Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
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# Late-onset bipolar disorder

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## Abstract

Much is still unknown about late-life bipolar disorder (BPD), especially late-onset BPD. Late-onset BPD may be etiologically different from early-onset BPD, and may be related to the medical and neurological problems that can occur with aging; alternately, it may be an underlying progression of neurological illness associated with certain cases of BPD early in life.

Treatment of late-life BPD requires knowledge of 'best treatment' practices and an understanding of the effect aging has on psychopharmacotherapy. This chapter discusses the various treatment options available to this population. These include the mood stabilizers (e.g., lithium) and anticonvulsants (e.g., valproate, lamotrigine) most often used to treat BPD, as well as alternative treatments such as atypical antipsychotics and ECT. However, adequate clinical trials that would provide good evidence-based treatment recommendations for late-life BPD are not currently available. Therefore, extrapolation from trials in mixed-age populations and adaptation to the older patient is necessary to establish treatment recommendations.

## Introduction

The diagnosis of bipolar disorder (BPD) is based on a phenomenological presentation of symptoms rather than etiological criteria [1]. Therefore, there is a large heterogeneity of presentations in patients that may affect course, prognosis, and response to treatment of the disorder. Several divisions have been proposed that provide guidance in treatment decisions. For example, the current phase of illness or the severity of symptoms at presentation for treatment has been recognized by the American Psychiatric Association [1] and multiple other expert consensus treatment guidelines [2–5] as being meaningful in clinical decision-making. Medication selection may vary if patients present in a manic, depressive, or mixed state, or have psychotic symptoms.

Other groupings within the bipolar spectrum may also have heuristic meaning for understanding the etiology of BPD or in modifying clinical decision-making. For example, efforts are currently underway to determine if structural or functional neuroimaging findings, genetic variability, or other biological markers may inform treatment decisions.

Similarly, clinical factors may also serve as markers for modifying clinical treatment. One clinical characteristic proposed as a modifying risk factor is the effect of age and age-of-onset in patients with BPD. This chapter will focus on the impact of older age and aging in late-life BPD, and explore late-life relat-

ed issues. For instance, do patients with BPD early in life 'burn out' with age? Is there a difference in BPD symptoms throughout the life cycle? Are there etiological and phenomenological differences if the disease begins early in life *versus* later in life? Does aging affect treatment?

This chapter is divided into two parts. The first discusses the current literature on aging in BPD with an emphasis on late-life and late-onset disease, and the second part discusses treatment of late-life BPD.

## BPD in late life

### *Prevalence*

Although BPD has been a recognized mental illness since the mid 1800s and codified in the first publication of the *Diagnostic and Statistical Manual of Mental Disorders* [6], the prevalence of BPD in the geriatric population remains unclear. From various inpatient program reports, it appears that hospitalization for BPD in patients over the age of 60 is not uncommon. Depp and colleagues [7] reviewed 11 published surveys of geriatric psychiatric admissions and found that 8.7% (mean prevalence) of admissions were for the treatment of BPD. The authors argued that this prevalence rate actually underestimated bipolar admissions because many of the studies focused only on mania (excluding admissions for bipolar depression), or on patients whose BPD began after the age of 60. The mean prevalence rate of geriatric bipolar admissions, however, was similar to findings in a study of Medicare patients admitted for a primary psychiatric diagnosis in the 1990–1991 calendar year [8]. That study of 240,000 geriatric psychiatry admissions found that 6.7% of admissions were for BPD (compared with an admission rate of 28.1% for unipolar depression and 5.7% for schizophrenia).

In the general community, the prevalence of BPD in the elderly has been less clear. Despite the reports of significant numbers of elderly admitted to hospitals for treatment of BPD, the Epidemiologic Catchment Area (ECA) study failed to capture any active manic elderly subjects in their survey of psychiatric disorders in the United States [9]. Using a statistical weighted analysis, the authors reported the 1-year prevalence range of elderly with BPD between 0.0–0.5% (with a cross-site mean of 0.1%). This was markedly lower than the prevalence of BPD reported among young (18–44 years; 1.4%) and middle aged (45–64 years; 0.4%) adults. This range, however, was consistent with three other community-based studies that included assessments of the prevalence of BPD in the elderly. Unutzer and colleagues [10] reviewed a large HMO database and found a prevalence rate of 0.25%. Klap and colleagues [11], reporting on a telephone survey of 9,585 households, found a prevalence rate of 0.08%. Finally, Hirschfeld and colleagues [12] reported results for 85,258 subjects who responded to a screening questionnaire. They found the screen rate for adults 65 and older was 0.5%.

Interestingly, each of these surveys suggested that the prevalence of BPD declines with age or in aging cohorts. This has led some researchers to suggest that bipolar episodes decrease with age [13]. Winokur [14] was the first to propose the concept that manic patients may 'burn out' after a finite number of episodes. In the Iowa 500 study, Winokur and colleagues followed 109 patients admitted for mania up to 20 years. The authors observed that bipolar episodes occurred in 'bursts', and then became quiescent. However in a prospective study, Angst and Preisig [15] followed 209 bipolar patients over a period of 40 years (median age 68). They found that manic episodes did not decrease with age and that many patients continued to have episodes into their seventh decade.

Overall, the decline in the prevalence of BPD with age noted by the community surveys is similar to that seen in prevalence rates of other mental illnesses (such as depression and schizophrenia), and may actually represent a cohort effect or an increased mortality rate.

## *Modifiers*

### *Presentation*

In general, the development of BPD in late life can be divided into four patterns: 1) those who had an early-onset of BPD and have reached old age; 2) those who were previously diagnosed with unipolar depression but had a switch to mania in late life; 3) those whose bipolar symptoms have never been recognized or were misdiagnosed; and 4) those who have never had an affective illness but develop mania in late life (possibly due to a specific medical or neurologic event, or for reasons unknown).

It is not known how common each presentation may be, though the most frequent experience is a patient who developed BPD earlier in life and is now seeking treatment [16]. However, based on findings by Hirschfeld and colleagues [12], it is not uncommon for the diagnosis of BPD to have been missed previously.

### *Gender*

In epidemiologic studies of mixed aged populations, BPD was equally prevalent among men and women [1]. Depp and colleagues [7] reviewed 17 studies reporting various sample populations of patients with late-life BPD. They found a higher prevalence of BPD among older women than men (mean 69%; range 45–89%). However, this percentage is similar to the gender ratio among older adults in the general population.

### *Age of onset*

Though BPD is a life-long illness, the literature tends to focus on the disease in younger individuals. Although the mean age of onset is around age 20 [9], some researchers have found heuristic evidence in dividing BPD into early-

and late-onset subtypes. Most surveys have found that the prevalence of BPD tends to be unimodal with a declining incidence in first-onset mania after the age of 40. A few studies, however, have noted two peaks: the first in the early/mid 20s, and a second peak (much smaller) closer to middle age [17–19]. This bimodal distribution is more prominent in women, with the second peak occurring around the time of menopause [17, 18, 20, 21]. A few studies have identified a second peak occurring in males in the eighth [22] or ninth [20] decade. Sajatovic and colleagues [16], assessed age of onset among 16,330 bipolar patients seen in the VA system during the 2001 fiscal year who were age 60 or older. While the majority of patients (13,477; 82.5%) had an earlier episode, 1,000 individuals (6.1%) had new-onset BPD. The authors analyzed clinical characteristics and suggested that age of onset did appear to create two different and meaningful subgroups of older adults with BPD.

What then is late-onset BPD and why is it important? There actually are no clear definitions of late-onset. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) [1] does not make a distinction, and various studies have used ages as young as 30 or as old as 50 to mark late-onset BPD [23–28]. However, identifying age of onset may suggest a marker for different etiologies of BPD, or even response to treatment.

For example, several studies [26–33] found that patients with early-onset illness have more family members with affective disorders compared to those with a later onset of illness. Researchers have postulated that early-onset patients have a higher genetic loading than those who develop the disease later in life. Countering this argument are several other studies that found no differences in family mental illness between the two groups [34–39], although this could be obscured by the consistent finding that all patients (but especially the younger groups) had high numbers of affectively ill relatives (as many as 4–22% in the late-onset groups) [26, 27, 29, 31, 32].

While family inheritance data are especially suggestive in the younger onset groups, the relationship of late-onset illness to neurological abnormalities is much more consistent across the studies. Though the definition of neurological illness varied, of the five studies assessing this, three [36, 40, 41] showed significantly higher rates in late-onset patients, while the other two [35, 37] showed trends toward increased levels. Snowdon [33], reviewing the admission data of 75 elderly bipolar subjects, found that the 13 patients with a known neurological disease had their first-episode of mania after the age of 50. Cook and colleagues [42] reported that 39 patients with neurological disease preceding the onset of mania had significantly later ages of onset, less family history of mood disorders, fewer depressive episodes, and more irritability and assaultive behavior during the manic episode. These data suggest that a neurological insult may induce BPD, especially late-onset BPD. Alternatively, it is possible that neurological developmental abnormalities that eventually cause neurological illness may also be associated with late-onset illness.

Age of onset has been less consistent in differentiating clinical course and associated factors. Carlson and colleagues [39] noted that age of onset as an

independent variable did not predict either the course or prognosis of BPD. These findings were echoed by Depp and colleagues [34], who found that later age of onset had few significant clinical differences from earlier onset, except that later onset of BPD predicted a lower intensity of psychiatric pathology. Carlson and colleagues [43] also noted that patients with early-onset BPD (first episode before <21 years) were less likely to experience complete episode remission during the following 24 months than later-onset (first episode after 30 years) patients. However, they also found that early-onset subjects were more likely male, had childhood behavior disorders, had substance abuse co-morbidity, and exhibited more paranoia in their psychotic features than late-onset subjects.

### *Differential diagnosis and co-morbidity*

As noted previously, the incidence of new onset mania in late life is relatively uncommon; therefore, all patients presenting with mania should be evaluated for potential medical illnesses that cause manic symptoms. This evaluation would include a thorough neurological examination. Also, because geriatric patients are usually taking multiple medications, these must be reviewed for a temporal association with illness presentation. Laboratory tests should include basic health panels (complete blood count and blood chemistries) as well as a thyroid panel. Consideration should also be given to conducting a neuroimaging test such as an MRI or CT scan. This would be especially important if the new presentation includes psychosis.

Due to the higher association of secondary causes of mania in late-life BPD, several studies have assessed the presence of co-morbid medical problems, the most common being neurological illnesses. Depp and colleagues [7] reviewed eight studies that reported the co-morbid neurological illnesses in the populations, and noted that despite a wide variety in reporting strategies, the sample-weighted prevalence was 23.1%. Shulman and colleagues [44] compared 50 geriatric patients hospitalized for mania to 50 age-matched patients hospitalized for unipolar depression. They found that the rates of neurological illness in manic patients were significantly higher (36% *versus* 8%) suggesting that a risk factor for the development of mania in late life was neurological disease. However, there has been no clear consensus on what neurological diseases or damage location may induce BPD.

Starkstein and Robinson [45] demonstrated that strokes that occur in the right hemisphere (especially the limbic region) are more likely to be associated with manic symptoms than left hemispheric strokes (see also [46–48]). A review of the literature reveals multiple case reports and case series that generally support a tentative association between mania and vascular risk factors, and also between mania and cerebrovascular disease [49–51]. This association has been termed ‘vascular mania’ [52]. Proposed diagnostic criteria have defined a late-age at onset (50+ years) sub-type of mania, with associat-

ed neuroimaging and neuropsychological changes that are not specific to this age group.

Other medical co-morbid disorders are also common in BPD and especially late-life BPD. These include cardiovascular disorders, obesity, diabetes mellitus, respiratory infections, and infectious diseases [53–56]. A clustering of traditional and emerging (e.g., immuno-inflammatory activation) risk factors presage somatic health issues in this population. Iatrogenic factors and insufficient access to primary, preventive, and integrated healthcare systems are also contributory [55].

In addition to medical co-morbidities, psychiatric co-morbidities are frequently seen in patients with BPD, though there is very little information about their prevalence in late-life BPD. There are a few reports of substance abuse, PTSD, and personality disorders in late-life BPD, but no published reports on co-morbid eating disorders, anxiety disorders, or attention disorders – conditions frequently reported to be present in younger bipolar populations. The National Co-morbidity Study (NCS) found that 61% of adults with BPD also had a substance use disorder at some point [57]. However, this nationwide survey did not include anyone over the age of 55. Cassidy and colleagues [58] reviewed rates of substance abuse in 392 patients hospitalized at a state psychiatric facility for BPD. Nearly 60% reported some history of substance abuse (a finding consistent with the NCS), but in the 51 patients over the age of 60 only 29% reported a history of substance abuse. This unexpectedly low prevalence of substance abuse in older patients with BPD was also found in two small inpatient studies [59, 60], a review of elderly patients with BPD in an outpatient mental health system [61], and a large review of the Veterans Health Administration database [62]. The reason for a lower prevalence of substance abuse in older patients with BPD compared with younger is unclear. It may be due in part to poor insight or recall of significant substance use history, or it may represent a better earlier life adaptation that decreased risk for substance abuse.

Molinari and Marmion [63] found an unusually high rate of personality disorders (70%) co-morbid to BPD in a sample of 27 geriatric outpatients and inpatients. The authors suggested that this high rate could be due in part to the difficult and chronic patterns of affective disorders. Sajatovic and colleagues [62] conducted a review of the national Veterans Health Administration database to examine the prevalence of dementia, substance abuse, PTSD, and other anxiety disorders in older patients with BPD. 4,668 subjects with BPD were identified (mean age 70). Of these, 4.5% had co-morbid dementia, 5.4% were found to have PTSD, and 9.4% had an anxiety disorder. The prevalence of anxiety disorders and PTSD is much less than that seen in younger BPD cohorts; however, the prevalence of dementia was higher than expected for this age group, making this a special concern. Four inpatient samples found that co-morbid dementia was highly variable, ranging from 3–25% [37, 60, 64, 65], often depending on the population being assessed. Several researchers have raised the concern that BPD, especially late-life BPD, may be associated with

a higher risk for the development of dementia. Co-morbidity does not necessarily imply an association.

*Mortality*

Dhingra and Rabins [66] reported that the mortality rate among 25 elderly patients with BPD who had been hospitalized 5–7 years previously was higher than expected compared with the general population. While it is known that individuals with mental illness at all ages have a higher mortality rate than the general population [67], Shulman and colleagues [44] found that the mortality rate of elderly hospitalized patients with BPD was significantly higher than that of elderly hospitalized unipolar depressed patients over a 10–15 year follow-up (50% *versus* 20%). They suggested that late-life mania was a more severe form of affective illness than unipolar depression and had a poorer prognosis. Alternatively, the increased medical and neurological co-morbidities seen in late-life BPD may be a causative factor in the higher mortality rate.

*Course*

As noted previously, there are different paths to the diagnosis of BPD in late life. Shulman and Post [68] reviewed the course of illness in 67 elderly patients with BPD whose first manic episode occurred around age 60, and described a subset of patients who experienced depression early in life with a long latency (mean = 15 years) before the onset of mania. They hypothesized that cerebral changes that occur with age (or possibly developmental disease) transformed the affective illness to mania. Other investigators have described a similar latency period of 10–20 years in a subgroup of patients between their first depressed episode and the onset of mania [33, 37, 44, 64]. Interestingly, Post [32] and Spar and colleagues [69] found that when mania presents in late life, patients are more likely to exhibit a mixed symptom pattern rather than the classic manic presentation. The literature also has numerous case reports [70–73] of a rapid cycling pattern in older patients, though it is unclear if this is more or less common than among younger patients.

Finally, it should be noted that several reports suggest that late-life BPD is either more difficult to treat or responds more slowly to treatment. Sajatovic and colleagues [59] found that older patients with BPD were hospitalized at the same rate as older patients with schizophrenia. Young and Falk [74] found that older patients with mania who needed hospitalization tended to have a slower resolution of symptoms, and a longer duration of hospitalization, than younger adult patients. Bartels and colleagues [75] found that older adults with BPD used outpatient services at four times the rate of a similarly aged group of unipolar depressed patients. Overall, BPD was associated with substantial disability, comparable to schizophrenia, and incomplete improvement in functioning even among those classified as remitters [76].

## Treatment

### *Pharmacological interventions*

Treatment of BPD at any age is a challenge. It is a complex disease with varying intensities of mood and behavioral alterations set in a variable cycle of frequent relapses and residual symptoms. Further, as noted above, the disorder has a high number of medical and psychiatric co-morbidities that demand an individualistic treatment focused on the whole person. Finally, the high incidence of poor insight and resulting poor adherence to medications (or poorly tolerated medications) has made the disease especially challenging to control. In the last few years, there have been several publications of structured guidelines or algorithms for treatment of acute BPD based on systematic reviews of the literature or expert opinions [2–5, 77]. These guidelines have been constructed to assist clinicians in navigating the complexity of pharmacotherapy in BPD; however, recent studies have found that clinical practice frequently differs from guideline recommendations [78–80].

Patients with late life BPD have several additional complications. First, the aging body may affect pharmacologic tolerance or sensitivity. Thus, multiple pharmacological considerations, such as changes in the absorption, distribution, and elimination of medications, must be understood when prescribing medications in this population [81]. While we will reference specific examples below, a fuller review can be found in Catterson and colleagues [82].

Secondly, aging is associated with an increasing number of medical problems [60] and associated medication use. A recent review of BPD treatment in geriatric patients found that the average number of total medications prescribed to a patient was 8.0 ± 4.6 (range 1–24) [83]. The presence of medical problems may also limit treatment options, or cause problems secondary to the treatment. Further, with the increased number of medications used, there is an increased risk of problematic medication interactions. The higher number of associated medical problems may be associated with the higher mortality rate found in BPD patients compared with similar aged non-psychiatrically ill and unipolar depressed groups [44, 66].

Thirdly, older adults frequently have age-related psychosocial problems that potentially complicate treatment (such as loss of ability to drive or limited social support) [84, 85]. Finally, an additional challenge for optimal treatment of the late-life patient with BPD is the limited data available about treatment response of older adults to medications for BPD, even common, currently FDA-approved treatments [86]. While mixed-aged studies have included some geriatric subjects, there have been no controlled prospective studies of acute or long-term management of mania in the geriatric patient population. Of the mixed-aged studies that did include older subjects, only a few have examined the effects of age within their study population [86, 87], thus making informed, evidence-based treatment even more difficult.

*Treatment efficacy*

*Lithium*

Multiple studies have validated the role of lithium over the past four decades as the 'gold standard' for treatment of BPD. Until the turn of the century, lithium was the most commonly prescribed medication for BPD, as well as the primary choice in late-life BPD [88–90]. However, there have been no placebo-controlled, double-blind, clinical trials in geriatric patients establishing its efficacy and tolerability. The studies that are available for review have primarily been either naturalistic or retrospective in design.

Young and colleagues [86] reviewed studies that reported on the use of lithium in more than 10 elderly patients with BPD [65, 91–93]. They found that 66% of elderly manic patients improved overall. However, certain groups of late-life patients did better than others. Patients with dementia and drug abuse were found to be especially resistant to treatment, in part due to their increased difficulty in tolerating lithium. This may have contributed to the observation that in the various studies, lithium concentrations varied widely (0.3–2.0 mEq/L). Thus, the recommended lithium level for acute mania in geriatric patients is unclear. Case series [94, 95] have suggested that elderly patients may respond to lower lithium levels (0.5–0.8 mEq/L) than those recommended for younger adults, while other reports have found no difference [96, 97]. Chen and colleagues [93] noted that patients who were able to achieve a serum lithium concentration ≥0.08 were much more improved at discharge than those who did not obtain or could not tolerate this level. Complicating dosing recommendations is the fact that the use of lithium in older patients, especially those over the age of 70, is frequently associated with adverse effects that may occur even at 'therapeutic' levels [98, 99]. Commonly reported adverse effects of lithium in the elderly include cognitive impairment, ataxia, urinary frequency, weight gain, edema, tremor, worsening of psoriasis, or arthritis. Thus, lithium dosing (and 'adequate' serum levels) in the elderly are primarily determined by the patient's medical status and frailty [86, 100].

Guidelines for the use of lithium in the elderly recommend starting at half the dosage normally recommended for younger patients because aging causes significant effects on lithium pharmacokinetics. Although absorption is generally unchanged, the renal clearance of lithium and the volume of distribution are decreased, while the elimination half-life is increased [101–103]. Furthermore, medications commonly prescribed to the elderly may affect lithium levels. Thiazide diuretics, nonsteroidal anti-inflammatory agents, and angiotensin-converting enzyme inhibitors can increase lithium concentrations while other medications, such as theophylline, can decrease lithium concentrations. Finally, the use of lithium itself may be associated with a decline in renal clearance or hypothyroidism. Therefore, lithium should be used with caution in patients with kidney problems or thyroid disorders. Because of these

Table 1. Studies of acute treatment of mania in late-life bipolar patients

| Study | Design | N | Age | Diagnosis | Study drug | Dose mg/day | Level mcg/ml | Results |
|---|---|---|---|---|---|---|---|---|
| Van der Velde, 1970 | Retrospective | 12 | 67 (60–74) | Mania | Lithium | NA (900 mg–2,100 mg) | NA (0.60–2.00) | 4/12 (33%) improved acutely; 1/12 maintained stability after 3 years. Younger patients appeared more responsive to lithium |
| Himmelhoch et al., 1980 | Retrospective | 81 | 63.3 ± 6.9 (55–88) | Bipolar I – 74 Bipolar II – 7 | Lithium | NA | NA | 56/91 (69%) responded to lithium. 23/25 (92%) non-responders had neurological illnesses |
| Schaffer and Garvey, 1984 | Prospective | 14 | 69 (65–77) | Mania | Lithium | NA | NA (0.50–0.90) | 11/14 (71%) responded |
| Puryear et al., 1995 | Retrospective | 13 | 70 (63–77) | Mania or mixed mania – 7 Other – 6 | Valproate | 1,000 | 57 (34–82) (100–1,750) | 12/13 (92%) responded with decrease in BPRS |
| Kando et al., 1996 | Retrospective | 35 | 71.3 (63–85) | Mania – 24 Other – 11 | Valproate | 743 (250–2,000) | 52.9 (11–102) | 18/29 (62%) responded |
| Noaguil et al., 1998 | Retrospective | 21 | 71 (60–85) | Mania | Valproate | 1,405 (500–3,000) | 72 (31–106) | 19/21 (90%) responded. 20/21 (95%) were on antipsychotics |
| Nedermier and Nasrallah, 1998 | Retrospective | 39 | 67 (60–82) | Mania – 16 Dementi – 7 | Valproate | 1,029 (500–2.250) | 72 (36–111) | 14/16 (88%) responded. Response was best in females, bipolar, younger age |

(Continued on next page)

Table 1. (Continued)

| Study | Design | N | Age | Diagnosis | Study drug | Dose mg/day | Level mcg/ml | Results |
|---|---|---|---|---|---|---|---|---|
| Chen et al., 1999 | Retrospective | 29 | 70 (55+) | Mania | 30 – Lithium<br>29 – Valproate | NA | Valproate (25–116)<br>Lithium (0.30–1.3) | 20/30 (68%) improved on lithium; 11/29 (38%) improved on valproate; Patients taking lithium with serum levels ≥0.8 mmol/L were more improved at discharge. Patients taking valproate with serum levels between 65–90 microg/mL were more improved at discharge. When response rates among only patients with these 'therapeutic' levels were assessed, they were similar for lithium (82%) and valproate (75%). The difference in efficacy between drugs was maintained in classic mania, but the two drug groups were similar when only mixed mania was analyzed (lithium 63% *versus* valproate 67% improved) |
| Beyer et al., 2001 | Subanalysis, Prospective study | 94 | 57 (50–75) | Mania | 47 – olanzapine<br>31 – valproate<br>14 – placebo | Valproate – 1,354 (500–2,500)<br>Olanzapine – 15.8 (5–20) | NR | Both olanzapine and valproate groups improved significantly compared to placebo |
| Sajatovic et al., 2004 | Subanalysis, Prospective study | 59 | 62.9 ± 5.7 | Mania | 59 – quetiapine<br>31 – placebo | NR | NR | Older and younger subjects had significant improvement compared with placebo. Older adults particularly had a rapid and sustained reduction in symptoms |

challenges, approximately one-fifth of geriatric patients have experienced lithium toxicity [102].

Prior to starting lithium, a preliminary medical work-up should include laboratory assessment of renal function, electrolytes, thyroid function tests, fasting blood glucose, and ECG [99]. These should also be rechecked every few months. McDonald [99] has also suggested that slow-release forms of lithium may be better tolerated by elderly patients.

### *Anticonvulsants*

#### *Valproate*

Approved by the FDA for the treatment of bipolar mania in 1993 (and originally approved for use as an anticonvulsant), valproate is the most frequently prescribed medication for the treatment of BPD among the elderly [83, 90]. This appears to be due to the poorer tolerance of lithium by older adults, and the reported efficacy of anticonvulsants in non-classic mania [99, 104]. This increased use is even more remarkable considering that, similar to lithium, there are no prospective trials comparing valproate with placebo or lithium in the elderly; only retrospective and open-label studies in the geriatric population have been published.

Young and colleagues reviewed the five published studies of valproate that included more than 10 elderly manic subjects [93, 105–108]. They found that 59% of the combined sample met the various improvement criteria, though again the dose concentrations varied widely (25–120 mcg/ml). In the general population, recommended blood levels for valproate are 50–120 mcg/ml [109], though Chen and colleagues [93] noted that higher concentrations were associated with more improvement in elderly manic patients than lower concentrations (65–90 mcg/ml). Chen and colleagues [93] also noted that valproate was as effective as lithium when atypical mania, rather than classic mania, was the predominant symptoms.

It should be noted that the blood level measurement should be used only as a guide in treatment. As patients age, the elimination half-life of valproate may be prolonged and the free fraction of plasma valproate increased. Thus, the total valproate level (which is the most common laboratory test for valproate concentration) may underreport the amount of valproate clinically available. The clinical significance of this is unknown [86,100]. In addition, common medications may also influence the level of valproate. Aspirin can increase the valproate free fraction while phenytoin and carbamazepine may decrease it. Valproate itself may influence the pharmacokinetics of other medications. It inhibits the metabolism of lamotrigine (thus requiring lower doses) and may also increase the unbound fraction of warfarin (thus requiring careful monitoring of coagulation times) [110].

Prior to initiation of valproate therapy, a medical work-up should include liver enzymes, complete blood count (with platelets), and an ECG [84].

Starting doses for elderly patients are 125–250 mg per day with a gradual titration every 2–5 days of 125–250 mg depending on the medical condition/frailty of the patient. Extended release preparations of valproate are now available. These appear to be well tolerated by the elderly, but it should be noted that correctly drawn trough blood levels may need to be collected 24–36 h after the last dose [111].

In general, valproate is fairly well tolerated in elderly patients. The most common side effects are nausea, somnolence, and weight gain, while less common side effects of special concern in older adults are the possibility of hair thinning, thrombocytopenia, hepatotoxicity, and pancreatitis (though the latter two are less likely to occur with age) [112, 113]. It also should be noted that valproate is available in a sprinkle and liquid formulations for patients who may have difficulty swallowing. In addition, Regenold and Prasad [109] have reported on the intravenous use of valproate in three geriatric patients with good success.

Table 2. Side effects of concern in patients with late-life BPD

| | |
|---|---|
| Lithium: | cognitive impairment, ataxia, urinary frequency, weight gain, edema, tremor, worsening of psoriasis/arthritis, diabetes insipidus, hypothyroidism |
| Valproate: | nausea, somnolence, weight gain, hair thinning, gait disturbances, thrombocytopenia, hepatotoxicity, pancreatitis |
| Carbamazepine: | sedation, ataxia, nystagmus/blurred vision, leucopenia, hyponatremia, agranulocytosis |
| Lamotrigine: | headache, nausea, Stevens-Johnson Syndrome |
| Atypical Antipsychotics: | sedation, akathisia, weight gain, diabetes, dyslipidemia, stroke |

*Carbamazepine*

Carbamazepine has been approved for the treatment of bipolar mania since 1996, while the extended release form was approved in 2005. Despite this, there is very limited information on the use of either carbamazepine preparation in elderly patients with BPD. The literature is currently limited only to case reports and the inclusion of some elderly patients in larger studies. Okuma and colleagues [114] noted that seven elderly manic patients were included in a larger sample of 50 treated with carbamazepine in a double-blind study that showed good efficacy. Some researchers have suggested that in contrast to lithium, carbamazepine may best be used as a preferred agent in secondary mania [84, 104].

Possible adverse effects associated with carbamazepine include sedation, ataxia, nystagmus/blurred vision, leukopenia, hyponatremia (secondary to SIADH), and agranulocytosis. Severe and sometimes life threatening skin reactions have been noted to be a rare side effect. These include toxic epider-

mal necrolysis and Stevens-Johnson syndrome. The FDA [115] recently recommended that patients of Asian ancestry have a genetic blood test to identify an inherited variant of the gene HLA = B*1502 (found almost exclusively in people of Asian ancestry) before starting therapy. Those patients testing positive should not be treated with carbamazepine.

Prior to beginning carbamazepine, medical work-up should include assessment of liver enzymes, electrolytes, and complete blood count, and ECG. In the elderly, carbamazepine doses should be initiated at 100 mg either once or twice daily, and gradually increased every 3–5 days to 400–800 mg/day [99]. As in the younger population, targeted serum levels are between 6–12 mcg/l. Because carbamazepine can induce its own metabolism, dose increases may need to be adjusted in the first 1–2 months.

Carbamazepine is metabolized in the liver by cytochrome P450 enzyme 3A4/5. Studies in patients with epilepsy have found that carbamazepine clearance was decreased in an age-dependent manner, presumably due to a reduction in CYP 3A4/5 metabolism [116]. The implication is that elderly patients may require lower doses to achieve similar levels of drug as younger patients. Carbamazepine can also alter the pharmacokinetics of other medications, including oral hormones, calcium channel blockers, cimetidine, terfenadine, and erythromycin [84].

*Lamotrigine*

Lamotrigine is another anticonvulsant recently found to be effective in the treatment of BPD. Though lamotrigine has not demonstrated efficacy in the treatment of acute mania or depression in BPD, it was approved by the FDA in 2003 for use in the maintenance phase. As with the other pharmacologic treatments for BPD, lamotrigine has not been well-studied in geriatric patients. However, Sajatovic and colleagues [117] conducted a secondary analysis of two placebo-controlled, double-blind, clinical trials for maintenance therapy that included 98 subjects over the age of 55. Focusing on this ‘older’ group, they found that older patients taking lamotrigine who had been stabilized from either an acute episode of mania or depression, demonstrated a significant delay in the recurrence of another mood episode. Response was consistent with that seen in younger patients. When the results were further evaluated, the authors found that lamotrigine was significantly more effective than lithium or placebo in increasing the time-to-intervention for depressive recurrences; however, lithium was more effective in increasing the time-to-intervention for manic recurrences. The mean daily dose of lamotrigine in this older group was 243 mg/day, and the mean daily dose of lithium was 736 mg/day. Overall, the authors found that lamotrigine was well-tolerated (compared with lithium) by older patients with BPD and no increased incidence of rash was noted [117, 118].

Lamotrigine has also been noted to be helpful as an augmentation treatment for bipolar depression in elderly patients. In a case report of five female geriatric bipolar patients with depressive episodes [119], three of the five reported

a remission of depressive symptoms after 6 weeks of augmentation treatment to either lithium or valproate.

Lamotrigine is metabolized in the liver and eliminated through the hepatic glucuronide conjugation. Aging may cause some decrease in hepatic glucuronidation but the effect does not appear to significantly change lamotrigine dosing [120, 121]. The dose of lamotrigine should be halved when administered with valproate because valproate inhibits the metabolism of lamotrigine [122]. Its most common adverse effects are headache and nausea, though serious skin rashes (Stevens-Johnson Syndrome) have also been reported. Because of studies suggesting that lamotrigine may be better tolerated than lithium [117] or carbamazepine [123] in elderly patients, some researchers have suggested that lamotrigine will play an increasingly important role in the treatment of late-life BPD.

### *Other anticonvulsant agents of interest*

Because of the success of valproate, carbamazepine, and lamotrigine for the treatment of various phases of BPD, several other anticonvulsant agents have been evaluated for use as well. Early open-label clinical trials showed gabapentin, oxcarbazepine, topiramate, tiagabine, and zonisamide to be promising treatments for BPD. However, controlled clinical trials have not supported the efficacy of gabapentin as monotherapy or combined therapy [124–126] in acute BPD. Further, at the time of this writing, there is only one published double-blind, placebo-controlled, clinical trial of oxcarbazepine monotherapy [127], and no double-blind, placebo-controlled trials of the other medications supporting their use in BPD. There are even less data about the use of these medications in the elderly [100, 128–131]. It should be noted that the oxcarbazepine study was conducted in adolescents with acute bipolar mania, and the authors did not find any improvement over placebo [127]. The metabolite of oxcarbazepine, licarbazepine, and other related compounds, such as eslicarbazepine, are currently being studied for use in BPD [132].

### *Antipsychotic agents*

Antipsychotic medications have been used empirically for the treatment of acute bipolar mania for many years, either as monotherapy or adjunctive treatment. However, use of conventional antipsychotics has always been problematic in the elderly because of the anticholinergic effects, higher risks of extrapyramidal symptoms, and tardive dyskinesia [100]. In the past decade, five ‘atypical’ antipsychotic agents have been approved by the FDA for the treatment of acute mania (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole); two are FDA-approved for the treatment of acute depression (olanzapine/fluoxetine, quetiapine); and two are approved for the treatment of

the maintenance phase (olanzapine, aripiprazole). These have largely supplanted the use of conventional antipsychotics as first-line antipsychotic treatment in geriatric patients [133]. However, in the treatment for late-life BPD, published controlled clinical trials of atypical antipsychotics are lacking. Most of the current practice recommendations are based on the extrapolated data from mixed population trials, or studies conducted in elderly populations of patients with schizophrenia or dementia.

Information is especially crucial because a black box warning was added [134] to each of the atypical antipsychotic agents indicating that clinical trials of atypical antipsychotics for the treatment of elderly patients with dementia-related psychosis had an increased risk of death compared to placebo. Presumably, the fatalities were related to an increase of cerebrovascular or cardiovascular incidents. The risk of strokes in late-life BPD is unknown.

The other major concern with use of atypical antipsychotics is an increased risk of metabolic abnormalities, such as obesity, diabetes, and dyslipidemia [135]. While the elderly may have less weight gain associated with atypical antipsychotics use [136], each of these medical conditions is frequently observed in elderly patients with BPD (see discussion above concerning medical co-morbidities). Clozapine and olanzapine appear to have a higher risk, while aripiprazole and ziprasidone appear less likely to cause these changes. When using these medications, it is recommended that clinicians monitor weight, waist measurement, blood pressure, and serum glucose and lipid levels at time of initiation and periodically throughout treatment [135].

In general, a lower dose strategy in the elderly has been recommended for most atypical antipsychotics [137], though this may be less of a concern in the acute state.

*Olanzapine*

Olanzapine is FDA-approved for the treatment of bipolar mania and maintenance phases. The combination pill of olanzapine and fluoxetine was approved for the acute treatment of bipolar depression. There are limited data on its use in late-life BPD. Two subanalyses have been conducted evaluating the efficacy and tolerability of olanzapine in older adults who were included in mixed-age, double-blind, placebo-controlled trials of olanzapine in acute mania. Street and colleagues [138] found that in a subset of eight older manic patients (ages 61–67), those treated with olanzapine improved while those treated with placebo worsened. Beyer and colleagues [139] conducted a pooled subanalysis of subjects over the age of 50 in three double-blind, placebo-controlled acute bipolar mania clinical trials with olanzapine and valproate. Of the 94 older adults (mean age 57), the 78 treated with either olanzapine or valproate demonstrated a significant improvement compared to those on placebo. Olanzapine and valproate were noted to be equally effective for the treatment of acute mania. The mean daily dose of olanzapine was 15.8 mg (range 5–20 mg) and the mean daily dose of valproate was 1,354 mg (range 500–2,500 mg). The side effects experienced by the older group were compa-

rable to those seen in younger patients; the most common were dry mouth, somnolence, asthenia, and headache.

*Quetiapine*

Quetiapine has been FDA-approved for the treatment of acute mania and depression in BPD. However, again, there are limited data concerning treatment response in elderly patients. Madhusoodanan and colleagues [140] and Tariot and colleagues [141] reported on a series of elderly patients with psychosis, some of who had BPD, who were treated successfully with quetiapine. Sajatovic and colleagues [142] reported on a subanalysis of 59 older adults (mean age 63) from two 12-week double-blind, placebo-controlled studies of quetiapine in bipolar mania. They noted that both older and younger subjects responded compared to placebo, but that the older subjects had a particularly rapid and sustained reduction of symptoms apparent by Day Four. The most common adverse effects were dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness. Few side effects or EPS was noted. The dosing recommendation for quetiapine in bipolar depression is between 300–600 mg, while in mania it is up to 800 mg. Due to the occurrence of common side effects such as sedation, dizziness, and postural hypotension, geriatric patients may start with lower doses, to be titrated as tolerated.

*Risperidone*

Risperidone is approved by the FDA for the treatment of acute bipolar mania, though again, there are very limited data in late-life bipolar use. Madhusoodanan and colleagues [143, 144] reported on retrospective case reviews noting efficacy in elderly patients with BPD. Significant adverse events included postural hypotension and dose-dependent EPS. It is recommended that for elderly or debilitated patients, risperidone be initiated in doses of 0.5 mg once or twice a day [100] and titrated carefully.

*Other atypical antipsychotics*

Ziprasidone and aripiprazole have both been FDA-approved for the treatment of bipolar mania. Aripiprazole is also approved for the maintenance phase of BPD. Both medications may be advantageous for use in the elderly due to their less common propensity for dyslipidemias and orthostasis. However, there are currently no published reports about use of these medications in elderly patients with BPD.

Clozapine is not FDA-approved for use in BPD; however, it has been reported to be helpful in the treatment of bipolar mania, rapid cycling, and treatment-resistant disease. There are some limited case reports of its successful use in geriatric patients with BPD [124, 145]. However, the adverse effects of particular concern in the elderly include sedation, postural hypotension, anticholinergic effects, and risk for seizures. In addition, the potential for agranulocytosis has effectively limited its use to refractory conditions.

*Antidepressants*

In BPD, depressive phases are much more prevalent than manic ones [146, 147]. For many bipolar patients, the depressive phase is also the most problematic, highly associated with morbidity and prompting them to seek treatment [148]. Because of this, antidepressants have been widely used to treat bipolar depression [83]. However, the use of antidepressants in BPD is also controversial among psychiatrists [149]. There are three primary causes of concern: an ambiguity in the literature as to the efficacy of antidepressants in bipolar depression, the potential for antidepressants to induce a manic episode, and the potential of antidepressants to induce rapid cycling. Thase and Denko (2008) reviewed the literature, focusing especially on two recently completed large clinical trials that attempted to clarify the benefits and risks of antidepressant use in bipolar depression [150]. The results did not produce clear guidelines regarding the optimal treatment for bipolar depression. Antidepressant augmentation of mood stabilizers did not distinguish itself as effective compared with placebo, or with the use of a second mood stabilizer. However, based on the data, the authors could not conclude that antidepressants should be avoided or used only in severe cases [151]. Given these limitations, the APA [77] has maintained its recommendations that primary treatment of the depressed phases of BPD should be initiated with a mood stabilizer, and that antidepressant augmentation of the mood stabilizer may be considered if there is limited or no response.

Given the general ambiguity of antidepressant use in bipolar depression, it should not be surprising that there are no specific studies examining the use of antidepressants in geriatric populations. It should be noted that Young and colleagues [152] conducted a retrospective study of elderly inpatients with antidepressant-induced mania. They found that tricyclic antidepressants were more likely than others to induce manias in late life, suggesting that SSRIs may be used preferentially in the elderly.

*Electroconvulsive therapy (ECT)*

Electroconvulsive therapy (ECT) has been demonstrated to be very effective in the treatment of mania and mixed affective states [153, 154]. However, there are very limited data on the use of ECT in elderly patients with BPD, especially when compared with the literature on unipolar depression [155]. McDonald and Thompson [156] reported on a case series of three elderly manic patients who also had some dementia and who were resistant to pharmacotherapy, but did respond to ECT treatment. Little and colleagues [157] reported on a case series of five elderly bipolar depressed patients treated with bifrontal ECT. They found this method could be effective, although a third of the patients experienced cognitive side effects. Tsao and colleagues [158] reported on the case of a man with refractory mania who responded to acute

and maintenance ECT. Frequent side effects noted in the elderly include confusion, memory impairment, and hypertension [159].

*Current treatment patterns*

Evident in the above discussion is that there are very limited data available to guide an evidence-based approach to the treatment of BPD in late-life. Furthermore, the data that are available focus almost exclusively on just one phase of the disorder: the treatment of mania. Therefore, treatment of the depressed phases, hypomanic phases, and maintenance phases must be extrapolated from studies in younger populations. In addition, it is unclear whether certain clinical factors (such as late- *versus* early-onset) or biological and genetic markers may modify treatment response.

There are some data available that describe the current state of treatment in late life. Beyer and colleagues [83] reviewed the treatment of 138 late-life patients with BPD experiencing an affective episode. Mood stabilizers accounted for the highest proportion of medications used (68% of patients), though atypical antipsychotics were frequently used as well (54% of patients). The latter appeared to be used more frequently than is traditional in younger populations. The researchers also noted that despite there being no data on combination treatment in late life, polypharmacy was almost twice as common as monotherapy. This involved the use of some combination of lithium, mood stabilizers, antipsychotics, or antidepressants. Finally, despite using 'good clinical practice', by the end of the treatment period (mean 342 days), 67% of the subjects met criteria for treatment response, but only 35% of the patients progressed to remission.

*Recommendations*

1. In general, the history of treatment response and tolerability to specific medications will provide the best data for guiding current treatment selection and dosing. It is therefore essential that a good history of illness be obtained, including adverse events and related doses/concentrations [86].
2. Elderly patients (especially those with a new onset of illness) should have a thorough physical and neurological exam. Laboratory evaluations should include basic metabolic panels, complete blood counts, thyroid studies, and liver function tests. Consideration should be given to vitamin B12 and folate levels. Vital signs, including an orthostatic blood pressure and pulse, weight, and waist measurement should be taken.
3. Elimination of unnecessary psychotropic agents along with conservative management may be an effective intervention by itself.
4. In the treatment of mania, monotherapy with a mood-stabilizer is a reasonable first approach. The minimal duration for a medication effectiveness trial is 3–4 weeks [86].

5. Lithium and valproate are the primary first choice options for the treatment of late-life mania. Classic manic symptoms may be more responsive to lithium, while atypical or rapid-cycling mania may be more responsive to valproate. Clinicians should initially target moderate concentration ranges (lithium 0.4–0.8; valproate 50–100); however higher concentration ranges may be more effective acutely (lithium 0.8–1.0, valproate 65–100). Carbamazepine may be used as a second-line agent. Valproate or carbamazepine may be preferred treatments when neurological disease is present. Atypical antipsychotic medications (particularly olanzapine and quetiapine) have shown efficacy as monotherapy treatments and are increasingly being used. Special caution may be required if using these agents in elderly patients with dementia.
6. If monotherapy is only partially effective, consideration should be given to the addition of an atypical antipsychotic or another mood stabilizer.
7. In the treatment of acute bipolar depression, monotherapy with a mood stabilizer is preferred. Lamotrigine may be especially useful for bipolar depression. Antidepressants may be used to augment the mood stabilizer or atypical antipsychotic, but should not be used as monotherapy or in rapid cycling BPD.
8. ECT should be considered in patients in an acute affective illness when they have been shown to be treatment resistant, or are suicidal and require critical intervention.
9. Effective acute treatment should continue for 6–12 months. Ongoing treatment with a mood stabilizer is essential. If remission is sustained, a slow discontinuation of the augmenting agents may be considered. In cases of late-onset mania without previous episodes, the optimal duration of treatment is unknown [86].
10. In the absence of specific treatment recommendations for elderly patients, general guideline recommendations should be followed with the proviso ‘start low and go slow’.

## Conclusions

Much is still unknown about late-life BPD, especially late-onset BPD [160]. Generally speaking, late-life BPD is a fairly common presentation to psychiatric practitioners and treatment facilities, despite the prevalence being fairly low in the community. This suggests that the disease may be difficult to manage and recurrences are not uncommon. Late-onset illness may be etiologically different than early-onset, and related to the medical and neurological problems that can occur with aging or to an underlying progression of neurological illness associated with some cases of BPD early in life. The concept of ‘vascular mania’ may be of both heuristic and treatment value in the future.

Treatment of late-life BPD requires knowledge of ‘best treatment’ practices and an understanding of the effect aging has on psychopharmacotherapy.

Adequate clinical trials are not currently available that would provide good evidence-based treatment recommendations for late-life BPD, requiring extrapolation from trials in mixed-age populations and adaptation to the older patient.

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