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A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force

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Abstract

Objectives—In the coming generation, older adults with bipolar disorder (BD) will increase in absolute numbers as well as proportion of the general population. This is the first report of the

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International Society for Bipolar Disorder (ISBD) Task Force on Older-Age Bipolar Disorder (OABD).

Methods—This task force report addresses the unique aspects of OABD including epidemiology and clinical features, neuropathology and biomarkers, physical health, cognition, and care approaches.

Results—The report describes an expert consensus summary on OABD that is intended to advance the care of patients, and shed light on issues of relevance to BD research across the lifespan. Although there is still a dearth of research and health efforts focused on older adults with BD, emerging data has brought some answers, innovative questions, and novel perspectives related to the notion of late onset, medical comorbidity, and the vexing issue of cognitive impairment and decline.

Conclusions—Improving our understanding of the biological, clinical, and social underpinnings relevant to OABD is an indispensable step in building a complete map of BD across the lifespan.

Keywords

bipolar disorder; cognition; elderly; geriatric; manic depressive disorder; mood stabilizers

Growth in the world's older population has reached unprecedented levels (1). By 2025–2030, the population over age 60 years will grow 3.5 times more rapidly than the general population (1). Planning for medical care that meets the health needs of this growing population of older adults is critical.

Although topics related to older-age bipolar disorder (OABD) have been relegated to a minor place in research and professional training, the growing elderly population means we can no longer conceptualize OABD as a ‘special population’ for whom understanding of the disorder and recommended management can simply be extrapolated from experience in mixed age groups. The study of OABD is a research opportunity where answers to important questions that have widespread implications for all people with bipolar disorder (BD) may be found (e.g., the long-term effects of medications on general health, cognitive function, and brain integrity).

OABD, defined by many reports as BD in individuals aged ≥ 60 years, represent as much as 25% of the population with BD (2). Furthermore, OABD represents a heterogeneous group including those with early-onset BD (EOBD) as well as late-onset BD (LOBD) with a potentially different pathogenesis, clinical course and care needs (3). Despite the lack of therapeutic data, OABD presents an opportunity to evaluate the neuropathology and pathogenesis of BD and the overall effectiveness of treatments.

This is the first report of the International Society for Bipolar Disorders (ISBD) Task Force on Older-Age Bipolar Disorder (OABD). Improving understanding of the biological, clinical and social underpinnings in OABD is an indispensable step in building a complete map of BD across the life-span. Although there is still a significant deficit in data, emerging research has brought some answers, innovative questions and novel perspectives.

Methods

The initiative for forming an OABD task force stemmed from ISBD leadership with expertise in aging (SAS), co-chaired by clinical researchers with long-standing interest in OABD (MS and KIS). Leading international experts were recruited and participated in a series of teleconferences and an in-person meeting at the 10th International Conference on Bipolar Disorders (ICBD) held in Miami, FL, USA in June of 2013 to review, discuss and arrive at a consensus on topics most relevant to OABD.

Five foci were identified: (i) epidemiology and clinical features of OABD, (ii) neuropathology and biomarkers, (iii) physical health, (iv) cognition, and (v) care approaches. Each topic focus was assigned a subgroup chair (RKA, AD, BPF, AGG, and LVK) who worked with other subgroup members to: (i) conduct a selective topic review of the literature, (ii) summarize the present state of knowledge unique to OABD in the topic, and (iii) highlight opportunities and practical recommendations for further research. Expert clinical experience supported by published and unpublished data was used by each subgroup to summarize key *take-home* points specific to OABD. This expert consensus summary is intended to be a resource for researchers as well as clinicians.

Results and Discussion

Epidemiology and clinical features

Some individuals develop new-onset mania later in life, often associated with vascular changes or other brain pathology, some experience their first manic episode after previous depressive episodes, while others, diagnosed with BD in early life, survive into old age (3, 4). Figure 1 illustrates a proposed hierarchical terminology for OABD that considers age of onset and course of illness in OABD. The task force recommended that consideration be given to defining OABD as BD occurring in individuals ≥ age 50 years. While many studies have used age ≥ 60 years to define OABD, emerging data on medical comorbidity and reduced life-span, discussed later in this review suggest that in order to understand OABD we need to study it across the life-span, not just in the healthy cohort who survive into what our society generally considers *elderly* age (60+ and beyond).

Epidemiological studies report that types I and II BD affect 0.5–1.0% of older adults (5-7). This conservative estimate does not include all individuals within the BD spectrum (4). Epidemiologic and large-scale treatment studies suggest that BD becomes less common with age, and similar to schizophrenia patterns, BD in the geriatric population is approximately one-third as common as in younger populations (3).

In contrast to low rates in the community, OABD accounts for 6% of geriatric psychiatry outpatient visits and 8–10% of geriatric inpatient admissions (3) with an overall prevalence of late-life mania of 6.0% in older psychiatric inpatients (8). Studies in North America report that 3% of nursing home residents and 17% of elderly in psychiatric emergency rooms have BD (3, 9). Approximately 70% with OABD are women (3). Demographic changes and greater awareness of BD may be causing a rise in the number of OABD seeking

care. An Australian study noted that the proportion of individuals over age 65 with BD increased from 2% in 1980 to 10% in 1998 (10).

Age at onset—It is estimated that 5–10 % of individuals with BD will be ≥ age 50 at time of first manic or hypomanic episode (3, 5, 11, 12). There is no firmly established cut-off for EOBD versus LOBD, but consensus in previous reviews consistently used age ≥ 50 years as a demarcation (3, 13). It is appropriate to acknowledge this cut-point while at the same time recognizing additional and recent research that considers age of onset from a broader life-span perspective (14-16). Leboyer and colleagues (15) and Azorin and colleagues (14) have conducted analyses of BD subgroups based upon age of onset and note some distinct differences in phenomenological characteristics among these subgroups. Onset ages in early, intermediate and LOBD in the review by Leboyer and colleagues (15) were ages 17, 27, and 46 years, respectively. In a separate investigation of OABD, Nivoli and colleagues (16) noted that elderly patients with BD (> age 65 years) were more likely to have a first affective onset after the age of 40 compared to younger people with BD (≤ 65 years).

Depp and Jeste (3) identified 13 OABD studies (defined as age ≥ 50 years) that reported age of onset of any psychiatric disorder (mostly affective) and eight studies that reported age of first-onset of mania. Sample-weighted mean age was 68.2 years [standard deviation (SD) = 3.9, range: 60–72]. However, a limitation of the estimate is that age 72 was the highest mean age at onset across study samples and some patients had an older age of onset. The weighted mean age of onset of any affective disorder was 48.0 years (SD = 6.4, range: 28–65) and age of onset of mania was 56.4 years (SD = 7.3, range: 38–70). Affective symptoms were present for 20 years on average in OABD.

In spite of methodological limitations in the extant literature that preclude a definitive conclusion regarding the cut-point age for EOBD versus LOBD, the Task Force felt it was important to make a recommendation that might help move the field forward in further investigation and a future broad consensus. As illustrated in Figure 1, the age of 50 years appears to be a reasonable cut-off with at least some consensus for EOBD versus LOBD. Given the emerging data on subgroups with differential age of onset across the life-span, the OABD task force suggested further study and possible consideration of age 40 as a cut-off that might capture a fuller picture of later-onset BD. Future research studies should aggressively attempt to recruit and enroll individuals above the age of 50 years in order to better understand how BD may present and evolve across the life-span.

EOBD and LOBD may be different forms of BD, as EOBD is more closely associated with a family history of affective disorder (17) whereas LOBD is associated with brain (i.e., cerebrovascular) disease (18-20). While some individuals with LOBD may have a particularly poor response to treatment and a high risk of cognitive deterioration (21) other reports (22-25) note that LOBD may recover faster or more robustly with treatment compared to EOBD.

Clinical presentation and missed diagnosis—Only minor differences have been found in the phenomenology of older versus younger patients with BD (10, 26) and of EOBD versus LOBD (3). Differences are most pronounced among hospitalized patients

(26). Most (17, 26-28), but not all studies (25, 29, 30), have found psychotic features to be less frequent in OABD, whereas the prevalence of depressive episodes in OABD may be increased (26).

For BD in general, the prevalence of misdiagnosis is high, ranging from 48% (31) to 69% (32). One study (33) found that although diagnostic misclassification seemed to decrease with age, among OABD the prevalence of misclassification is still substantial.

Course of illness—Limited data on the clinical course in OABD have been published. Although some patients have a progressive course of illness with an increasing risk of recurrence for every new episode (34), overall, relapse leading to psychiatric hospitalization seems to decrease with age (35). This may reflect an attenuation of symptom severity over time. However, data from a prospective long-term study conducted in Zurich suggested that recurrence risk following any affective episode seems to be increased among the elderly (36).

Recovery rates appear relatively constant across affective episodes in modern treatment settings for OABD (37). It is unclear whether the rate of functional recovery varies with age or whether the prevalence and presentation of rapid cycling differ between elderly and younger persons (3).

Risk of completed suicide in BD is highest for patients under age 35 years (38) suggesting that OABD is associated with a decreased rate of suicide. This is presumably because individuals included in samples of OABD may represent a *survivor cohort* (3). The rate of suicide among older patients with LOBD has not been specifically investigated, but no cases of suicide were identified in a retrospective cohort study of hospitalized elderly manic patients over a six-year follow-up (39). Nevertheless, a recent systematic review and meta-analysis on correlates of suicide attempts and suicide deaths in BD found that earlier age of illness onset correlated significantly with suicide *attempts* (40).

Take-home points

- While some reports define OABD as occurring in individuals ≥ 60 years of age, the OABD task force proposes that ≥ 50 years be considered as a demarcation.
- BD affects 0.5–1.0% of older adults and BD in older people is approximately one-third as common as in younger people.
- Previous literature suggested age > 50 years as the cut-off for LOBD (age at first manic or hypomanic episode), but based upon more recent evidence, the OABD task force proposes that ≥ 40 years be considered as the age cut-point.
- There are only minor differences in the phenomenology of EOBD versus LOBD. Based only on limited data, in LOBD, the course of illness may be progressive with an increasing risk of recurrence.
- Unique opportunities in OABD epidemiological research include studying the interaction of age and illness onset on outcomes.

Neuropathology and biomarkers

Neuroimaging is used in clinical practice to help identify structural brain abnormalities such as stroke, tumor or hydrocephalus that may be associated with the clinical manifestation of OABD. Neuroimaging provides the opportunity to examine the relationship between structural, biochemical and functional biomarkers and clinical symptoms of OABD such as mood instability and cognitive impairment. Historically, the majority of magnetic resonance imaging (MRI) studies in BD have demonstrated neuroanatomical abnormalities in gray matter (41). The role of cerebrovascular disease in the pathophysiology of mood and cognitive symptoms in OABD has been an increasing focal point. However, the literature on OABD is limited to small numbers of structural MRI studies, including volumetric analyses of white matter hyperintensities and gray matter volume, and two Diffusion Tensor Imaging (DTI) studies. No functional MRI (fMRI) studies have focused specifically on OABD.

Of particular relevance to OABD, markers of inflammation, oxidative stress and mitochondrial dysfunction could potentially help characterize pathways supporting a model of progressive deterioration as individuals with BD age (neuroprogression). Confounding variables that must be considered when studying OABD with neuroimaging include phenotypic heterogeneity, illness onset, medical co-morbidity, cognitive impairment and concomitant medication.

Structural findings—The majority of MRI studies in BD have demonstrated regional gray matter abnormalities, including frontal and subcortical structures. Studies focused on OABD have noted reduced volume in the caudate, in contrast to younger patients with BD (41). Diffusion tensor imaging (DTI) measures the diffusion patterns of water molecules, thereby providing evidence for microstructural alterations of white matter. Fractional anisotropy (FA) refers to the coherence of white matter tracts with higher FA associated with greater white matter structural integrity and representing better brain health (42). DTI studies in OABD demonstrate altered white matter diffusivity in the orbitomedial prefrontal cortex, potentially impacting prefrontal corticolimbic connectivity and mood regulation (43). However, DTI studies in OABD are limited. A recent report investigated gray matter concentration changes and microstructural alterations in white matter in neocortical regions and the corpus callosum in OABD compared with controls (44). Gray matter concentration was reduced in the right anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex, while an analysis of DTI parameters demonstrated reduced FA in the ventral corpus callosum in OABD compared with controls.

Magnetic resonance spectroscopy (MRS) markers of brain biochemistry in OABD—MRS is a non-invasive neuroimaging technique that measures brain biochemical alterations. Such alterations may eventually serve as biomarkers for OABD, assisting diagnostic efforts and clarifying the neurobiological etiologies of disease state and trait characteristics.

Neuroimaging as a window on the neuroprogression hypothesis—Neurochemical dysregulation, neuroinflammation, oxidative stress, and mitochondrial dysfunction have been speculated to play a role in the etiology and longer-term course of

BD (45, 46). Other putative mechanisms include excessive dopamine and glutamate neurotransmission, decrease in brain neurotrophins such as brain-derived neurotrophic factor (BDNF) and the possible role of epigenetics. These mechanisms might explain the toxic effects of recurrent mood episodes that can become particularly evident in OABD as neuroprogression characterized by functional and cognitive decline. Studies that demonstrate volumetric differences as a function of age are used to assess the hypothesis that increased activity of the stress hormone cortisol during episodes of BD depression may drive cumulative excitotoxicity in specific brain regions (47). Although neuroimaging studies demonstrate a reduction of regional gray matter volume and microstructural alterations in OABD (48), there is inconsistent data to support a neurodegenerative/ neuroprogressive BD model. However, studies examining longitudinal volumetric and white matter microstructural changes are limited to follow-up measured over a few years rather than decades. Future studies examining structural MRI changes over the lifespan (which also identify individuals who die early due to medical causes) may be a more fruitful approach to determining evidence for BD as a neuroprogressive disorder.

Neuroimaging techniques to identify neurobiological and clinical effects of lithium—Given the concern regarding cumulative effects of BD over time, there is an interest in using neuroimaging to help assess possible ameliorative efforts of treatment, particularly lithium therapy but also other novel neuroprotective strategies such as the use of N-acteyl cysteine (NAC), omega-3 fatty acids, anti-inflammatory medications and statins (46). Long-term lithium treatment is associated with increased total gray matter (49), increased hippocampal volume (50, 51) and decreased white matter microstructural abnormalities (52). Lithium's effect on hippocampal and gray matter volume is more pronounced than other mood stabilizers (53, 54).

Findings using lithium-7 MRS hold promise for a clinical application of MRS to help regulate lithium dosing more accurately in OABD. Examining the superior edge of the corpus callosum in a 4-Tesla MRS study of OABD treated with lithium, increased brain but not serum lithium levels were associated with increased depression symptoms as well as frontal executive dysfunction (55). In addition, brain lithium levels were associated with increased myoinositol (mI) and N-acetyl aspartate (NAA) levels (56). Increased NAA suggests neuroprotective and neurotrophic effects of lithium treatment while increased mI levels may reflect increased inositol monophosphatase activity with chronic lithium treatment.

Take-home points

- Structural neuroimaging studies in OABD show regional gray matter volume reduction, white matter hyperintensities, and biochemical alterations.
- At the moment, multi-model neuroimaging techniques such as fMRI, DTI, and MRS do not clearly support a neuroprogression model in BD. However, additional studies that take a life-span and longitudinal perspective are needed to definitively address this area of controversy.

- Neuroimaging techniques that can inform an understanding of brain neurobiology may potentially lead to the development of neuropathologically informed therapies that improve mood, functioning and cognition in OABD.

Physical health

BD has been conceptualized as multi-system rather than a brain-specific disease (57, 58). Cardiovascular disease, diabetes, obesity, substance abuse and other comorbidities complicate outcomes in people with BD although a limited number of studies have focused specifically on OABD (59). Patients with OABD have an average of three to four comorbid medical conditions, including metabolic syndrome (up to 50%), hypertension (45–69%), diabetes mellitus (18-31%), cardiovascular disease (9–49%), respiratory illness (4–15%), arthritis (16–21%), endocrine abnormalities (17–22%), as well as atopic diseases such as allergic rhinitis and asthma (6–20%) (59, 60). Although patients with OABD have a greater burden of endocrine, metabolic, and respiratory diseases than unipolar depressed comparators (61), the overall prevalence of medical comorbidity in OABD appears similar to community-based geriatric samples (59).

There are no longitudinal studies and only five studies of medical comorbidity that have included 50 or more patients with OABD. In a register-based study, patients with BD had higher mortality due to cardiovascular and other physical illnesses and died an average of 10 years earlier than the general population (62). In light of this premature mortality, patients with EOBD who survive into old age almost certainly represent a healthy *survivor* BD sub-population and studies that focus only on individuals in their 60s and beyond may not be truly representative of the larger BD population.

Cerebrovascular disease and OABD—Cerebrovascular disease appears related to symptom expression in OABD although the literature is limited (63-66). Steffens and Krishnan (64) proposed criteria for vascular mania as a subtype when mania occurs in the context of cerebrovascular disease or neuropsychological impairment. Some (67-69), but not all (65), reports suggest that LOBD is associated with significant cognitive impairment. One study noted that those with LOBD had a greater prevalence of white matter hyperintensities in the deep parietal region and basal ganglia compared to patients with EOBD and healthy controls (66). Silent cerebral infarctions may be present in over one-half of patients with OABD, regardless of age at onset (63). Metabolic abnormalities and systemic inflammation may also be critical risk factors for cerebrovascular disease in OABD (70). Although a recent sample of OABD found the self-reported prevalence of cerebrovascular disease was 3% (8) it is possible that future studies that specifically focus on cerebrovascular risk and age of onset in OABD may help to differentiate a different course of illness (Fig. 1).

Implications for clinical care and research—Although LOBD is generally associated with a higher burden of cerebrovascular disease than EOBD, the majority of patients with OABD have radiological evidence of cerebrovascular disease regardless of age of onset. Clinicians should address vascular risk factors and be sensitive to early signs of disease, using laboratory testing, imaging and additional evaluations as necessary. Given that lifestyle factors such as exercise and avoidance of smoking are potentially modifiable and

impact outcomes in people with bipolar disorder (71), preventative strategies to address cardiovascular and other medical risk factors are an important component of care. Longitudinal studies in OABD need to address the role of cerebrovascular burden and investigate how preventative measures may mitigate risk.

Physical comorbidity and OABD psychopharmacology—A recent ISBD report on safety monitoring with the use of BD pharmacotherapies (72) is particularly relevant to OABD given that older patients are susceptible to age-related changes in mood-stabilizer pharmacodynamics, pharmacokinetics, metabolism, and excretion (73). There is little high-quality data in OABD examining medical effects of pharmacotherapy, with the majority of studies being cross-sectional and using small samples. The relationship of long-term lithium use with renal dysfunction remains to be confirmed in geriatric populations (74). In older patients using lithium, potential correlates of renal disease include use of diuretics and angiotensin-converting enzyme (ACE) inhibitors, and higher lithium levels in the context of inadequate lithium monitoring (73). The most robust renal risk factors in older adult are diabetes, hypertension (75) and age-related renal decline (76). Other long-term effects of mood stabilizers remain understudied. Older lithium users have elevated incidence (6%/person-year) and prevalence rates (32%) of hypothyroidism (77, 78). The incidence of hospitalization due to delirium is similar in older patients treated with lithium and valproate (78). Antipsychotic use in older patients is associated with higher rates of hyperglycemia (79) as well as increased mortality and risk for cerebrovascular accidents (80, 81).

Take-home points

- OABD is associated with extensive medical comorbidity. Death occurs an average of 10 years earlier than the general population.
- The majority of patients with OABD have cerebrovascular disease regardless of age of onset.
- OABD should be regularly screened for medical comorbidity. Preventative care should address modifiable life-style factors such as exercise and smoking. Close collaboration between mental health, primary care, and specialty clinicians is essential.
- Medical comorbidity can limit treatment options for OABD because of drug tolerability, drug–drug interactions, and altered drug-metabolism. Clinicians must choose treatments\accounting for medical burden, while minimizing side effects.
- Prospective multi-center longitudinal and population-based administrative data studies are needed to evaluate the burden, risk factors, and consequences of medical comorbidity in OABD. These ideally should include non-psychiatric comparators and patients with BD across the life-span.

Cognition

Cognitive dysfunction, reflecting static and dynamic brain abnormalities (82), is found in ≥ 30% of patients with OABD (83). The cognitive reserve hypothesis posits that those with higher IQ, education, or occupational attainment have lower risks of developing dementia

(84). BD might reduce cognitive reserve or act synergistically with other neuropathological mechanisms (e.g., vascular diseases) to accelerate aging and cognitive deterioration (35, 85-90).

As noted previously, whether BD causes neuroprogression or even eventual dementia is controversial. Existing studies on cognition in OABD do not resolve this issue. Early cross-sectional (91) and longitudinal studies (92) on cognition of OABD found pronounced neuropsychological deficits. However, these early studies had methodological limitations. The seven studies reviewed by Young and colleagues (91) included only two studies that evaluated euthymic patients and no study discriminated EOBD versus LOBD. Some newer studies with better methodology confirmed the presence of significant cognitive dysfunction in euthymic OABD, but did not support worsening of previous cognitive dysfunction (93-96) or faster cognitive decline in old age (93, 96, 97). However, it should be emphasized that these were relatively short-term studies with a follow-up period between 1–3 years. A recent meta-analysis (68) that included euthymic OABD, using comprehensive cognitive batteries and control groups, found effect sizes of impairment for ten cognitive variables analyzed in the medium range, except for phonemic fluency and cognitive flexibility (d = 0.80–0.88). Differences in magnitude of cognitive impairments were not found in younger versus older adult patients, but findings pointed to greater impairment associated with LOBD (68).

Few long-term studies on the association between BD and cognitive functioning have been published. Out of four older studies (85, 98-100) the three population-based studies (85, 98, 99) found a positive association between BD and cognitive progression and pooling all these data in a meta-analysis confirmed the association (86). One study specifically found that the risk of developing dementia increased with each new affective episode (101). An additional population-based study further confirmed the association when adjusted for important covariates including cerebrovascular disease, diabetes mellitus, hypertension, head injury, chronic pulmonary disease, alcohol-related disorder, substance-related disorder, outpatient visit, and inpatient visit (90). A recent report by Gildengers et al. (48) noted that longer duration of illness is associated with lower gray matter volume. Additional studies that control for confounding factors (including treatments that may be neuroprotective), use longitudinal designs of reasonable duration (decades rather than < 10 years), and start in early adulthood are needed to definitively clarify this important and yet-to-be-resolved issue.

Cognitive function in LOBD—Recent reports using an extensive cognitive battery have compared LOBD versus EOBD. Patients with LOBD had more extensive neurocognitive impairments despite the differences in chronicity, including neurocognitive domains such as the Boston Naming test (69, 95, 102). The worse cognitive outcomes observed for LOBD versus EOBD support the view that different etiological mechanisms might be involved. Additionally, some neurodegenerative diseases (e.g., frontotemporal dementia) have clinical overlap with OABD symptomatology, which can result in misdiagnosis in some cases (88, 103). New imaging techniques, such as amyloid imaging or positron emission tomography imaging, may be helpful in the diagnostic evaluation of older individuals with behavioral symptoms.

Treatments for cognitive dysfunction in BD—There are no accepted treatments for cognitive dysfunction in BD. Conventional and novel treatments have been examined, but to date no clear treatments are effective and there is evidence that some treatments, such as cholinesterase inhibitors, may cause destabilization (104). Functional remediation is a new and promising intervention that trains patients in the use of neurocognitive skills, but cognitive performance may not necessarily improve, and there are no data in OABD (105). Large population based studies have suggested that lithium might potentially ameliorate risk of dementia or Alzheimer's disease (106-109) but the methodological limitations of observational data do not provide a sufficient basis for treatment recommendations specific to cognition in OABD.

Take-home points

- Cognitive dysfunction is prevalent in OABD and adversely affects overall functionality.
- Cognitive functioning is more impaired in LOBD versus EOBD and supports different mechanistic models of pathophysiology.
- Data on cognition in OABD does not provide sufficient evidence to reject or accept a BD neuroprogression model. Future studies need to control for possible confounders, have longer follow-up periods, use healthy controls, and consider medication status and attrition.
- Clinicians need to consider cognitive dysfunction in the overall treatment of OABD, and should try to avoid medications that may worsen cognitive function (e.g., medications with high anticholinergic burden).

Care approaches

Pharmacologic treatment—Excluding a single randomized controlled trial that has not yet been published (110), no large-scale prospective pharmacologic studies have been conducted in OABD. The limited literature consists of uncontrolled, retrospective, open label, or secondary analyses of larger mixed-age studies.

Bipolar depression studies in OABD—In a multisite, 12-week, open-label trial, 57 type I and II patients with OABD (mean age 66.5 years, range: 60–90) received add-on lamotrigine (111). Response and remission rates were 64.8% and 57.4%, respectively, with a mean lamotrigine dose of 150.90 mg/day. A post-hoc, secondary analysis of two eight-week, double-blind, randomized, placebo-controlled studies in bipolar depression (112), compared quetiapine with placebo in mixed-age patients. In a subgroup of 72 patients aged 55–65 years, remission occurred more often with quetiapine (300 mg/day and 600 mg/day) than placebo at 45%, 48%, and 28%, respectively. A post-hoc data analysis of monotherapy and adjunctive therapy mixed-age studies with lurasidone examined response in older adults (≥ 55 years) with bipolar I depression randomized to six weeks of lurasidone 20–60 mg/day or 80–120 mg/day, or placebo in the monotherapy study; or lurasidone 20–120 mg/day or placebo with either lithium or valproate in the adjunctive therapy study (113). The proportion of older adults was 83/485 (17.1%) in the monotherapy study, and 53/340

(15.6%) in the adjunctive therapy study. Mean change on Montgomery–Åsberg Depression Rating Scale (MADRS) in OABD was significantly greater for the lurasidone 20–60 mg [−15.4, $p < 0.01$, effect size (ES) = 0.86] and 80–120 mg groups (−14.1, $p < 0.02$, ES = 0.74) versus placebo (−7.1). Adjunctive therapy with lurasidone (versus placebo) in OABD was associated with numerically greater but not statistically significant improvement in MADRS (−13.9 versus −11.1, not significant, ES = 0.26). Uncontrolled studies have noted improvement in OABD with aripiprazole (mean dose 10.3 mg/day) (114), and with asenapine (115). Older adults can be generally expected to have reduced tolerability and relatively more drug-related adverse effects than younger individuals and in the case of antipsychotic drugs, this may be manifested in particular by tremor or other extrapyramidal symptoms (4).

Data on lithium and valproate in OABD with acute depression are derived from a few mixed-age retrospective studies (116-118). Sharma et al. (119) reported improvement in depression in 12 patients with OABD (≥ 50 years of age) with rapid cycling with the addition of lithium to valproate. Data on treatment with lithium or anticonvulsants in mixed age BD populations are strongly suggestive for prevention of suicide attempts and deaths, but additional randomized data are required before conclusions about relative anti-suicide effects can be determined (120). The relevance of these data to OABD remains to be established.

Patients with OABD are more prone to acute lithium toxicity due to reduced renal clearance, vulnerability to medical comorbidity, and drug–drug interactions with ACE inhibitors, calcium antagonists, thiazide and loop diuretics, and non-steroidal anti-inflammatory drugs (121). Valproate levels should be checked regularly, and clinicians should monitor for drug-drug interaction especially in the patients with co-administration of aspirin, warfarin, digitoxin, phenytoin, and lamotrigine (2, 122). Ammonia levels can become elevated even with normal valproate levels (123). Remarkably, lithium use has decreased in spite of the absence of any data showing better tolerability or efficacy of one medication over the other (124).

There is very little systematic data on the use of electroconvulsive therapies (ECT) in OABD, Data are restricted to case reports, case series, expert consensus and extrapolation from mixed age patient populations. A review of the literature suggests that ECT is a safe and effective treatment for older adults including those suffering from severe or intractable mania (125). Special attention to baseline cognitive function is necessary with particular concern for bilateral ECT treatment. ECT remains an important option in the treatment of OABD when safety is a concern (suicide and medical risk) or when adequate pharmacological trials have proven ineffective.

Acute bipolar mania—One completed randomized, controlled trial (RCT), and several open label and retrospective small studies have supported the efficacy of lithium in the treatment of acute mania in OABD. But a retrospective study (126) of 12 patients with OABD (age range 60–74 years) had only four (33%) with improvement after two weeks of lithium therapy. The efficacy and tolerability of valproate in OABD mania as monotherapy or adjunct has been suggested by several non-controlled studies (119, 127-133). In a

retrospective report, Chen et al. (134) found comparable efficacy between lithium (blood levels: 0.8–1.3 mmol/L) and valproate (blood levels 65–90 ug/ml); with response rates of 82% and 75%, respectively. The findings from the National Institute of Mental Health (NIMH)-funded multisite, RCT of lithium versus valproate for acute treatment of mania in type I OABD (age ≥ 60 years) is awaiting publication. Results will address questions on tolerability and efficacy of lithium versus valproate in the treatment of OABD in acute mania, hypomania or mixed episodes (135).

A post-hoc analysis of a mixed-age olanzapine study (136) reported on within-group treatment response of older adults (> 50 years of age) with acute mania treated with either olanzapine or divalproate. Efficacy of quetiapine has been reported in a pooled analysis of two 12-week randomized trials comparing quetiapine to placebo in a mixed-age BD sample (137). In a subgroup of 59 older patients, symptoms improved significantly more with quetiapine (modal dose 550 mg/day) than placebo. Recently, Baruch et al. (138) reported a 63% remission rate in 11 elderly manic patients receiving asenapine. Finally, there are case reports and case series with carbamazepine (139, 140), gabapentin (141, 142), and clozapine (143).

BD maintenance treatment—In a secondary analysis of 86 patients with OABD, lamotrigine was more effective in delaying relapse of depression while lithium was more effective in delaying manic symptoms (2). In a prospective NIH-funded mixed-age BD treatment trial, 79% of patients with OABD achieved a recovered status of at least eight symptom-free weeks (144). While patients on average took 2.05 psychoactive medications, 42% of patients with OABD who achieved a recovered status were on lithium monotherapy. In a prospective study of OABD, Murray and colleagues (145) found that response to lithium is independent of age. Finally, a randomized open-label study comparing lithium to divalproex for BD maintenance in a mixed-age BD sample showed that lithium monotherapy or lithium in combination with valproate was superior to valproate alone (146) and that response and tolerability in OABD did not appear to differ from that of younger patients.

Psychosocial interventions—Most literature on psychosocial interventions in OABD is extrapolated from mixed–age studies or based on reports of elderly with serious mental illness more broadly. In a two-year randomized trial comparing the effectiveness of *The Helping Older People Experience Success* (HOPES) and treatment-as-usual (TAU) in OABD, Mueser and colleagues (147) found HOPES improved social skills, community functioning, self-efficacy, leisure and recreation. The HOPES combines skills training and health management intervention (148). Another focus of psychosocial intervention is medication adherence. A small study of medication adherence skills training for OABD (MAST-BD) showed feasibility acceptability and improvement in medication adherence, depression and some indices of health-related quality of life (149). Other psychosocial interventions hold promise for improving health and functioning in older adults with serious mental illnesses (150). Given the known cognitive impairment seen in OABD (151) specific strategies to improve cognitive performance (e.g., cognitive rehabilitations) are greatly needed.

Factors associated with functional outcomes—A key component in assessing medication response is the assumption that the *right* medication dose has been used. Lack of evidence specific to OABD limit prognostic projections and data-driven formulation of treatment guidelines. However, the literature is fairly consistent that poor medication adherence, concomitant substance use, and comorbid neurological illnesses decrease response to treatment in OABD (152). Additional factors affecting functional outcomes in OABD include premorbid levels of psychosocial, residential, and occupational status (153).

Novel treatment approaches and targets—Novel BD treatments that may target biological mechanisms such as inflammatory dysregulation, oxidative stress and mitochondrial dysfunction (45) have drawn interest. Novel agents include anti-oxidants (e.g., N-acetyl-cysteine), mitochondrial modulators (e.g., CoQ10), or inflammatory modulators (e.g., NSAIDs) (45). To date, there are few specific studies of novel agents in OABD (154).

Take-home points

- Excluding a single randomized trial not yet published, no large-scale prospective controlled studies have been conducted in OABD.
- Emerging data support the potential usefulness of lithium in OABD. More limited data provide information on the use of lamotrigine and several of the atypical antipsychotic medications, in particular quetiapine and lurasidone.
- There are no controlled psychosocial studies specific to OABD although studies in serious mental illness more broadly suggest potential for positive effects on health and functioning.
- There is a need for well-designed and adequately powered treatment studies in OABD.

Conclusions and future directions

The number of individuals with OABD will increase and already overburdened healthcare systems will need to adapt to this demographic change. BD can be a devastating illness that reduces life-span by a decade or more, as well as causing substantial psychiatric and medical comorbidity. Accumulating research on OABD underscores the importance of a life-span perspective in research and clinical care. Comorbidities associated with OABD are also evident throughout the lifespan including in youth and younger adults with BD (155, 156).

The hierarchical terminology proposed by the ISBD task force on OABD (Fig. 1) considers cumulative medical burden and shortened life-span and proposes defining (and studying) individuals age ≥ 50 years as OABD. There is a need to better understand mechanistic factors explaining EOBD versus LOBD and the ISBD task force suggests that future research includes greater numbers of individuals age 50 years and older to better appreciate potential etiological variables and processes that impact health outcome in the second half of life for individuals with BD.

As noted in both Tables 1 and 2, critical questions about BD across the lifespan could find their answers in the research of OABD. For example, do cognitive findings support LOBD as a distinct subtype? Additionally, what is the expected trajectory and prognosis for OABD? Can we verify the postulated neuroprotective effect of some treatments such as lithium? Do lifestyle factors such as activity/exercise impact long-term outcomes for people with BD?

The field of BD research needs a model that describes long-term illness evolution (157, 158) and the debated BD staging model (157) is particularly relevant to OABD. A core issue is whether BD causes neuroprogession (45). This was the most contested issue within the OABD task force. If cognitive impairment and associated biomarkers increase with chronicity, one could expect greater deficits among OABD. However, research findings are mixed depending on study methodology. Short-term clinical studies have generally not found a significant age-related impact on cognition but long-term population-based studies have found progressive risk of cognitive impairment among patients with BD. An important caveat is that patients with OABD in research samples represent a survivor cohort assessment across the life-span is essential to fairly test a BD neuroprogression hypothesis and resolve the continued controversy.

The treatment evidence base for OABD is very limited. Given the recent withdrawal of pharmaceutical companies and some national research programs from clinical trials research, it is unlikely that we will see the types of prospective and head-to-head trials in OABD that have long been a ‘gold-standard’ in guiding treatment recommendations. Alternative approaches such as mining of case registries and other large databases that include reasonable samples of OABD may help in understanding effects of existing therapies. However, even analysis techniques that attempt to control for confounding variables may not allow researchers to answer questions about brain health effects of commonly used treatments. Technological advances in neuroimaging may help clarify biological and clinical effects of pharmacological treatment. These techniques applied to OABD may help identify the underlying pathophysiology and pathology relevant to BD across the life-span.

Finally, conceptualizing BD as a multi-system condition allows clinicians and researchers to address the challenges of comorbidity. Integrated care models that manage both physical and mental health (159) are particularly relevant for OABD. It is our hope that increased interest in BD as it affects individuals in their later years, healthcare systems and society will advance care for all individuals with BD.

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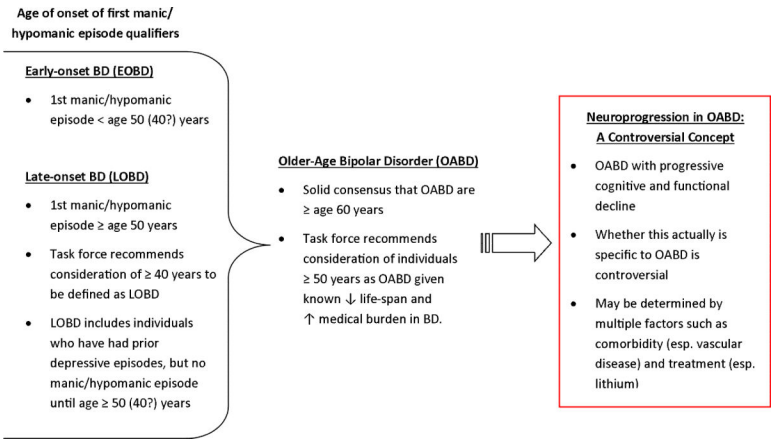

Fig. 1.

A proposed hierarchical terminology for bipolar disorder (BD) across the life-span from the ISBD Task Force on Older-Age Bipolar Disorder.

Table 1

Important research questions and recommendations for older-age bipolar disorder (OABD) 2015–2025

Research questions	• Is there a significant difference in age of onset for neurophysiology (possibly identified on brain magnetic resonance imaging or computerized tomography scan), treatment response, or genetic associations? Is LOBD a unique subtype? • Is BD associated with cognitive decline or eventual dementia (neuroprogression)? • What is the longitudinal course of patients with a manic episode in late life? Does previous pattern predict late-life pattern? Does BD 'burn out'? Does episode type or frequency predict functional declines? • How may medical (especially vascular) comorbidity affect the expression and outcome of OABD? • For medications measured by blood level (lithium, valproate), what is the optimal dose and serum range for OABD compared with younger patients with BD? Can lower dose or lower serum levels of lithium be as effective as higher dose or levels in OABD? Does lithium's effect on renal function outweigh its impact on mood stabilization and quality of life? • Given the mortality (black box) warnings for atypical antipsychotic use in geriatric patients with dementia, can they be safely used in OABD? • Can lithium and other mood stabilizers be protective from cognitive decline? • What are long-term side effects of medication treatments in BD? • Are specific psychosocial treatments effective in acute and maintenance treatment? • How might preventative care approaches that integrate lifestyle and physical health impact health outcomes in OABD?
Research recommendations	• Aggressively enroll/recruit individuals age 50 years and older into future research studies in order to inform a better understanding of the presentation and evolution of BD in the second half of life. • Investigate integrated care models that manage both physical and mental health. • Specifically attempt to prove or refute the issue of neuroprogression in BD. Develop a network of associated centers that will follow subjects with OABD using similar initial assessment and longitudinal protocols. • Develop an anonymized clinical database that can be used for basic research questions. • Develop an anonymized genetic bank. Include an assessment of age of onset in BD pedigrees. Develop an anonymized cognitive assessment database that includes an annual assessment protocol. Establish consensus on common cognitive assessments that are most relevant to OABD. • Develop recommendations of minimum standards for neuroimaging techniques.

BD = bipolar disorder; LOBD = late-onset bipolar disorder.

Table 2

Unique opportunities afforded by the study of older-age bipolar disorder (OABD)

• OABD research can help elucidate the relationship of mood regulation and cognition given the intersection of BD and cognitive decline.
• Researchers can longitudinally follow BD clinical course throughout the life-span and in particular, test the *Neuroprogression hypothesis*.
• OABD research can help identify factors associated with resilience and survival into late life.
• Study of OABD can help identify neuro-circuitry of mood regulation by examining changes in brain functioning and structure associated with aging and medical/neurological conditions such as stroke and hypertension (volumetric and neuro-connectivity changes). Newer imaging modalities carry great potential in characterizing the nature and location of neuropathology in older adults. The increased prevalence of neuropathology in OABD can help to shed light on the pathogenesis of BD in younger adults.
• Use of registries and large administrative health databases to provide epidemiologic input when there is limited data from randomized, controlled trials in older adults. This can be especially fruitful in jurisdictions where there is available data on prescription drugs for older adults. These data can then be linked to other administrative data including hospitalizations, diagnosis and mortality.

BD = bipolar disorder.