mortality (43). In spite of RCT evidence supporting its effectiveness, the use of lithium in treating OABD compared with second-generation antipsychotic agents and divalproex is limited, possibly because of concerns about its potential toxicity, limited familiarity among younger clinicians with the use of lithium, and perhaps the lack of commercial sponsorship and marketing (44).

Besides lithium, there are more pharmacological treatment options, such as anticonvulsants, antipsychotics, and antidepressants (6, 20, 21, 30). Valproic acid and its derivatives are generally tested in trials, with lithium as the comparison (43). For instance, divalproex has demonstrated efficacy in bipolar disorder acute type I mania in an RCT that specifically targeted older adults, although lithium demonstrated a greater reduction in mania scores after 9 weeks (43). Valproic acid has good tolerability and is frequently used with OABD for mania, even though it appears to be inferior to lithium (20). A study comparing divalproex plus memantine (N=27) with divalproex plus placebo (N=31) in the treatment of patients over 60 years of age with acute bipolar mania found that both groups showed significant reduction in mania severity but that mania reduction was higher in the memantine group (45). Valproic acid is a good alternative to lithium for OABD but it is important to adjust the dose, as older adults have reduced clearance of valproic acid because of the way it is metabolized (20).

Other published data on additional anticonvulsant treatments are based on post hoc subgroup analyses or uncontrolled smaller studies. The anticonvulsant lamotrigine may have antidepressant effects in OABD on the basis of an open study add-on to lithium or divalproex (46). A pooled analysis of two RCTs of lamotrigine found reduced time to depressive relapse (47), and an additional secondary analysis from this same data set confirmed the effect in patients ages 55 years and older (48). A multisite, 12-week, open-label trial of lamotrigine augmentation in older adults with either bipolar disorder type I or type II depression showed improvement in depression, psychopathology, and functional status (49). However, physicians should start at a lower dosage to reduce the potential for rashes and Stevens-Johnson syndrome and use a reduced dosage in cases of liver or kidney dysfunction (20).

Carbamazepine, an anticonvulsant, has been reported to have negative side effects such as undesirable neurotoxic symptoms, changes in blood count, allergies, hyponatremia, urinary retention, and blood dyscrasias (20, 50). Because of the amount of negative side effects and limited data on its benefits, this should be used as a last resort (20, 51).

There is some positive evidence for the use of the second-generation antipsychotics quetiapine, risperidone, aripiprazole, asenapine, and lurasidone to treat patients with OABD for mania (52–59). A secondary analysis of an RCT demonstrated the safety and efficacy of quetiapine among older adults (N=59) with bipolar I mania (59). Furthermore, a secondary analysis of an RCT demonstrated that lurasidone was well tolerated and effective for treating depressive symptoms in OABD (57, 58). Clinically, antipsychotics are a very helpful treatment option for bipolar disorder among older adults; however, clinicians should be aware of the potential for adverse effects, such as increased cardiovascular mortality risks, risk of stroke, and extrapyramidal side effects or falls (20).

The use of antidepressants remains controversial because of the potential risk for a switch to mania (60). To our knowledge, there are no clinical studies, and certainly no clinical trials, that have examined antidepressants for the treatment of OABD. However, from our clinical experience in treating these patients, it can be helpful to use an antidepressant in combination with a mood stabilizer or antipsychotic medication to address residual depressive symptoms. When using antidepressants to treat bipolar disorder among older adults, it would be most cautious to use medications with the least likelihood of manic switch, such as mirtazapine or bupropion (60).

The use of benzodiazepines is controversial, especially so in older adults because it can be associated with falls, respiratory issues, and cognitive issues (61). In addition, the short duration of benzodiazepine use when treating bipolar disorder is important, as it has been associated with worsening mania and depressive symptoms in long-term use (62, 63). Nonetheless, in the guidelines for treating adults with bipolar disorder, short-term benzodiazepine use can be helpful in managing poor sleep quality and agitation (6, 61).

Transcranial magnetic stimulation (TMS) treatment for OABD is lacking data, with most TMS studies focused on younger patients with bipolar disorder or late-life depression (64–66). Recent reviews have reported that TMS was safe and improved depressive and anxiety symptoms for older adults (64, 66).

In cases of treatment resistance, some data suggest the safety and efficacy of pramipexole as augmentation of antidepressant treatment for treatment-resistant unipolar and bipolar depression (67). However, this needs to be confirmed for OABD. Ketamine is another treatment option that has been beneficial for depressive symptoms and is most known for its rapid effects (68). The literature confirms its safety and efficacy for use with older adults with unipolar depression (69, 70); however, specific studies for OABD are lacking.

Electroconvulsive therapy (ECT). In most treatment guidelines, ECT is positioned as a second- or third-line therapy for adults with bipolar disorder, without further specification for OABD given the lack of evidence from large clinical trials of patients with OABD who are treated with ECT. Among patients with unipolar depression, response rates with ECT are up to 90%, and older age is a strong predictor (71). For treatment-resistant bipolar depression, ECT is the treatment option with the most supporting evidence (72). Therefore, a favorable effect of ECT in OABD is generally to be expected. Indications for treatment with ECT among these patients are cases of treatment resistance, previous ECT response, or urgent safety concerns (severe suicidality, physical exhaustion, or refusal of all foods and fluids). There are concerns about safety and cognitive side effects; however, given the extensive data in older adults with unipolar depression, ECT appears to be a safe and effective treatment for OABD (73) that is probably underutilized.

Tolerability, side effects, and complications. Adverse drug reactions generally increase with age, even at lower drug concentrations, and adverse effects can lead to even more complications, such as falls, fractures, and head injury (20, 33). Sedation and/or dizziness, a common adverse effect of many medication treatments for bipolar disorder, can increase fall risk. Some cellular or metabolic functions such as reduced enzyme activity can affect the dose of medications for older adults, often requiring lower doses (20). Metabolic pathways that involve CYP3A4 function tend to have reduced function with age, whereas those that involve CYP2D6 function tend to have minimal changes that are related to age (20).

Lithium use remains as a significant topic of debate because of the potential for adverse effects on renal, thyroid, and parathyroid functioning (31, 34, 74, 75). A recent systematic review examined 33 studies on lithium in the past decade and concluded that long-term lithium use was strongly associated with nephrogenic diabetes insipidus and chronic kidney disease. Furthermore, they also mention the association of lithium with acute kidney injury, although its causal relationship is less clear (74). However, one important point is that lithium, even in monotherapy, is associated with higher rates of remission in OABD than other agents (76), and side effects can be greatly minimized by adopting a therapeutic range of 0.3–0.7mmol/L in OABD (42, 77). In addition, antipsychotic medications in OABD have the risk of extrapyramidal symptoms and tardive dyskinesia (78). There is an FDA boxed warning regarding the use of antipsychotic drugs in elderly patients with dementia (79), although it is not clear how this might apply to individuals with bipolar disorder. More research on lithium and other medications for OABD in individuals with dementia is needed; however, a recent RCT found low-dose lithium for behavioral complications in older adults with Alzheimer's disease to be safe (80). Older adults are particularly susceptible to cardiovascular risks such as QTc prolongation when using psychotropic drugs such as antipsychotics and antidepressants (81–83).

Because older adults tend to have more medications compared with their younger counterparts, polypharmacy is an ongoing concern; older adults usually have a higher probability of increased drug-drug interactions, and this may complicate the use of pharmacological treatments (20, 33). One example is the use of benzodiazepines and anticholinergics for OABD. Such use may lead to an increased risk of falls and delirium, which tends to be already elevated for older adults (33). In addition, some older adults may have preexisting cognitive impairments, and certain medications for bipolar disorder may exacerbate the risk of cognitive impairments.

Behavioral Treatments

Top treatments. Considering that older adults may have multiple illnesses with prescription medications, the use of behavioral treatments provides a lower risk of drug-drug interactions and a reduced risk of negative side effects. The current treatment of choice for OABD is a combination of pharmacological and behavioral/psychosocial treatments (21). Behavioral treatments have been shown to be efficacious. Some examples include cognitive-behavioral therapy (CBT), medication adherence skills training for bipolar disorder (MAST-BD), psychoeducation, family-focused therapy (FFT), interpersonal and social rhythms therapy (IPSRT), the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), exercise, nutrition, coping

strategies, and psychotherapy (33, 84–88). CBT is a form of talk therapy that can be conducted one-on-one or in group settings. It focuses on managing the patients' thoughts, perceptions, and behaviors (33, 84, 86, 87). MAST-BD is an intervention that provides patients with OABD with educational, motivational, medication management skills, and symptom management training (88). Similarly, psychoeducation also provides information on the illness, treatments, and management to enhance the patient's knowledge and understanding (84, 86, 87, 89). FFT is a form of psychoeducation, but it focuses on providing information to not only the patient but also their family (84, 86, 87). IPSRT is a therapy that focuses on increasing the regularity of patients' daily routines (e.g., sleep–wake cycles, meal times, and rest vs. activity) (84). Last, STEP-BD combines aspects from CBT, FFT, IPSRT, and psychoeducation (84–86). Benefits for behavioral treatments are reduced risk of relapse, general feelings of wellness, reduced hospitalizations, and reduced number medications (87, 89). Behavioral treatments are recommended to be used in combination with the biological therapies and can aid in adherence to medication, stigma, stress, and mental health (26, 33, 84, 89). However, behavioral treatments are often difficult to access with long wait times, high costs, and require caregiver support (90). Similar to the limitations noted for pharmacological treatments, there are very limited publications on behavioral interventions for bipolar disorder among older adults.

Barriers to care and treatment. As is the case among younger individuals, older people with bipolar disorder may be undiagnosed or misdiagnosed with conditions other than bipolar disorder (91). Specifically in late-onset bipolar disorder, patients often overlook and dismiss their own psychiatric symptoms, leading to a missed diagnosis (91). For older individuals with new-onset behavioral symptoms, it may be challenging to disentangle bipolar disorder from a neurodegenerative condition, such as frontotemporal dementia (92).

Approximately 50% of all individuals with bipolar disorder become medication nonadherent during their long-term treatment (26, 93). Variables that affect treatment adherence are not completely understood; however, patient-centered variables such as stigma and attitudes toward medication may play a significant role (26). Treatment nonadherence is an especially important barrier to overcome, as it may lead to increased risk of relapse, suicide, and rehospitalization.

Barriers to behavioral treatments, especially for older adults, include accessibility, cost, and may increase caregiver burden. Older adults with bipolar disorder may have mobility issues, which increases the barriers for access. Moreover, behavioral therapies often have long wait times, require travel, and can have costs associated with them. Although technology-based interventions are beginning to be used to improve accessibility and scheduling and reduce the burden on caregivers, there is a lack of studies examining technology-based interventions for OABD. A focus on interventions to provide more information on bipolar disorder and reducing the stigma of bipolar disorder among older adults is needed (33).

QUESTIONS AND CONTROVERSIES

Recent findings in research on bipolar disorder among older adults have benefited from large, harmonized international data sets such as the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) project, which focuses on the collection and harmonization of international data sets that include geriatric populations with bipolar disorder (3, 94). A key goal thus far of the GAGE-BD project has been to examine patterns of mood trajectories in OABD. Manic and depressive symptom severity was found to be lower in older people (24). However, a replication analysis showed somewhat inconsistent findings, potentially because of the differential age and clinical characteristics of more recent research samples (24).

Classifying clinical presentations on the basis of mood states notably also involves mixed states. Existing research findings suggest that there may be important differences in bipolar disorder among older people versus younger people, including the attenuation of manic symptoms with age (24). In a cross-sectional OABD sample, mixed features predominated and were associated with worse everyday function. Further, among those with mixed symptoms, functional status related strongly to current depression severity (95).

Another relevant distinction is between bipolar disorder types I and II, with limited success in identifying disease specifiers. Findings from the Global Aging & Geriatric Experiments in Bipolar Disorder project found no differences in global functioning and cognition or somatic burden (96). However, patients with bipolar disorder type II were shown to have late-onset bipolar disorder more often and more current severe depression than patients with bipolar disorder type I, who were more likely to have a history of psychiatric hospitalization and current use of antipsychotic medication treatment. It is possible that these findings could be related, at least in part, to diagnostic classification methods (96).

On the basis of the observed increase of comorbid somatic conditions with aging and the association with bipolar disorder, physical health burden is highly relevant to the therapeutic management of bipolar disorder among older adults. On the basis of findings from another GAGE-BD analysis, more older women than older men showed evidence of morbidities affecting the respiratory, gastrointestinal, musculoskeletal, and endocrinological systems. Further, more older men with bipolar disorder than without it showed evidence of cardiovascular, renal, and endocrinological diseases (97). The study by Almeida and colleagues points out the need for further investigation into the

TABLE 2. Biological and behavioral treatment options for older-age bipolar disorder (OAPD)

Treatments	Background references	Overview comments
Biological treatments		
Lithium	(25, 30–35, 42, 43, 80)	Lithium is a first-line treatment for OABD. Expert recommendation for therapeutic blood levels is 0.4–0.8 mmol/L for adults between the ages of 60 and 79 and 0.4–0.7 mmol/L for those ages 80 and older. Lithium may have neuroprotective effects for OABD. More research on lithium and other medications for OAPD—and for individuals with dementia—is needed; however, a recent RCT found low-dose lithium for behavioral complications in older adults with Alzheimer's disease to be safe.
Anticonvulsant mood stabilizers (e.g., divalproex, lamotrigine)	(6, 21, 43)	Divalproex appears similarly efficacious compared with lithium in bipolar disorder type I mania in older adults. Lamotrigine may have a relatively benign side-effect profile, which is relevant in OABD, where drug-related adverse effects (e.g., sedation, falls risk, weight gain) are a particular concern.
Antipsychotics (e.g., quetiapine, risperidone, aripiprazole, asenapine, and lurasidone)	(6, 21, 44, 52–58)	If possible, avoid first-generation antipsychotic drugs in OABD because of the risk of extrapyramidal effects and tardive dyskinesia. Multiple secondary analyses support the efficacy and relatively good tolerability of second-generation drugs in OABD. There is a boxed warning from the Food and Drug Administration regarding the use of antipsychotic drugs in elderly patients with dementia, although it is not clear how this might apply to individuals with bipolar disorder.
Electroconvulsive therapy (ECT)	(71–73)	In older adults with bipolar disorder who have treatment-resistant depression, comorbid somatic conditions limiting pharmacotherapeutic options, and life-threatening situations (e.g., suicidality or dehydration), ECT should be offered as a safe and effective option. Because of the lack of evidence in OABD, ECT is probably underutilized.
Behavioral treatments		
Cognitive-behavioral therapy (CBT)	(33, 84, 86, 87)	CBT is advantageous when paired with pharmacological treatments; it improves social function and reduces prescriptions, number of hospitalizations, and risk of relapse.
Family-focused therapy (FFT)	(84, 86, 87)	Patients with family support tend to have lower risk of relapse and hospitalization, and overall improved functioning; FFT enhances communication skills in family members and overall support.
Psychoeducation	(84, 86, 87, 89)	Patients learn coping mechanisms, self-management of illness, recognition of early warning signs, and techniques to avoid full-blown episodes, and so forth.
Interpersonal and social rhythm therapy (IPSRT)	(84)	IPSRT improves routine and daily structure and is beneficial for relapse prevention.
Systematic Treatment Enhancement Program (STEP-BD)	(84–86)	STEP-BD has multiple components and includes components of CBT, IPSRT, and FFT.
General wellness, exercise, nutrition	(87, 89)	These provide additional support to improve overall mental and physical symptoms.

potential role of sex hormones in outcomes for bipolar disorder among older adults.

Additional ongoing work across the GAGE-BD consortium focuses on cognitive deficits in OABD, given that such deficits were found by other researchers to be among the most persistent symptoms of bipolar disorder and contribute substantially to disability in OABD (98, 99). Most studies have been small individual studies or meta-analyses, making it difficult to understand the relationship between measures and detect small effects. Therefore, the association between age, cognitive functioning, and bipolar disorder symptoms, using a harmonized measure for global cognition, bears the potential to increase generalizability of findings. Given the entangled nature of aging-associated cognitive decline and cognitive deficits as integral part of bipolar disorder in older adults, neuroimaging studies also bear the potential to yield novel insights into neuroprogression in OABD (100).

Further, ongoing clinical trials focusing specifically on bipolar disorder among older adults can be found on ClinicalTrials.gov, such as a current study that currently includes plans to investigate functional remediation therapy in OABD (ClinicalTrials.gov ID: NCT05186337).

RECOMMENDATIONS

A critical review of the literature in 2015 (3) and a 2016 survey of bipolar disorder treatment guidelines for specific recommendations for OABD (27) both indicated that there remains limited research and a lack of evidence-based guidelines for treating OABD. Existing research studies from which evidence-based clinical recommendations can be made continue to be mostly retrospective in nature, with methodological limitations such as small sample size and limited follow-up duration. Although efforts such as the

GAGE-BD project have increased the collective body of evidence on OABD, there is a still critical need for additional research on bipolar disorder across the full life span.

In the GAGE-BD project, differences in evaluation methods across studies and the loss of data that occurs in the process of harmonization when pooling data (101) brings a whole new set of challenges that may affect the interpretation of results. A systematic review of the most commonly used measures in the assessment of OABD has been identified (102) and recently led to a recommended set of essential data dimensions for future research studies and clinical practice (103). Rigorous prospective RCTs using common evaluation instruments and specific to OABD are a needed next step to advance knowledge on which treatments might be optimal and best tolerated.

Future research should also emphasize biological variables and gender differences, cognitive measures, and the recruitment of understudied patient populations within OABD (e.g., patients with high somatic illness burden or cognitive impairment) to foster the inclusion of more diverse populations. Given the projected rapid and substantial increases in absolute numbers and proportions of individuals living with OABD across the globe, such efforts have important public health implications.

Existing research findings suggest that there may be important differences in older versus younger people with bipolar disorder, including the attenuation of manic symptoms with age (24) and the occurrence of multiple comorbid somatic conditions, especially cardiovascular, musculoskeletal, and metabolic-endocrine conditions. It is also clear that bipolar disorder symptom severity is a key driver of functioning in OABD and that optimizing treatments that will stabilize mood is critical across the life span. It is important that clinicians be continuously willing to revisit pharmacological and behavioral therapies and make changes, as bipolar disorder may evolve over time in a given individual.

Biological therapies—including lithium, as well as anticonvulsant and antipsychotic mood-stabilizing drugs—are generally similar in older and younger people with bipolar disorder, with a key caveat for dosing and titration. Clinicians need to consider how biological treatments for bipolar disorder might be optimally used, given the high likelihood of concomitant medication for these somatic conditions, and coordinate care with other primary and other specialty care providers to minimize risk of drug-drug interactions and adverse effects, including risk of falls and other complications of particular relevance to older people. Other somatic therapies, such as ECT, remain an important consideration in OABD and psychotherapies can help improve global outcomes as well as reduce stigma and optimize adherence and engagement in care. A summary of treatment options is presented in Table 2.

In summary, emerging data suggest that bipolar disorder symptoms, comorbidity, and other clinical factors may change as individuals age. Clinical care needs to incorporate awareness of these changes to optimize health and quality of life.

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