CNS Neurosciences & Therapeutics

REVIEW

CNS Neuroscience & Therapeutics

Late-onset Bipolar Illness: The Geriatric Bipolar Type VI

Jean-Michel Azorin, Arthur Kaladjian, Marc Adida & Eric Fakra

Pôle Universitaire de Psychiatrie-Solaris, Hôpital Sainte-Marguerite, Cedex, France

Keywords
Alzheimer's disease; Bipolar disorders; Geriatrics; Neuropsychopharmacology.

Correspondence
Jean-Michel Azorin, Pôle Universitaire de Psychiatrie-Solaris, Hôpital Sainte-Marguerite, 13274 Marseille Cedex 9, France.
Tel.: +33 4 91 74 40 82;
Fax: + 33 4 91 74 55 78;
E-mail: jazorin@ap-hm.fr
Received 17 January 2011; revision 21 March 2011; accepted 6 April 2011

doi: 10.1111/j.1755-5949.2011.00255.x

SUMMARY

In parallel to considerable progress in understanding and treatment of bipolarity and despite growing interest in old age psychiatry, late-onset bipolar illness (LOBI) has remained relatively understudied so far, probably in reason of its complexity. To update available data, a systematic review was conducted, focusing on the main issues addressed in literature in regard to this topic. In addition to data on epidemiology, clinical features and treatment, five main issues could be identified: LOBI as secondary disorder, LOBI as expression of a lower vulnerability to the disease, LOBI as subform of pseudodementia, LOBI as risk factor for developing dementia, and LOBI as bipolar type VI (bipolarity in the context of dementia like processes). Levels of available evidence were found to vary according to the addressed issue. Although the concept of bipolar type VI could be criticized for subsuming under one single heading all the four other issues, this concept may be of pragmatic value in helping clinicians to orientate both diagnosis process and treatment decisions. Among others, the question as to whether some forms of bipolar type VI could constitute a special risk factor for developing dementia deserves further investigation. More studies are also needed to better disentangle the effects of age at onset from those of age itself.

Introduction

Elderly bipolar individuals are heterogeneous, at minimum representing two groups: (1) patients experiencing a late-life manic episode but whose bipolar illness began in young adult life and (2) patients without any manic episode prior to late life [1]. Within this latter group were ranged patients with no young adult history of mood disorder as well as those with an earlier onset mood disorder, but only with a history of major depression, never mania [1]. Growth in life expectancy in the general population yielded in the last decades is likely to have allowed the emergence of an increasing number of late-onset bipolar illness (LOBI) cases and therefore a renewed interest for this pathology [2].

Relevant articles were identified from a PubMed literature search (1970–2010) using the keywords "late-onset mania," "LOBI," "late-onset bipolar disorder," "geriatric mania," "geriatric bipolar illness," "geriatric bipolar disorder," "elderly bipolar illness," elderly bipolar disorder," and "bipolar type VI." We augmented the search by manually reviewing bibliographies from identified reports and recent reviews. Articles were selected for review if their content was instructive to the current topic. In addition to data on epidemiology, clinical features and treatment, five main issues were identified: LOBI as secondary disorder, LOBI as expression of lower vulnerability to the disease, LOBI as subform of pseudodementia, LOBI as risk factor for developing dementia, and LOBI as bipolar type VI.

This review is therefore organized around those issues, with a special focus on the relationship of LOBI with organic disorders and dementia, as heralded in the concept of "bipolar type VI" which may summarize the complexity of this relationship [3,4].

Epidemiology

Population-based surveys reveal a decrease in the prevalence of bipolar disorder with age, with rates from 1.4% in the young adult population to 0.1–0.5% among individuals 65 and older [5–9].

Available data indicate that an average annual rate of 8 elderly patients with mania are treated on inpatient psychogeriatric units [10,11].

In older adults bipolar depression may account for 8–10% of psychiatric admissions [12]. It is likely that persons age 60 years and older constitute about 25% of the population with bipolar disorder [13].

In parallel, the frequency of new-onset type I or type II bipolar disorder appears to decline with advanced age [12,14], with 6–8% of all new cases of bipolar disorder developing in persons age 60 years and older [13,15].

However, the first admission rates to psychiatric inpatients for bipolar disorder have shown an increase at the extremes of old age [16]. A Finnish study found that almost 20% of manic patients admitted were over the age of 60, with the highest incidence

occurring in the 50–59 age group for males and the 40–49 age group for females [17].

The mean age of a first mood episode among elderly bipolars may vary from less than 30 years up to 57 years, but for those studies that used a late-onset of 60 years or more, the mean age at onset of mood disorder ranged from 42 to 57 years whereas the mean age at onset of mania ranged from age 51 to 60 years [9].

Generally, about half of index elderly bipolar patients who have been hospitalized experience depression as their first mood disorder [10] whereas one-quarter experience a delay of at least 25 years between the first depressive episode and the onset of mania [10].

LOBI has been found to exhibit a lower association with family history, compared to early onset [18–22] and also seems to occur more frequently in women than in men [12,22].

Clinical Features

The presentation of LOBI appears to be roughly similar to that of early onset but with higher levels of premorbid psychosocial functioning [15] and classically less severe psychopathology [23].

Age carries a negative or low association with several factors of the Mania Rating Scale including the "activity-energy" score, sexual interest, religiosity, initiating, and creating plans [1].

Among patients suffering from late-onset bipolar II disorder, atypical features, including "mood reactivity", increased appetite or weight gain, hypersomnia, leaden paralysis, and/or a long-standing pattern of extreme sensitivity to perceived interpersonal rejection, are less common than among persons with earlier-onset forms of this condition [14].

The high risk of suicide in older people and in patients with bipolar disorder appears to be additive; however the highest risk for completed suicide occurs during the first 7–12 years postonset and in those under age 35 [24].

Older bipolar patients show a higher prevalence of mixed episodes [12,15]. Some studies found that subjects with a late disorder onset (>60 years) presented more affective episodes per year [2], corroborating the hypothesis put forward by a few authors that there is an increase of the frequency of the affective episodes in the elderly patients when compared to younger ones [25]. An association between increased age at onset and increased episode duration or chronicity was reported as well [1].

Many studies have shown cognitive impairment in older bipolar patients, which are similar to those evidenced in younger patients. Compared to age-matched controls, older patients had more extrapyramidal symptoms and worse performance in psychomotor speed, selective attention, verbal memory, verbal fluency, and executive functions, as well as poorer psychosocial functioning [26–30].

However, late-onset bipolar patients were reported to be more impaired in psychomotor performance and mental flexibility than the early onset patients in some studies [31].

Geriatric patients with bipolar disorder also have higher rates of comorbid alcohol use disorders, dysthymia, generalized anxiety disorder, and panic disorder than elderly patients without bipolar disorder, but these rates are lower than those seen in younger bipolar patients [32].

As regards medical comorbidities they are common in both geriatric and late-onset bipolar patients, with no difference in mortality rates between the two populations [1].

LOBI as "Secondary" Disorder

The concept of "secondary" mania was elaborated by Krauthammer and Klerman [33] to describe a subform of bipolar illness associated with a wide variety of organic factors, which could be responsible for the occurrence of the illness. These authors emphasized the relative lack of familial predisposition and prior psychiatric history in contrast to "primary bipolar disorders" which are associated with a stronger genetic predisposition and no obvious neuropathology.

Neurological illness (most frequently cerebrovascular disease) was found to be twice as frequent amongst late-onset bipolar patients then early onset ones [34].

The diagnosis of dementia has also been associated with increased risk of manic episodes at follow-up. It was found that older adults with dementia were 9.9 (95% CI = 4.2–23.2) times more likely to develop mania within 6 months of follow-up, and 21.1 (95% CI = 4.2–105.3) and 6.9 (95% CI = 4.6–10.5) times more likely than controls to receive the diagnosis of mania after 6–12 months and 12 or more months, respectively [35].

Brain injury, epilepsy, brain tumors, encephalitis, and various forms of cerebral infection were reported to be associated with LOBI as well. The same holds true for several medical conditions and medications [36].

In parallel is a robust neurological literature, which describes under the term of "disinhibition syndrome" a similar condition [37]. The neurological literature shows a consistent finding of a predominance of right hemisphere lesions in association with desinhibition syndromes as well as secondary mania [38]. Lesions impacting the connections of the orbito-frontal circuit seem to be more particularly concerned [39].

Neuroimaging research studies found that brain lesions more frequently associated with LOBI were subcortical hyperintensities, decreased cerebral blood flow, and silent cerebral infarcts [40].

Interestingly, it was reported that patients with poststroke mania had right cortical lesions only, whereas patients who had experienced both mania and depression had lesions limited to the subcortical areas of the right cerebral hemisphere [41].

LOBI as Expression of a Lower Genetic Vulnerability to the Disease

Several authors [3,36,40] argued that LOBI is not the direct consequence of organic processes but the expression of an attenuated vulnerability to bipolar disorder, triggered by heterogeneous factors. While genetic factors tend to be less prominent in late-onset disorders these elderly bipolar patients have a 50% prevalence of mood disorder in first-degree relatives [10]. Moreover, if the "organic hypothesis" of LOBI was true, one would expect to see an increase in the number of older adults with bipolar illness with increasing age, as the frequency of neurodegenerative conditions, cerebrovascular disease, cancer, and use of medications rises sharply for people in their 70s and 80s [36]. An evaluation

of age at onset for the entire population of bipolar patients in contact with the Western Australian health services between 1980 and 1998 found no evidence for a bimodal distribution of the age at onset of illness in this population; furthermore the frequency of patients who received the diagnosis of organic mental disorder during the study period was very low, arguing against the fact that many of the patients might have been correctly diagnosed as suffering from an organic mental disorder rather than bipolar illness [36].

As patients with a late disorder onset were found to be more frequently females [12,22], it has been suggested that in this population bipolarity could be triggered by antidepressants [2], as females are seeking medical help more readily and earlier than males, and also have more depressive episodes [42].

Bipolarity may also have been revealed by psychophysiological changes associated with ageing, such as reduction of total sleep time which produces a robust deregulation of the hypophysis–adrenal axis causing an elevation of the cortisol levels as well as dopamine metabolism [43]. White matter hyperintensities have been associated with both ageing [44] and risk for bipolar disorder [45], so that the latter may also have been revealed in some vulnerable elderly patients. Of course, organic disorders could also trigger this vulnerability.

According to some authors [10] it might be necessary that lesions associated with ageing occur in the right location in the brain to contribute to LOBI, so that only a combination of complex predisposition interacting with precipitating factors and brain localization may give rise to the expression of the latter.

LOBI as Subform of Pseudodementia

The concept of pseudodementia refers to a clinical picture that may evoke dementia but is usually reversible and provoked by psychiatric disorders [46]. Although depression was found to be the main etiology, some cases were still attributed to conversive reactions [46]. However, case studies reported that mixed stated accounted more frequently for such picture than classic major depression, including melancholia [47]. Recently, bipolar-type pseudodementia was opposed to depression-type, as more likely to mimic or caricature dementia pictures [4].

In bipolar-type pseudodementia, the clinical picture may be close to that of mixed or agitated depression [48]. Patients present with cognitive, behavioral, and mood symptoms; they display dysphoria, lack of retardation, forgetfullness, vivacious facial expression, dramatic description of suffering, spells of weeping, talkativeness, psychic agitation, emotional liability, high levels of anxiety and impulsive suicidal attempts [48]. The partner reports continuous complaining, occasional overt expression of irritability and sexual hyperactivity. If they are somehow stimulated, these patients show motor agitation and exaggerated expressive movements. Because of this mode of reacting and the intense expression of their suffering, these patients may be misdiagnosed as histrionic personality disorders. The term "pseudohysterical behavior" has been sometimes used to characterize such excessive reactions and extravagant attitudes patients may develop in response to requests from their close [47]. Another characteristic of this picture is a special form of anxiety, which appears to be related to excitation or arousal. Patients feel anxious because, due to their inner agitation, they may be unable to think, concentrate or do anything. Racing thoughts are likely to have the same annihilating effect, probably because they are conveyed by this abnormal energy [48].

These patients are usually refractory to antidepressant treatments which most of the time contribute to aggravate the clinical picture by increasing inner tension. Similarly, they show nonreponse to acetylcholinesterase inhibitors or worsening of agitation after memantine exposure [4].

However, when they are treated as depressive mixed states, they display improvement of mood, behavior but also cognition [4].

It is therefore important for clinicians to be able to recognize these pictures in order to avoid using antidepressants and select the best appropriate treatment.

Finally, it is worth mentioning that, albeit rare, chronic mania which onsets, in most cases, in late life, may yield a dementia-like clinical picture. People with chronic mania were found to be deprived of social support and less amenable to medical care, which may contribute to their overall deteriorative course [49].

LOBI as Risk Factor for Dementia

A few studies have suggested that bipolar disorder could be a risk factor for developing dementia. Kessing and Andersen conducted a case register study including all hospital admission with primary affective disorder in Denmark during 1970–1999 [50]; the effect of the number of prior episodes leading to admission on the rate of readmission with a diagnosis of dementia following the first discharge after 1985 was estimated. A total of 18,726 patients with depressive disorder and 4,248 patients with bipolar disorder were included. The study showed that the rate of dementia tended to increase 13% with every episode leading to admission for patients with depressive disorder and 6% with every episode leading to admission for patients with bipolar disorder when adjusted for differences in age and sex.

Nunes et al. [51] compared the prevalence of Alzheimer's disease between 66 elderly euthymic patients with bipolar disorder who were on chronic lithium therapy and 48 similar patients without recent lithium therapy. The prevalence of dementia in the whole sample was 19% versus 7% in an age comparable population. Alzheimer's disease was diagnosed in 3 patients (5%) on lithium and in 16 patients (33%) who were not on lithium.

Moreover in some case series, a specific profile was suggested for dementia following bipolar disorder in elderly patients [52].

In general, the risk for developing dementia is much less documented for bipolar illness than it is for depressive disorder [53,54]. Even in the latter case the issue remains controversial as to whether the risk is associated with the number of previous episodes or a particular cognitive decline related to late-onset illness [53,54]. This is all the more true for bipolar disorder. Similarly if this risk does exist, there is still debate about the type of dementia, which may be more particularly concerned. Vascular dementia and Alzheimer disease are likely to be involved in regard depressive disorder [53,54].

Many hypotheses have been raised on a pathopsysiological level to account for such a risk [50,53,54].

LOBI as "Bipolar Type VI"

It has been recently proposed to include LOBI into the bipolar spectrum under the "bipolar type VI" category [3,4].

The spectrum concept is based on the idea of a natural continuum from transient to persistent hypomanic and manic manifestations of varied length, frequency, and severity, with a probable lack of clear delineation among all the subtypes [54]. This concept is supported by the close relatedness of clinical manifestations within the spectrum, data from family history, response to treatment, and psychosocial consequences of the disorders [55]. A model to depict this spectrum has been proposed by Akiskal [56] that differentiates type I (mania and depression), type II (cyclothymia and hypomania), type III (depression plus drug-induced hypomania), type IV (late-onset depression superimposed on hyperthymic temperament), type V (recurrent unipolar mixed states), and finally type VI (mixed-labile-agitated episodes in the setting of dementia).

Actually, cases subsumed under the heading of "bipolar type VI" could represent the various forms of LOBI reviewed previously, including secondary disorders, bipolar liability revealed by dementing process, bipolar pseudodementia as well as predictors of true dementia [3,4], even though the first of these hypotheses does not seem to fit the opinion of those who were at the origin of the concept.

Regardless, creating a new category at the intersection of bipolarity and dementia may account for several commonalities in pathophysiological processes of both disorders, which have been recently described in literature [3,4].

Those include clinical presentation, temperament characteristics, neuroanatomical alterations, neurobiological as well as neuroendocrine processes, and genetic factors [3]. Response to treatment may also be involved [3].

Bipolar type VI constitutes therefore a further step in the evolving bipolar spectrum with late-life dementia like onset. Bipolar disorder and dementia have been so far considered as distinct clinical entities. That may hold true for some but not all of the cases.

Actually, for most of them, the similarities in several features between soft bipolar and dementia suggest an overlooked continuum between these disorders [3].

Treatment Issues

These is a limited evidence base for treatment of bipolar disorder in the elderly and a need for more controlled studies before definitive treatment strategies can be enumerated [57–59]. However, by extrapolating from nonelderly populations and also reviewing available evidence most treatment options are applicable.

In treating elderly bipolar patients, one has to keep in mind that pharmacokinetic and pharmacodynamic changes that occur with ageing, associated with frequent concomitant medical illnesses and their treatments, are likely to increase the risk of adverse events and drug interactions [40].

The management of LOBI must begin with a thorough medical assessment in search for neurological and/or medical conditions that may be associated with bipolar symptoms [40]. If most guidelines for younger patients make no recommendation for neuroimaging, in contrast, neuroimaging may be essential for late-onset bipolars [40].

Current data suggest that anticonvulsants such as valproate and lamotrigine may be of benefit and better tolerated as mood stabilizers than lithium, which may require lower target serum levels, on the order of 0.4–0. 7 mEq/L [40,57].

Valproate and atypical antipsychotics could therefore be first-line drugs for mania; carbamazepine causes more drug interactions [57]. The use of typical antipsychotics is problematic in the elderly due to the risk of cardiovascular problems and movement disorders [60]. An increased incidence of mortality has been reported in patients with dementia-related psychosis treated with atypical antipsychotics [61]. However, preliminary reports suggest a role for the use of atypical in older adults with bipolar disorder although potential benefit must be balanced against the potential risks of treatment [60]. If monotherapy fails, the addition of an atypical, an anticonvulsant or lithium may be useful [57]. In the treatment of bipolar depression, monotherapy with a mood stabilizer is reasonable, especially lamotrigine, but also the combination of olanzapine and fluoxetine as well as quetiapine [58,59]. These drugs may also be useful in combination. In bipolar patients the administration of antidepressants involves the risk of conversion to mania. The latter are therefore recommended to be used in combination with mood stabilizers or antipsychotics, in order to prevent the risk of switching. SSRIs and bupropion seem to be better tolerated in this regard [58,59].

For maintenance therapy, a pragmatic option could be to maintain those drugs, which demonstrated efficacy in the management of acute episodes [58,59].

ECT may be useful in patients who are refractory to drug treatment and in those who need rapid resolution of symptoms [57]. Psychotherapy has much to offer in enhancing treatment adherence, addressing relapse risks, and helping patients and close cope with the implication of a chronic mental disease [58,59].

On the long run the preventive efficacy of drugs like lithium toward the risk of dementia deserves further investigation [51].

In the context of bipolar type VI disorder, it is worth mentioning that the appropriate treatment of bipolar symptoms can contribute to improve mood, behavior, and cognition in both bipolar-type pseudomentia and dementia with secondary mood instability. However, if drugs targeting dementia may also be useful in the latter, they have no action on the former or could even aggravate the clinical picture [4].

Actually, there is some debate about the usefulness of drugs like valproate for the treatment of behavioral and psychological symptoms of dementia. Despite contradictory findings, current literature suggests that valproate could be useful for both bipolar and dementia symptoms [62]. However, the onset of drowsiness may be an obstacle to its prescription. The gradual uptitration by 125–250 mg/day to a maximum dose of between 500 mg and 1,000 mg/day is likely to improve tolerability [62].

Conclusion

LOBI remains a complex and relatively understudied disorder. For several of the issues reviewed in this article, the effect of age

at onset may be difficult to disentangle from that of age itself. Recall bias in elderly patients may be partly responsible for this [63]; studies which addressed the distinction between patients with a late-life manic episode but a history of earlier mood disorder and patients without a prior history of mood disorder are rare, and thus far did not yield very meaningful results [1,63]. LOBI appears less frequently than previously believed the direct physiologic consequence of a general medical condition despite high rates of organic comorbidity. It is nevertheless of paramount importance to look for such comorbidity in clinical practice.

However, even in cases of organic comorbidity in which organic disorders and particularly dementia are in the foreground, bipolarity has to be documented as it may orientate therapeutic decisions. This could be achieved by looking for the existence of premorbid bipolar temperament, the notion of previous behavior with negative psychosocial consequences and the presence of a family history of affective disorders [62]. The diagnosis of bipolarity may be easier when late-onset mania has been preceded by depressive episodes.

It is also important to keep in mind that contrary to a generally received opinion, LOBI can give rise to pseudodemential pictures, more often than unipolar depression.

Even if the concept of "bipolar-type VI" may be theoretically criticized for lumping together in one category heterogeneous entities, it has the advantage, for practitioners, to keep open and draw attention to all the issues raised by late-onset bipolarity.

Further research could contribute to better differentiate subtypes of bipolar-type VI from late-life manias with earlier disease onset, and specify the risk profiles for developing dementia. The question is, given the urgent needs to treat these patients, how feasible it is to do these studies prospectively.

Authors Contributions

Jean-Michel Azorin contributed to data collection and writing of the report.
Arthur Kaladjian, Eric Fakra, and Marc Adida contributed to data collection.
All authors reviewed the manuscript critically and approved the version that has been submitted.

Conflict of Interest

Jean-Michel Azorin has received research support and has acted as a consultant and/or served on a speaker's bureau for, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck and Sanofi-Aventis.
Arthur Kaladjian has received grant/research support from Lilly and Sanofi-Aventis.
Eric Fakra has received great/research support from Lilly.
Marc Adida has received great/research support from Lilly and Servier.

References

1. Young RC. Bipolar disorder in the elderly. *Psychiatry Clin N Am* 1997;**20**:121–136.
2. Zung S, Cordeiro Q, Lafer B, et al. Bipolar disorder in the elderly: clinical and socio-demographic characteristics. *Scientia Medica* 2009;**19**:162–169.
3. Akiskal HS, Pinto O, Lara DR. Bipolarity in the setting of dementia bipolar type VI? Medscape Family Medecine/Primary Care. Available at: http://www.medscape.com/viewarticle/495795 [Accessed July 2010].
4. Ng B, Camacho A, Lara DR, et al. A case series on the hypothesized connection between dementia and bipolar spectrum disorders: Bipolar type VI? *J Affect Disord* 2008;**107**:307–315.
5. Weissman M, Leaf P, Tischer G, et al. Affective disorders in five United States communities. *Psychol Med* 1988;**18**:141–153.
6. Hirschfeld R, Calabrese J, Weissman M, et al. Screening for bipolar disorder in community. *J Clin Psychiatry* 2003;**64**:53–59.
7. Unutzer J, Simon G, Pabiniak C, et al. The treated prevalence of bipolar disorder in a large staff-model HMO. *Psychiatry Serv* 1998;**49**:1072–1078.
8. Klap R, Unroe KT, Unutzer J. Caring for mental illness in the United States: A focus on older adults. *Am J Geriatr Psychiatry* 2003;**11**:517–524.
9. Chen ST, Altshuler LL, Spar JE. Bipolar disorder in late life: A review. *J Geriatr Psychiatry Neurol* 1998;**11**:29–35.
10. Shulman KI, Thomen M, Satlin A, et al. Mania compared with unipolar depression in old age. *Am J Psychiatry* 1992;**149**:341–345.
11. Yassa R, Nair V, Nastase C, et al. Prevalence of bipolar disorder in a psychogeratric population. *J Affect Disord* 1988;**14**:197–201.
12. Depp C, Jest D. Bipolar disorder in older adults: A critical review. *Bipolar Disord* 2004;**6**:343–367.
13. Sajatovic M, Blow FC, Ignacio RV, Kaless HC. New-onset bipolar disorder in later life. *Am J Geriatr Psychiatry* 2005;**13**:282–389.
14. Benazzi F. Bipolar II depression in late life: Prevalence and clinical features in 525 depressed outpatients. *J Affect Disord* 2001;**66**:13–18.
15. Almeida OP, Fenner S. Bipolar disorder: Similarities and differences between patients with illness onset before and after 65 years of age. *Int Psychogeriatr* 2002;**14**:311–321.
16. Eagles JM, Whalley LJ. Ageing and affective disorders: The age at first onset of affective disorders in Scotland, 1966–1978. *Br J Psychiatry* 1985;**147**:180–187.
17. Rasanen P, Tiihonen J, Hakko H. The incidence and onset-age of hospitalized bipolar affective disorder in Finland. *J Affect Disord* 1998;**48**:63–68.
18. Schurhoff F, Bellivier F, Jouvent R, et al. Early and late onset bipolar disorders: Two different forms of manic-depressive illness? *J Affect Disord* 2000;**58**:215–221.
19. Taylor M, Abrams R. Manic States. A genetic studies of early and late onset affective disorders. *Arch Gen Psychiatry* 1973;**28**:656–658.
20. James NM. Early-and late-onset bipolar affective disorder. A genetic study. *Arch Gen Psychiatry* 1977;**34**:715–717.
21. Baron M, Mendlewicz J, Klotz J. Age-of-onset and genetic transmission in affective disorders. *Acta Psychiatr Scand* 1981;**64**:373–380.
22. Moorhead SRJ, Young AH. Evidence for a late onset bipolar-I disorder sub-group after 50 years. *J Affect Disord* 2003;**79**:271–277.
23. Depp CA, Jin H, Mohamed S, et al. Bipolar disorder in middle-aged and elderly adults: Is age of onset important? *J Nerv Ment Dis* 2004;**192**:796–799.
24. Tsai SY, Kuo CJ, Chen CC, Lee HC. Risk factors for completed suicide in bipolar disorder. *J Clin Psychiatry* 2002;**63**:469–476.
25. Suppes T, Leverich GS, Keck PE, Jr., et al. The Stanley Foundation bipolar treatment outcome network II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord* 2001;**67**:45–59.
26. Martino DJ, Igoa A, Marengo E, et al. Cognitive and motor features in elderly people with bipolar disorder. *J Affect Disord* 2008;**105**:291–295.
27. Tsai SY, Lee HC, Chen CC, Huang YL. Cognitive impairment in later life inpatients with early-onset bipolar disorder. *Bipolar Disord* 2007;**9**:868–875.
28. Gildengers AG, Butters MA, Chisholus D, et al. Cognitive functioning and instrumental activities of daily living in late-life bipolar disorder. *Am J Geriatr Psychiatry* 2007;**22**:856–861.
29. Shouws SN, Zoetman JB, Comijs HC, et al. Cognitive functioning in elderly patients with early onset bipolar disorder. *Int J Geriatr Psychatry* 2007;**22**:856–861.
30. Radonovic M, Nunes PV, Gattaz WF, Forlenza OV. Language impairment in euthymic, elderly patients with bipolar disorder but no dementia. *Int Psychogeriatr* 2008;**20**:687–696.
31. Shouws SN, Comijs HC, Stek M., et al. Cognitive impairment in early and late bipolar disorder. *Am J Geriatr Psychiatry* 2009;**17**:508–515.
32. Goldstein BI, Hermann N, Shulman KI. Comorbidity in bipolar disorder among the elderly: Results from an epidemiological community sample. *Am J Psychiatry* 2006;**163**:319–321.
33. Krauthammer C, Klerman GL. Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. *Arch Gen Psychiatry* 1978;**35**:1333–1339.
34. Tohen M, Shulman KI, Satlin A. First-episode mania in late-life. *Am J Psychiatry* 1994;**151**:130–132.
35. Nilsson FM, Kessing LV, Sorensen TM, et al. Enduring increased risk of developing depression and mania with dementia. *J Neurol Neurosurg Psychiatry* 2002;**73**:40–44.

36. Almeida OP. Bipolar disorder with late-onset: An organic variety of mood disorder. *Rev Bras Psiquiatr* 2004;**26**:27–30.
37. Starkstein SE, Robinson RG. Mechanism of desinhibition after brain lesions. *J Nerv Ment Dis* 1997;**185**:108–114.
38. Starkstein SE, Mayberg HS, Berthier ML, et al. Mania after brain injury: Neuroradiological and metabolic findings. *Ann Neurol* 1990;**27**:652–659.
39. Starkstein SE, Migliorelli R, Teson A, et al. The specificity of cerebral blood flow changes in patients with frontal like dementia. *J Neurol Neurosurg Psychiatry* 1994;**57**:790–796.
40. Schulman KI, Herrmann N. Bipolar disorder in old age. In: Marneros A, Angst J, editors. *Bipolar Disorders: 100 years after Manic-depressive Insanity*. Dordrecht: Kluwer Academic Publishers, 2000;153–174.
41. Starkstein SE, Fedoroff JP, Berthier MD, Robinson RG. Manic depressive and pure manic states after brain lesions. *Biol Psychiatry* 1991;**29**:149–158.
42. Perugi G, Micheli C, Akiskal HS, et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: A systematic retrospective investigation of 320 bipolar patients. *Compr Psychiatry* 2000;**41**:13–18.
43. Spiegel K, Lepoult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;**354**:1435–1439.
44. Guttmann CR, Jolesz FA, Kikinis R, et al. White matter changes with normal aging. *Neurology* 1998;**50**:972–978.
45. McDonald C, Bullmore ET, Sham PC, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry* 2004;**61**:974–984.
46. Wells CE. Pseudodementia. *Am J Psychiatry* 1979;**136**:895–900.
47. Garcia C, Sander HJ. Pseudohysterical behavior patterns in endogenous depressions (Pseudohysterische Verhaltensweisen bei endogenen Depressionen). *Nervenarzt* 1983;**54**:354–362.
48. Koukopoulos A, Koulopoulos A. Agitated depression as a mixed state and the problem of melancholia. *Psychiatric Clin North America* 1999;**22**:547–564.
49. Perugi G, Akiskal HS, Rossi L, et al. Chronic mania. Family history, prior course, clinical picture and social consequences. *Br J Psychiatry* 1998;**173**:514–518.
50. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and inpatients with bipolar disorder? *J Neurol Neurosurg* 2004;**75**:1662–1666.
51. Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorders. *Br J Psychiatry* 2007;**190**:359–360.
52. Lebert F, Lys H, Haëm E, Pasquier F. Dementia following bipolar disorder. *Encephale* 2008;**34**:606–610.
53. Chen P, Ganguli M, Mulsant B, Dekosky ST. The temporal relationship between depressive symptoms and dementia. *Arch Gen Psychiatry* 1999;**56**:261–266.
54. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk of Alzheimer disease. *Arch Gen Psychiatry* 2006;**63**:530–538.
55. Marneros A, Angst J. Bipolar disorders: roots and evolution. In: Marneros A., Angst J, editors. *Bipolar Disorders: 100 years after Manic-depressive Insanity*. Dordrecht: Kluwer Academic Publishers, 2000;1–35.
56. Akiskal HS. The interface of affective and schizoprhenic disorders: a cross between two spectra? In: Marneros A, Akiskal HS, editors. *The Overlap of Affective and Schizophrenia Spectra*. Cambridge: Cambridge University Press, 2007;277–291.
57. Aziz R, Lorberg B, Tampi RR. Treatments for late-life bipolar disorder. *Am J Geriatr Psychiatry* 2006;**4**:347–364.
58. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patient with bipolar disorder: Consensus and controversies. *Bipolar Disord* 2005;**7**(suppl 3):5–69.
59. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 2009;**11**:225–255.
60. Sajatovic M, Madhusoodanan S, Coconcea N. Managing bipolar disorder in the elderly: Defining the role of the newer agents. *Drugs Aging* 2005;**22**:39–54.
61. FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances, 2006. Avalaible at: http://www.fda.gov/cder/drug/advisory/antipsychotics.htm [Accessed March 2011].
62. Dorey JM, Beauchet O, Thomas Anterion C, et al. Behavioral and psychological symptoms of dementia and bipolar spectrum disorders: review of the evidence of a relationship and treatment implications. *CNS Spectr* 2008;**13**:796–803.
63. Oostervink F, Boomsma MM, Nolen WA; EMBLEM Advisory Board. Bipolar disorder in the elderly; different effects of age and of age of onset. *J Affect Disord* 2009;**116**:176–183.