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Date deposited: 25th October 2010

Version of file: Author final

Peer Review Status: Peer-reviewed

Citation for published item:

Vasudev A, Thomas A. ['Bipolar disorder' in the elderly: What's in a name?](#). *Maturitas*, 2010, **66** 3 231-235.

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<http://dx.doi.org/10.1016/j.maturitas.2010.02.013>

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'Bipolar disorder' in the elderly: what's in a name?

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KEYWORDS

Late life bipolar disorder; Late onset bipolar; Early onset bipolar; Vascular mania; White matter hyperintensities

ABSTRACT

Bipolar disorder is a chronic disorder of mood which leads to episodes of either elevated mood or depression in a sizable number of adults in the community (1%). Though the prevalence rates in the elderly are lower in the community (up to 0.1%), there is significantly higher morbidity in protected environments like care homes and hospital settings where prevalence rates may be as high as 10%. Bipolar disorder in the elderly is probably heterogenous and its etiopathogenesis is complex. Bipolar disorder may be divided into two distinct subtypes, the late onset bipolar (LOB) and the early onset bipolar (EOB) groups. LOB patients tend to have a milder illness in terms of manic severity but they have higher medical and neurological burden. They also have lower familial burden of bipolar illness as compared to EOB patients. There is an increased risk of dementia and stroke in patients with late life bipolar disorder (and there may be a protective effect of lithium in preventing dementia). White matter changes, as seen by increased white matter hyperintensities on neuroimaging, are also increased, providing further evidence of cerebrovascular disease. Treatment of late life bipolar is currently based on guidelines drawn up for younger bipolar disorder patients. Good quality intervention studies are needed to estimate the possible protective effect of cognitive enhancers and/or vascular prevention strategies. This review suggests that late life bipolar disorder, particularly late-onset bipolar disorder, is probably a distinct diagnostic entity compared to the younger bipolar patients as it has a different presentation, etiology and hence perhaps needs different treatment strategies.

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1. Bipolar disorder is a chronic disease of abnormal mood and is characterized by episodes of either elevated mood or depression, or, less frequently a mixed affective presentation of both elevated mood and depression. To satisfy a clinical diagnosis of bipolar disorder the abnormal mood episodes should have a detrimental effect on the social and occupational functioning of the individual. Though the diagnostic criteria of this disorder (1, 2) are well demarcated in the younger adult population, the same cannot be said for bipolar disorder in the elderly. Research evidence suggests that the disorder in the elderly is different in terms of its presentation, epidemiology, and etiopathology.

In 'Romeo and Juliet' Shakespeare has Juliet say "What's in a name? that which we call a rose by any other name would smell as sweet". Whilst it is true that the reality matters, not the name used to denote it, the opposite is clearly not the case and using the same name for different things does matter. Since older people with late-onset 'bipolar disorder' seem to have a different symptom profile, a different epidemiology and different aetiologies compared with younger people, we question whether 'bipolar disorder' is really the right name for this group at all.

2. Epidemiology and clinical presentation

- a. Age: Data from epidemiological studies suggest that bipolar disorder in the adult population has a prevalence rate of around 1% in the community(3). This prevalence rate may though be higher if current thinking of psychiatric diagnosis is accounted; evidence is accumulating that bipolar disorder and schizophrenia illnesses are two ends of a spectrum and often there is an overlap of symptoms and progress(4). Indeed, if screening tools like the Mood Disorder Questionnaire (MDQ) are used for estimation of prevalence, 4% of the population might be considered to have had a lifetime episode of hypomanic or manic symptoms(5).

Bipolar illness usually affects people by the age of 30, it has been estimated that 90% are aged less than 50 when they have their first episode (5). This indicates that 10% of bipolar patients will develop their illness after the age of 50. A study found that 9% of bipolar patients were over the age of 60 (6). Epidemiological studies conducted in the elderly in the community using strict diagnostic criteria have indeed found prevalence rates to be varying from 0.08% to 0.25%, which is close to the figure of lifetime prevalence of around 0.1% in the elderly that we would expect (5, 7, 8). However, in selected populations i.e. in nursing homes (9.7%, (9)) and inpatients (varying from 8 to 10%,(10)) there are significantly higher prevalence rates and this is likely to relate

in part to the association of late-onset bipolar with physical illness, especially dementia and cerebrovascular disease.

Also, until recently, it was believed the bipolar disorder had a bimodal frequency distribution with a peak of episodes in early adulthood and another peak in late life(11). However, this view has been challenged as data also suggests a unimodal frequency distribution with no such peak later in life(12).

- b. Age at onset: The older person with bipolar disorder may be considered to be of two types. Late Onset Bipolars, (LOB) who have the first episode of the affective disorder for the first time late in their life; most studies consider this to be greater than 50 years of age. Another category is the Early Onset Bipolar (EOB), who when older are 'graduates' of the disorder having had the onset of the illness at a younger age (<50 years of age). The demarcation is useful as clinically these two groups seem different.

Unlike EOB which has a high familial rate, LOB has consistently been shown to be without this strong influence (10). Previous reviews have also shown that LOB seems to have higher medical and neurological co-morbidity(10). Some of these include dementias(13), neurological conditions (14)and cerebrovascular conditions(15). LOB patients have also been shown to have fewer and milder manic symptoms compared to the EOB or the young manic patient and a tendency to have irritable mood rather than elated mood(16). In a recent longitudinal study comparing the outcome of LOB and EOB patients followed up after a manic or a mixed affective relapse it was reported that LOB patients had a remission of their illness quicker and a greater proportion were discharged from an inpatient facility(17).

The elder bipolar patients (EOB and LOB considered together) seem to have a larger time gap between a depressive episode and a manic one. In a prospective study (18) the mean time between the first episode of depression and the onset of mania was 17 years in the elderly group versus 3 years in the younger group. This study also found that more elderly than younger manic patients had suffered three or more depressive episodes before their first manic episode. An interesting finding was that the elderly manic patient was more likely to relapse into depression after mania.

These findings indicate that older people with bipolar disorder have a different clinical pattern, involving more depression and possibly milder manic symptomatology especially in the LOB group. This could be a reflection of differences in co-morbidity as discussed below.

c. Co-morbidities

- i. Psychiatric: Bipolar disorder is often co-morbid with various axis I conditions (that is other psychiatric illnesses) including lifetime and current substance use, anxiety, and eating disorders in adult outpatients with bipolar disorders(19). However, most studies have tended to include adult as well as the elderly in the same group; in only some studies has subgroup analysis been attempted. Cassidy et al, (20) found a lifetime substance abuse rate of around 29% in a subgroup of elder bipolar, these patients tended to have more hospital admissions compared to the younger bipolar. In a more recent study, (21) the one year prevalence rate in late life bipolar was found to be highest for alcohol abuse (38.1%), followed by panic attack (11.9%), generalised anxiety disorder (9.5%) and dysthymia (7.1%). There is some data on the prevalence of axis II conditions in late life bipolar. In a study on outpatients as well as inpatient population of late life affective disorders, 63% had a personality disorder based on their responses to a structured interview for personality. There was no difference in the prevalence rate between the depressed and the bipolar group(22).
- ii. Physical illnesses: A number of studies have shown increased prevalence of neurological illnesses, defined variously by different authors, but including dementia and cerebrovascular disease in patients with LOB (10). A large longitudinal study confirmed that the elderly bipolar have double the odds of developing stroke compared to age matched controls over a period of six years(23). These findings appear similar to those in unipolar disorder(24).

A recent study has also attempted to estimate other medical illness burden in patients with late life bipolar disorder (25). Gildengers et al, found that patients with late life bipolar greater than 60 years of age had similar total medical morbidity as measured by the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) compared to age matched depressed patients but had a higher BMI; however, there was increased burden of endocrine/metabolic and respiratory disease as measured by the CIRS-G subscores. However, because CIRS-G scores in late-life depression are increased compared with non-psychiatric controls, then this study suggests the same is true for late-life bipolar disorder, although direct comparisons are needed (26).

Another interesting finding is the link of affective disorders and dementia. Though the risk of developing dementia, particularly Alzheimer's increases with age, this risk appears to increase even

more in patients with affective disorders. The link between unipolar depression and dementia is now relatively well established; conservative estimates have shown an increased odds ratio of 2 times of developing a dementia syndrome in patients with late life depression(27-29). Though studies in patients with late life bipolar are fewer, there is emerging evidence that patients with EOB do present with cognitive impairment later in life(30). In this study a multiple regression model was used for prediction of cognitive impairment: years of education and the age at the last manic/hypomanic were the most important variables which accounted for the greatest variance. Other important predictors were age at the first depressive episode and the first manic episode before the age of 40 years. In another study (31) of 33 late life bipolar patients followed up longitudinally over a period of three years they developed more cognitive dysfunction and more rapid cognitive decline than expected for their age and education. Consequently, it has been hypothesised that better control of bipolar disorder might reduce or delay dementia. One study has reported the use of mood stabilisers in preserving cognitive function. Rybakowski et al (32) found a beneficial effect of lithium prophylaxis on executive cognitive function. There have also been interesting results from a large longitudinal cohort follow up analysis over 10 years (1995 to 2005) conducted in Denmark(33). Two groups were compared: 16,238 persons who had purchased lithium at least once in the community (implying a possible diagnosis of bipolar disorder) and 1,487,177 persons from the general population who had not purchased lithium. Patients who purchased lithium at least once had an increased rate of dementia compared with persons not exposed to lithium (relative risk, 1.47; 95% confidence interval, 1.22-1.76), providing further evidence that bipolar disorder increases the risk of dementia, but for persons who continued to take lithium, the rate of dementia decreased to the same level as the rate for the general population suggesting a protective effect of lithium. More disappointing are findings from another small population study(34). 12 older adults with bipolar disorder were prescribed Donepezil for 12 weeks. There was no improvement in either ADL score or cognitive test scores at the time of completion of the study.

The above findings suggest that late life bipolar disorder patients are at increased risk of stroke, cognitive impairment and dementia. There is some data on a possible protective effect of lithium for preventing dementia but good quality intervention studies are needed to investigate this and to determine if better control of vascular risk factors improves outcome.

- d. Prognosis: Suicide has been consistently shown to be one of the leading causes of mortality in patients with affective disorders. In a large longitudinal follow up study of patients suffering from affective disorder admitted to an inpatient unit who were followed up for more than 34 years it was observed that those patients who were on psychotropics (including antidepressants, neuroleptics and lithium) had significantly reduced completed suicide rates versus those not treated(35). Indeed, in a retrospective analysis of cases of elderly bipolar patients who had a suicide attempt, usage of antidepressants and mood stabilisers was noticed to have reduced suicide attempt rates compared to age and sex matched controls(36).

3. Etiopathology

- a. Vascular mania hypothesis: Similar to the vascular depression hypothesis in late life, the vascular mania hypothesis is getting increasing attention (37). In a sample of elderly bipolar patients (n= 119), more vascular risk factors predicted poorer cognitive performance(38). Also, in a study of patients with late life bipolar disorder higher Framingham Stroke Risk Score was found in LOB versus EOB (15). A key endpoint for cerebrovascular disease is the extent of brain White Matter Hyperintensities (WMH) on neuroimaging. There are an increased number of WMH consistently associated in patients with bipolar disorder(39) and more strongly so in LOB (40). Tamashiro et al (40) found that there was more WMH in deep frontal, parietal and putamen in LOB patients compared to age matched elderly and EOB. In unipolar disorder in older people WMH are due to hypoxia-ischaemia (41)but there have been no studies in bipolar disorder. The etiology of WMH may be thus conceptualised as a result of deficits in vascular perfusion(41). However, what is not known is the progress of WMH over a period of time in patients with late life bipolar disorder, indicating causality rather than association; there are currently no published longitudinal studies exploring this.
- b. Brain injury: Though it is relatively well established that traumatic brain injury in the adult population can cause secondary mania as a neuropsychiatric sequelae, the evidence for this association in the elderly is much weaker. There are only a few case reports of secondary mania in this population caused by either anoxic encephalopathy(42) or thalamic damage(43) and although it seems reasonable that brain injury would have similar or worse effects in older people good quality larger sample studies are needed to demonstrate this.
- c. Brain volume changes: Structural Magnetic Resonance Imaging (MRI) can be a useful tool for estimating brain volume. The temporal lobe is perhaps the most significant part of the brain involved in the etiopathogenesis of affective disorder. This is perhaps because of important brain structures within the temporal lobe responsible

for memory as well as mood. Increased temporal lobe volume has been found in some structural MRI studies in patients with adult bipolar disorder (44). However there are contradictory reports of the extent of brain volume changes in late life bipolar disorder. In a recent study (45), comparing grey matter volume, white matter volume and total brain volume in 71 elderly bipolar patients compared with 82 age matched controls there was no evidence of greater volume changes in the bipolar group.

The above findings show our knowledge of the etiopathology of late life bipolar disorder is limited and the best evidence supports a role of cerebrovascular disease.

4. Management

- a. Non pharmacological: The evidence base for psychotherapeutic treatments in the younger bipolar patient group is relatively strong and different approaches have been found to be effective in different phases of the illness. Family therapy, interpersonal therapy, and systematic care appear to be effective in preventing recurrences when initiated after an acute episode, whereas cognitive-behavioural therapy and group psycho-education appear to be most effective when initiated during a period of recovery(46). However, the evidence base for treatment of late life bipolar disorder with non-pharmacological approaches is weaker; although there are some encouraging results emerging from psychosocial interventions trials(47), there are no randomised trials reported.
- b. Pharmacological: Treatment of any disorder in the elderly is difficult as there are pharmacokinetic and pharmacodynamic changes as well as an increased risk of drug interactions. In a ward based study of the elderly psychiatry patients, it was found that 96% of prescriptions had a potential for drug-drug interactions, with an average of eight drugs prescribed for each patient (48).

There are no randomised controlled studies of pharmacological treatment of the elderly bipolar. Expert guidelines and statements, e.g.(49), are thus based on extrapolation from randomised trials in younger adults and limited evidence in late-life bipolar disorder from open label studies, naturalistic studies, case reports and clinical experience. Here we consider the latter evidence.

There is some evidence of Lamotrigine's efficacy in bipolar disorder in those greater than 55 years of age; (50). Amongst other mood stabilisers there is also some evidence for Leviteracetam(51).

Antidepressants have a role in the acute treatment of a depressive episode in unipolar depressive disorder in the elderly as well as prophylaxis in preventing relapse. For the treatment of bipolar disorder monotherapy with antidepressants is fraught as there is a risk of switching to a manic episode (52).

Some antipsychotics have displayed efficacy in late life bipolar disorder, especially as an anti-manic agent. In a post hoc analysis of non controlled data quetiapine monotherapy was found to be effective for the acute treatment of bipolar mania in adults greater than 55 yrs of age(53). The same authors found efficacy of aripiprazole in a small (n=20) population of older adults in acute mania when it was given in an open label trial(54).

In a retrospective study on patterns of pharmacotherapy and treatment response following up 138 acutely unwell patients in a single centre, it was observed that mood stabilisers were the most prescribed (68%), followed by antipsychotics (54%) and antidepressants (34%). Combination therapy with the above medications was more common than monotherapy (57% vs. 38%). Remission was achieved in only 35% of subjects, while 32% showed no significant improvement (55).

In the European multi centre naturalistic follow up study, EMBLEM, (17)of 2761 patients followed up, it was found that LOB patients tended to be maintained on typical antipsychotics, lithium and anticholinergics, much more than EOB patients. However, after an episode of manic or mixed affective relapse there was an increase in prescription of atypical antipsychotics and a consequent decrease in typical antipsychotic use. There was a high use of antidepressants in the elderly group who were cycling (40%) compared to other older patients. There was a steady increase in the prescription of antidepressants across all groups during active treatment.

Conclusion: Late life bipolar disorder, especially late-onset bipolar disorder, appears to be a different entity from bipolar disorder in the younger population. Important caveats to this conclusion are that there is a limited evidence base in this area and much of it is not the highest quality. It is also often difficult to disentangle evidence for late-onset bipolar from the wider field of late-life bipolar disorder. Currently results investigating its etiopathogenesis indicate there are vascular changes in the brain associated with late life bipolar disorder. If this 'vascular mania hypothesis' is true then perhaps preventive cardiovascular strategies might be effective; this area merits further exploration. There is also cognitive impairment associated with late life bipolar and there is some evidence that lithium might prevent further deterioration in cognition. Good quality randomised controlled trials of psychotropics in both acute and maintenance stages are needed as currently practice is based largely on extrapolation of clinical evidence from younger bipolar patients who may

have a different kind of illness. Fundamentally, however, progress in this area is likely to remain limited if people who have mental and behavioural symptoms due to organic brain disease are diagnosed with bipolar disorder, implying a different illness from the one that seems to be afflicting these patients.

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