Chapter 13
Treatment of Bipolar Disorder in Special Populations

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Abstract Though often considered a young person's disease because its mean age of onset is in late adolescence, bipolar disorder (BD) frequently demonstrates recurrent episodes and morbidities that continue throughout the lifetime of the patient and into old age. In fact, presentation of mood episodes in older age is quite common and requires clinicians to understand the unique challenges that the interaction of aging and mental illness present. Further, it has been well established that the depressive polarity of episodes increases in frequency over the life span with a decline in manic and mixed episode presentations. Finally, while new onset of illness is relatively rare in later ages, it is not unknown, and the variability of age of onset may allow for a better understanding of the disease process. This chapter reviews our current understanding of BD in the elderly and highlights the implications of age in understanding the heuristic causes of the disease, challenges to treatment, and the limitations of our knowledge for clinical care.

Keywords Bipolar disorder • Elderly • Age of onset • Treatment

13.1 Introduction

The diagnosis of bipolar disorder (BD) is based on presentation of symptoms and course rather than etiological criteria (American Psychiatric Association 2013). Therefore, there is a large heterogeneity of presentations in patients that may affect both course and treatment of the disorder. Several aspects of presentation 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 (2002) and multiple other expert consensus treatment guidelines (Grunze et al. 2009, 2010; Goodwin et al. 2009; Yatham

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et al. 2013) as being meaningful in clinical decision-making. Patients may be treated differently if they are 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 BD or for 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 serve as markers for modifying clinical treatment. One clinical characteristic that is a modifying risk factor is the effect of age and age-of-onset in BD patients. Here, we focus on the impact of older age and aging in late-life BD. Questions addressed include whether patients with BD early in life "burn out" with age; whether there is a difference in BD symptoms through the life cycle; whether there are etiological and phenomenological differences if the disease begins early in life versus later in life; and whether aging affects treatment response.

This chapter is divided into two parts. The first part will discuss the current literature on aging in BD with an emphasis on late-life and late-onset disease. The second part will discuss treatment in late-life BD, noting especially the current literature on bipolar depression in the elderly.

13.2 Bipolar Disorder in Late Life

13.2.1 Prevalence

Though BD has been a recognized mental illness since the mid-1800s, the prevalence of BD in the geriatric population remains unclear. It is known that between six and eight percent of psychiatric admissions are for geriatric BD (Depp and Jeste 2004; Ettner and Hermann 1998); however, the Epidemiologic Catchment Area (ECA) study failed to capture any active manic elderly cases during their community survey of psychiatric disorders in the United States (Weissman et al. 1988). Instead, using a statistical weighted analysis, the authors reported a one-year prevalence range of elderly with BD between 0.0 and 0.5 % (with a cross-site mean of 0.1 %). This was markedly lower than the prevalence of BD reported among young (18–44 years; 1.4 %) and middle-aged (45–64 years; 0.4 %) adults. This range, though, was consistent with three other community-based studies that included assessments of the prevalence of BD in the elderly. Unutzer and colleagues (1998) reviewed a large HMO database and found a prevalence rate of 0.25 % (compared with 0.46 % in adults aged 40–64). Klap and colleagues (2003) reported on the HealthCare for Communities (HCC) Household Telephone Survey of 9585 households and found a prevalence rate of 0.08 % (compared with 1.17 % for adults aged 30–64). Finally, Hirschfeld and colleagues (2003) reported results of

a screening questionnaire (Mood Disorder Questionnaire) sent to 125,000 individuals (85,258 responders). They found the screen rate for adults 65 and older was 0.5 % (compared with 3.4 % in adults younger than 65).

Interestingly, each of these surveys suggested that the prevalence of BD declines with age or in aging cohorts. This has led some researchers to suggest that bipolar episodes decrease with age (Angst et al. 1973). Winokur (1975) 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 (1995) followed 209 BD patients over a period of 40 years (median age 68). They found that manic episodes did not decrease with age, and many patients continued to have episodes into their seventh decade.

Overall, the decline in the prevalence of BD 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 noted in patients with mental illness.

In general, the development of BD in late life can be divided into four patterns: (1) those who had early-onset of BD and have reached old age; (2) those who were previously diagnosed with major depressive disorder (MDD) 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 BD earlier in life and is now seeking treatment (Sajatovic et al. 2005c). However, based on findings by Hirschfeld and Vornik (2004), it is not uncommon for the diagnosis of BD to have been missed previously.

13.2.2 Age of Onset

Though BD is a life-long illness, the literature tends to focus on the disease in younger individuals. Indeed, the mean age of onset is just under age 20 (Weissman et al. 1996). However, some researchers have found heuristic evidence in dividing BD into early- and late-onset subtypes. Most surveys have found that the onset of BD 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 (Petterson 1977; Angst 1978; Goodwin and Jamison 1984; Kessing 2006). This bimodal distribution is more prominent in women, with the second peak occurring around the time of menopause (Sibisi 1990; Petterson 1977; Zis et al. 1979; Angst 1978). A few studies have identified a second peak occurring in males in the eighth (Spicer et al. 1973) or ninth (Sibisi 1990) decade.

More recently, Bellivier and colleagues (2001) conducted an admixture analysis of age of onset and identified three distinct subgroups of early, intermediate, and late-onset, peaking at 17, 27, and 46 years, respectively. This finding of three distinct subgroups has been subsequently replicated in other independent samples, identifying very similar mean ages of onset (Bellivier et al. 2003; Manchia et al. 2008; Hamshere et al. 2009). Thus, there is support for distinguishing subgroups of BD patients based on age of onset, but does this classification have any meaningful difference?

It should be noted that in reviewing the literature, there actually are no clear definitions of late onset. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013) does not make a distinction, and various studies have used ages as young as 30 or as old as 60 to mark late onset (Loranger and Levine 1978; Eagles and Whalley 1985; Ghadirian et al. 1986; James 1977; Taylor and Abrams 1973; Hopkinson 1964; Sajatovic et al. 2005c; Kessing 2006; Chu et al. 2010; Oostervink et al. 2009, 2015). However, even with this variability, a few findings have stood out.

For example, several studies (Mendlewicz et al. 1972; Taylor and Abrams 1973; James 1977; Baron et al. 1981; Stenstedt 1952; Post et al. 2016; Hopkinson 1964; Snowdon 1991; Chu et al. 2010) found that patients with early onset of 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 (Depp and Jeste 2004; Hays et al. 1998; Tohen et al. 1994; Broadhead and Jacoby 1990; Glasser and Rabins 1984; Carlson et al. 1977), though 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 four to 22 % in the late-onset groups) (Mendlewicz et al. 1972; Taylor and Abrams 1973; James 1977; Stenstedt 1952; Post et al. 2016).

While family inheritance data is especially indicative in the younger onset groups, the relationship of late-onset illness to neurological abnormalities is much more consistent across the studies. Though the nature of a neurological illness varied, of the five studies assessing this, three (Tohen et al 1994; Wylie et al. 1999; Almeida and Fenner 2002) showed significantly higher rates in the late-onset patients, while the other two (Broadhead and Jacoby 1990; Hays et al. 1998) showed trends toward increased levels. Further, Tamashiro and colleagues (2008) noted that BD patients with late-onset illness (illness onset after age 60) had a greater prevalence of white matter hyperintensities in the deep parietal and basal ganglia regions and more severe white matter hyperintensities in the deep frontal, parietal, and putamen regions. Subramaniam and colleagues (2007), in a cross-sectional survey of elderly BD patients, found that the late-onset group (illness onset after age 60) had a higher stroke risk score even though cognitive function and physical health were no different from the early-onset group. These data suggest that a neurological insult (especially cerebrovascular disease)—either known or silent—may induce BD, especially late-onset. The kind and location of

neurological insult has yet to be determined (see below). Alternatively, it is possible that neurological developmental abnormalities that eventually cause neurological illness may also be associated with late-onset BD.

In regard to clinical symptomatology and course of treatment, age of onset may suggest only limited differences. In the European Mania In Bipolar Longitudinal Evaluation of Medications (EMBLEM) study, a two-year, prospective, observational study that evaluated treatment and outcome in 3459 BD patients (475 of whom were >60 years of age), the researchers divided the older group based on their age of onset (before or after age 50). They noted no differences in baseline severity scores between the early-onset group and the late-onset group, but more patients in the late-onset group recovered, and they recovered faster (Oostervink et al. 2009, 2015). Similarly, Carlson and colleagues (1977) noted that age of onset (adolescent-onset vs onset after age 45) as an independent variable did not predict either the course or prognosis of BD in their sample, though early-onset BD patients were less likely to experience complete episode remission during the following 24 months than late-onset BD patients (Carlson et al. 2000). Depp and colleagues (2004) also found that a later age of onset had few significant clinical differences from earlier onset, except that later onset of BD predicted lower intensity of psychiatric pathology. Biffin and colleagues (2009) reported findings from the Bipolar Comprehensive Outcomes Study in Australia and noted that the earliest-onset group had more depression, suicidal ideation, binge drinking, and poorer quality of life than the later-onset groups. Kessing (2006) reviewed data from the Denmark nationwide register and found that patients who were older at their first psychiatric hospitalization (>50 years) presented with fewer psychotic manic episodes but more severe depressive episodes with psychosis than younger patients. Finally, Chu and colleagues (2010) evaluated 61 older adults with BD and noted no significant differences on demographic or clinical variables, except for a slightly higher percentage of days spent depressed for the early-onset group.

Thus, the overall clinical usefulness of age of onset is limited, but it may prove important in genetic epidemiologic studies in order to reduce underlying genetic heterogeneity (Leboyer et al. 2005) or in neuroimaging to understand mood regulation circuitry.

13.2.3 Mortality and Comorbidity

It is well known that individuals with BD suffer a disproportionate amount of morbidity and die earlier than the general population (Sajatovic et al. 2013). Standardized mortality ratios in BD are 2.5 for men and 2.7 for women, with cardiovascular disorders, suicide, and cancer the most frequent causes of premature mortality (Osby et al. 2001; Laursen et al. 2007). For patients with BD who have survived to older age, mortality rates continue to be high (Dhingra and Rabins 1991). Further, Shulman and colleagues (1992) found that the mortality rate of elderly hospitalized BD patients was significantly higher than that of elderly

hospitalized MDD patients over a 10–15 year follow-up (50 % versus 20 %). They suggested that late-life mania was either a more severe form of affective illness than MDD, with a poorer prognosis, or was associated with increased medical and neurological comorbidities.

Indeed, elderly BD patients average three to four chronic medical conditions (Lala and Sajatovic 2012), the most common being cardiovascular and neurological in origin (Depp and Jeste 2004; Beyer et al. 2005; McIntyre et al. 2007). Approximately two-thirds of elderly BD patients have hypertension and a third have diabetes (Kemp et al. 2010). Neurological diseases are especially prevalent. Shulman and colleagues (1992) compared 50 geriatric patients hospitalized for mania to 50 age-matched patients hospitalized for MDD. They found that the rates of neurological illness in manic patients were significantly higher (36 % versus 8 %), supporting the hypothesis that neurological disease is a risk factor for the development of mania in late life. A review of the stroke literature (Starkstein and Robinson 1989) demonstrated that strokes occurring in the right hemisphere (especially the limbic region) are more likely to be associated with manic symptoms than left hemispheric strokes (see also Starkstein et al. 1987, 1990, 1991).

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 (Cassidy and Carroll 2002; Subramaniam et al. 2007; Wijeratne and Malhi 2007). In the limited neuroimaging literature, the few studies that have reported findings in elderly BD patients repeatedly note increased white matter hyperintense lesions compared with healthy controls (Altshuler et al. 1995; Beyer et al. 2004), a finding also noted to a lesser extent in children and adolescents with BD (Beyer et al. 2009). It is thought that these hyperintense lesions, which are not uncommon findings in aging brains, represent areas of ischemia, possibly a consequence of having more atherosclerotic risk factors. This association has been termed "vascular mania" (Steffens and Krishnan 1998). Proposed diagnostic criteria have defined a late age at onset (50 years +) subtype of mania, with associated neuroimaging and neuropsychological changes that are not specific to this age group.

Given these findings, one would also suspect that decline in cognitive functioning and dementia would be more prevalent in late-life BD. It should be realized that for all ages, having BD is associated with cognitive dysfunction (Sajatovic et al. 2013), especially in the areas of attention, working memory, executive function, verbal memory, and processing speed. While these changes are not "neurodegenerative," cognitive dysfunction in BD is thought to be a "neuroprogressive" process that includes neurodevelopment aspects, medical comorbidities, lifestyle causes, compounded by the aging process (Gildengers et al. 2012). Further, many medications used for the treatment of BD have been associated with cognitive blunting/impairment, often worsening the aging and underlying changes of BD. Thus, cognitive problems are not uncommonly seen in late-life BD, and comorbid dementia is often seen as well, ranging from 3 % to 25 % depending on the population being assessed (Broadhead and Jacoby 1990; Stone 1989; Ponce et al. 1999; Himmelhoch et al. 1980; Sajatovic et al. 2006).

13.3 Treatment

13.3.1 Pharmacological Interventions

Treatment of BD 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 comorbidities 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 BD based on systematic reviews of the literature or expert opinions (Grunze et al. 2009, 2010; Goodwin et al. 2009; Yatham et al. 2013). These guidelines have been constructed to help clinicians navigate the complexity of pharmacotherapy in BD; however, recent studies have found that clinical practice frequently differs from guideline recommendations (Lim et al. 2001; Perlis 2005; Sachs 2003).

For the geriatric BD patient, there are four additional complications. First, the aging body may affect pharmacologic tolerance or sensitivity. Multiple pharmacological considerations, such as changes in the absorption, distribution, and elimination of medications must be understood when prescribing medications in this population (Van Gerpen et al. 1999). While we will refer to specific examples below, a fuller review can be found in Catterson and colleagues (1997). Second, aging is associated with an increasing number of medical problems (see Beyer et al. 2005) and associated medication use. A recent review of BD treatment in geriatric patients found that the average number of total medications prescribed to a patient was 8.0 ± 4.6 (range 1–24) (Beyer et al. 2008). The presence of medical problems may 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 BD patients compared with similarly aged non-psychiatrically ill and MDD groups (Shulman et al. 1992; Dhingra and Rabins 1991). As noted previously, the incidence of a new onset mania in late life is relatively uncommon; therefore, every patient should be evaluated for potential medical illnesses that cause manic symptoms. This evaluation would include a thorough neurological examination. Also, since geriatric patients are usually taking multiple medications, these must be reviewed for a temporal association with the 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. Third, older adults frequently have age-related psychosocial problems that potentially complicate treatment (such as loss of ability to drive or limited social support) (Sajatovic 2002; Beyer et al. 2003).

Finally, an additional challenge for optimal treatment of the geriatric BD patient is the limited data available about treatment response of older adults to BD medications, even common treatments currently approved by the FDA (Young et al. 2004). 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. And of the mixed-aged studies that did include older subjects, only a few have examined the effects of age within their study population (see Mirchandani and Young 1993; Young et al. 2004), thus making informed, evidence-based treatment even more difficult.

13.3.2 Treatment Efficacy

13.3.2.1 Lithium

Until the turn of the century, lithium was the most commonly prescribed medication for treatment of BD in the elderly (Oshima and Higuchi 1999; Umapathy et al. 2000; Shulman et al. 2003), despite the fact that no placebo-controlled, double-blind clinical trials had been conducted in geriatric patients. In 2004, Young and colleagues reviewed studies that reported on the use of lithium in which more than 10 elderly BD subjects were enrolled (van der Velde 1970; Himmelhoch et al. 1980; Schaffer and Garvey 1984; Chen et al. 1999). They found that 66 % of elderly manic patients improved overall, but certain groups of elderly BD patients did more poorly than others. Patients with dementia and drug abuse were found to be especially resistant to treatment, in part due to the increased difficulty in tolerating lithium. This may have contributed to the large variation in reported lithium concentrations among studies (0.3 mEq/l to 2.0 mEq/l).

The recommended lithium level for elderly BD patients has been debated. Case series (Roose et al. 1979; Prien et al. 1972) have suggested that elderly patients in acute mania may respond to lower lithium levels (0.5–0.8 mEq/l) than what is recommended for younger adults, while other reports have not found a difference (Young et al. 1992; DeBattista and Schatzberg 2006). A large retrospective study (Paton et al. 2010) in the United Kingdom (UK) found that for maintenance treatment, therapeutic threshold was comparable between old and young patients. Older patients with a lithium level under 0.4 mEq/l were more likely to relapse than those with a higher level. Chen and colleagues (1999) noted that patients who were able to achieve a serum lithium concentration $\geq$0.8 were much more improved at discharge than those who did not obtain or could not tolerate this level.

In the UK study, Paton and colleagues (2010) reported that older patients required lower doses of lithium than younger patients to achieve a therapeutic lithium level. This was also reported in a secondary analysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Al Jurdi et al. 2008). The average lithium dose in older adults was 689 mg/day, compared with 1006 mg/day in the younger patients.

While serum levels of lithium are important in guiding dosage, the correlation between serum and brain levels of lithium appear to diminish, if not disappear, in older adults (Forester et al. 2009). It is speculated that this change is due to the age-related decline in the integrity of the blood–brain barrier or changes in sodium–lithium countertransport that result in a higher ratio of brain/serum concentration than in younger patients.

Possibly the most helpful study guiding the use of lithium in older adults with BD is the recent NIMH-sponsored Geriatric Enhancement Treatment in Bipolar Disorders (GERI-BD) clinical trial, which sought to establish the efficacy and tolerability of lithium and valproate in this fragile population. Preliminary results reported on 224 BD subjects aged 60 years and older who presented in a manic, hypomanic, or mixed episode. All subjects were randomized to double-blind treatment with either lithium or valproate at a targeted level of 0.80–0.99 mEq/l or 80–99 mcg/ml, respectively, over a nine-week period. Most subjects were able to tolerate the medications and achieve the targeted plasma concentrations (lithium: 57 %; valproate: 56 %) at week nine, though at week three achievement of targeted plasma levels was relatively much lower for both groups (lithium: 35 %; valproate: 33 %). The study found that both groups had a good response to treatment; however, the effect of lithium was significantly larger, especially in the more severely manic subjects. There were no significant differences in side effects, though the lithium group did experience more tremor.

This concern about side effects has complicated dosing recommendations because older patients, especially those over the age of 70, are more likely to have adverse effects with lithium, and these occur even at "therapeutic" levels (Tueth et al. 1998; McDonald 2000). Commonly reported adverse effects of lithium in the elderly include cognitive impairment, ataxia, urinary frequency, weight gain, edema, tremor, worsening of psoriasis or arthritis, or disruption of normal thyroid activity. Thus, in practical clinical application, lithium dosing and "adequate" serum levels in the elderly are primarily determined by the patient's medical status and frailty (Young et al. 2004; Sajatovic et al. 2005a).

Guidelines for use of lithium in the elderly recommend starting at half the normally recommended dosage in younger patients because aging significantly affects lithium pharmacokinetics. Although absorption is generally unchanged, the renal clearance of lithium and the distribution volume are decreased while the elimination half life is increased (Sproule et al. 2000; Foster 1992; Shulman et al. 1987). Thus, the risk of toxicity increases in the elderly. Further, the age-related decline in renal function is compounded by the deleterious effect lithium has on the kidneys. In a cross-sectional study comparing glomerular filtration rates of 61 patients treated with lithium for about 16 years, with that of 53 patients who only receive electroconvulsive therapy (ECT), 34.4 % of the lithium-treated patients had stage 3 chronic renal disease, compared with 15.1 % of the ECT group. When patients older than 70 were evaluated separately, about 70 % of the lithium-treated patients had stage 3 chronic renal disease, compared with 36.4 % of the ECT group (Tredget et al. 2010).

Finally, medical comorbidities that may increase risk of lithium toxicity (such as dehydration, heart failure, hyponatremia, etc.) and medications commonly prescribed to the elderly (such as thiazide diuretics, nonsteroidal anti-inflammatory agents, and angiotensin-converting enzyme inhibitors) may affect lithium levels. Prior to starting lithium, a preliminary medical workup should include laboratory assessment of renal function, electrolytes, thyroid function tests, fasting blood glucose, and ECG (McDonald 2000). These should also be rechecked every few months. McDonald (2000) has also suggested that slow-release forms of lithium may be better tolerated by elderly patients. Because of all these challenges, approximately one-fifth of geriatric patients have experienced lithium toxicity (Foster 1992).

13.3.2.2 Anticonvulsants

Valproate

Approved by the FDA for the treatment of bipolar mania in 1993 (and originally approved for use as an anticonvulsant), valproate is currently the most frequently prescribed medication for the treatment of BD among the elderly (Shulman et al. 2003; Beyer et al. 2008). This may in part be due to its reported efficacy for patients with non-classic manic symptoms and prominent depressive symptoms (Evans et al. 1995; McDonald 2000). This increased use is even more remarkable considering that, similar to lithium, there are no prospective trials comparing valproate with placebo in the elderly. Rather, with the exception of the lithium/valproate comparison trial in elderly manic subjects (GERI-BD; Young et al. 2010), only retrospective and open-label studies in the geriatric population have been published.

Young and colleagues reviewed the five published studies of valproate that have included more than 10 elderly manic subjects (Chen et al. 1999; Niedermier and Nasrallah 1998; Noagiul et al. 1998; Kando et al. 1996; Puryear et al. 1995). They found that 59 % of the combined sample met the various improvement criteria, though again the dose concentrations varied widely (25–120 mcg/ml). As noted previously, the NIMH-sponsored GERI-BD trial attempted to establish efficacy and tolerability data for the use of lithium and valproate in the elderly. Valproate was as well tolerated as lithium, and both medications were equally effective (though lithium appeared to be more effective in more severely manic patients).

In the general population, recommended blood levels for valproate are 50–120 mcg/ml (Bowden and Singh 2005), though Chen and colleagues (1999) noted that higher, compared with lower, concentrations (65–90 mcg/ml) were associated with more improvement in elderly manic patients. 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 (Young et al. 2004; Sajatovic et al. 2005a). Further, common medications may also influence the level of valproate. For instance, aspirin can increase valproate free fraction while phenytoin and carbamazepine may decrease valproate levels. 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) (Panjehshahin et al. 1991).

Prior to initiating valproate therapy, medical workup should include liver enzymes, complete blood count (with platelets), and an ECG. Starting doses for elderly patients are 125–250 mg per day with a gradual titration every two to five days of 125–250 mg depending on the medical condition/frailty of the patient. Extended release preparations of valproate 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 hours after the last dose (Reed and Dutta 2006).

The most common side effects associated with valproate 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) (Bowden et al. 2002; Fenn et al. 2006). It should also be noted that valproate is available in sprinkle and liquid formulations for patients who may have difficulty swallowing. In addition, Regenold and Prasad (2001) reported on the intravenous use of valproate in three geriatric patients with good success.

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 BD patients. The literature is currently limited only to case reports and the inclusion of some elderly patients in larger studies. Okuma and colleagues (1990) noted that seven elderly manic patients were included in the 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 utilized as a preferred agent in secondary mania (Evans et al. 1995; Sajatovic 2002).

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 epidermal necrolysis and Stevens–Johnson syndrome. The FDA (2007) 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 workup should include assessment of liver enzymes, electrolytes, 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 three to five days to 400–800 mg/day (McDonald 2000). As in the younger population, targeted serum levels are between 6 and 12 mcg/l. Since carbamazepine can induce its own metabolism, dose increases may need to be adjusted in the first one to two months.

Carbamazepine is metabolized in the liver by cytochrome P450 enzyme 3A4/5. Studies in patients with epilepsy found that carbamazepine clearance decreased in an age-dependent manner, presumably due to a reduction in CYP 3A4/5 metabolism (Battino et al. 2003). 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 (Sajatovic 2002).

Lamotrigine

Lamotrigine is another anticonvulsant medication that has more recently been found to be effective in the treatment of BD. Though lamotrigine has not demonstrated efficacy in the treatment of acute mania or depression in BD, it was approved by the FDA in 2003 for use in the maintenance phase. Sajatovic and colleagues (2005b) conducted a secondary analysis of two placebo-controlled, double-blind, clinical trials for maintenance therapy that had included 98 subjects over the age of 55. Focusing on this "older" group, they found that older patients on lamotrigine who had been stabilized from either an acute episode of mania or depression demonstrated a significant delay until 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. Sajatovic and colleagues (2011) then conducted a prospective open-label augmentation trial of 57 elderly subjects with bipolar depression who had been treatment resistant to current medications. Over the 13-week trial, 57 % of the subjects achieved remission while 65 % achieved treatment response (average daily dose was 114 mg). Overall, the authors found that lamotrigine was well tolerated in both studies by the older BD patients, and no increased incidence of rash was noted (Sajatovic et al. 2005b, 2007, 2011).

Lamotrigine is metabolized in the liver and eliminated through the hepatic glucuronide conjugation. Aging may decrease hepatic glucuronidation but the effect does not appear to significantly change lamotrigine dosing (Posner et al. 1991; Hussein and Posner 1997). The dose of lamotrigine should be halved

when administered with valproate since valproate inhibits the metabolism of lamotrigine (Calabrese et al. 2002).

The most common adverse effects are headache and nausea, though serious skin rashes (Stevens–Johnson Syndrome) have also been reported to be associated with lamotrigine. With studies suggesting that lamotrigine may be better tolerated than lithium (Sajatovic et al. 2005b) or carbamazepine (Aldenkamp et al. 2003) in elderly patients, some researchers have suggested that lamotrigine will have an increasingly important role in late-life treatment of BD.

13.3.2.3 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 anticholinergic effects, higher risks of extrapyramidal symptoms, and tardive dyskinesia (Sajatovic et al. 2005a). In the past two decades, the "atypical" antipsychotic agents have largely supplanted the use of conventional antipsychotics as first-line antipsychotic treatment in geriatric patients (Jeste et al. 1999). However, in the treatment of late-life BD, published controlled clinical trials of atypical antipsychotics are lacking. Most of the current practice recommendations are based on extrapolated data from mixed population trials or studies conducted in elderly populations of patients with schizophrenia or dementia. Information is especially crucial since a black box warning (FDA 2005) was added 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 increased cerebrovascular or cardiovascular incidents, problems that have been noted to be particularly relevant to patients with late-life BD.

The other major concern with use of atypical antipsychotics is increased risk of metabolic abnormalities, such as obesity, diabetes, and dyslipidemia (ADA 2004). While the elderly may have less weight gain associated with atypical antipsychotic use (Meyer 2002), each of these medical conditions are frequently observed in elderly BD patients. When using these medications, it is recommended to monitor weight, waist measurement, blood pressure, and serum glucose and lipid levels at time of initiation and periodically throughout treatment (ADA 2004).

In general, a lower-dose strategy in the elderly has been recommended for most atypical antipsychotics (Alexopoulos et al. 2004) 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 mania. There are limited data on its use in late-life BD. Two subanalyses have been conducted evaluating the efficacy and tolerability of older adults that were included in mixed-age, double-blind, placebo-controlled trials of olanzapine in acute mania. Street and colleagues (2000) 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 (2001) 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 with 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 1354 mg (range 500–2500 mg). The side effects experienced by the older group were comparable with that seen in younger patients, the most common of which were dry mouth, somnolence, asthenia, and headache.

Quetiapine

Quetiapine has been FDA-approved for the treatment of acute mania and depression in BD. However, again, there are limited data concerning treatment response in elderly BD patients. Madhusoodanan and colleagues (2000) reported on a series of elderly patients with psychosis, some of whom had BD, who were treated successfully with quetiapine. Sajatovic and colleagues (2004) 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 4. Most common adverse effects were dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness. Few side effects or extrapyramidal symptoms were noted. The dosing recommendations for quetiapine in bipolar depression is between 300 and 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 be started with lower doses and titrated as tolerated.

Other Atypical Antipsychotics

Risperidone is approved by the FDA for the treatment of acute bipolar mania, though again, there are very limited data regarding late-life BD use.

Madhusoodanan and colleagues (1995, 1999) reported on retrospective case reviews noting efficacy in elderly BD patients. Significant adverse events included postural hypotension and dose-dependent extrapyramidal symptoms. It is recommended that for elderly or debilitated patients, risperidone be initiated in doses of 0.5 mg once or twice a day (Sajatovic et al. 2005a) and titrated carefully.

Aripiprazole has been FDA-approved for the treatment of mania and the maintenance phase of BD. While this medication may be advantageous for use in the elderly due to less common propensity for dyslipidemias and orthostasis, the initial registration clinical trials did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients (Kohen et al. 2010). Sajatovic and colleagues (2008) conducted a 12-week, open-label, augmentation trial with aripiprazole for 20 older adult patients with BD who had not optimally responded to their prescribed medications. They found that the addition of aripiprazole (average daily dose was 10 mg) significantly reduced mean depression and mania scores and improved overall functioning.

Asenapine is the most recent second-generation antipsychotic approved in the treatment of BD, though its FDA approval has been designated only for treatment in depressive episodes. As with all the other similar medications, there have been no double-blind, placebo-controlled studies in elderly BD patients. There have been two small, open-label studies. Baruch and colleagues (2013) treated 11 consecutively admitted elderly bipolar manic patients with asenapine 10 mg twice a day. They noted that all subjects had responded by week four and that 64 % had achieved remission. Sajatovic and colleagues (2014) reported on an open-label augmentation trial for 15 sub-optimally responding elderly BD patients. Seventy-three percent of the patients completed the study and demonstrated significant improvements in mood and functioning. Mean daily dose of asenapine augmentation was 11.2 mg. In both studies, asenapine was well tolerated though GI discomfort was reported in 33 % of patients in the augmentation study.

Clozapine is not FDA-approved for use in BD; 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 BD patients (Shulman et al. 1997; Frye et al. 1996). However, the adverse effects of particular concern in the elderly include sedation, postural hypotension, anticholinergic effects, and risk for seizures. Further, the potential for agranulocytosis has effectively limited its use to refractory conditions.

13.3.2.4 Electroconvulsive Therapy

ECT has been demonstrated to be very effective in the treatment of mania and mixed affective states (Mukherjee et al. 1994; Valentí et al. 2008). However, there are very limited data on the use of ECT in elderly BD patients, especially when compared with the literature on MDD (Wilkins et al. 2008). McDonald and Thompson (2001) reported on a case series of three elderly manic patients who also had some dementia who were resistant to pharmacotherapy, but did respond to

ECT treatment. Little and colleagues (2004) reported on a case series of five elderly patients with bipolar depression treated with bifrontal ECT. They found this method could be effective though a third experienced cognitive side effects. Tsao and colleagues (2004) reported on a 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 (Kujala et al. 2002).

13.3.3 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 BD in late life. Further, the data that are available focus almost exclusively on just one phase of the disorder: treatment of mania. Therefore, treatment of the depressed phases, hypomanic phases, and maintenance phases must be extrapolated from studies in younger populations. Also, with the limited data, it is unclear if certain clinical factors (such as late- versus early-onset) or biological and genetic markers may modify treatment response.

There are some data available that are descriptive of the current state of treatment in late life. Beyer and colleagues (2008) reviewed the treatment of 138 late-life BD patients experiencing an affective episode. Mood stabilizers remained the highest proportion of medications used (68 % of patients), though atypical antipsychotics were frequently used as well (54 % of patients). The latter appears to be a higher percentage of use than found in younger populations. The researchers also noted that despite there being no data on combination treatment in late life, they found 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 % met criteria for treatment response, but only 35 % of the patients progressed to remission.

13.3.4 Treatment Recommendations

1. In general, the history of treatment response and tolerability to specific medications will present 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 (Young et al. 2004).
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 B_{12} 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 three to four weeks (Young et al. 2004).
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 target moderate concentration ranges initially (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 an acute bipolar depression, monotherapy with a mood stabilizer is preferred. Lamotrigine, asenapine, and quetiapine 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 BD (see Table 13.1).
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 be continued for six to 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 (Young et al. 2004).

Table 13.1 Side effects of concern in late-life bipolar patients

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

13.4 Conclusions

Much is still unknown about late-life BD, especially late-onset BD (Charney et al. 2003). Generally speaking, late-life BD 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 may be related to the medical and neurological problems that can occur with aging or to an underlying progression of neurological illness associated with certain bipolar disorders early in life. The concept of "vascular mania" may be of both heuristic and treatment value in the future.

Treatment of late-life BD requires knowledge of "best treatment" practices and an understanding of the effect aging has on psychopharmacotherapy. Adequate clinical trials are not currently available to provide good evidence-based treatment recommendations for late-life BD, requiring extrapolation from trials in mixed-age populations and adaptation to the older patient.

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