Diagnosis and Management of Bipolar Disorder With Comorbid Anxiety in the Elderly

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Currently, in individuals over 65 year of age, prevalence rates of bipolar disorder range from 0.1% to 0.4%. As is the case for bipolar disorder in younger individuals, bipolar disorder may be unrecognized or underrecognized among older adults. While anxiety disorders are frequently comorbid among younger individuals with bipolar illness, the prevalence and impact of comorbid anxiety is far less understood among geriatric individuals with bipolar disorder, in whom anxiety disorders may be underreported. This comorbidity may have serious consequences, since in older adult populations with depression, the presence of comorbid anxiety is associated with more severe depressive symptoms, more chronic medical illness, greater functional impairment, and lower quality of life; the same associations may prove to be true in older patients with bipolar disorder. As with younger individuals with bipolar disorder, effective treatment of the underlying mood disorder is critically important before treating comorbid symptoms. Unfortunately, few evidence-based studies are available to guide the treating clinician in the management of these vulnerable patients, many of whom have additional psychiatric or medical comorbidity. *(J Clin Psychiatry 2006;67[suppl 1]:21–27)*

The elderly are the fastest growing segment of the U.S. population, with a 12% increase in the number of persons 65 years and older from 1990 to 2000.[1] Additionally, over the next 3 decades, the number of individuals older than 85 years—the old old—is expected to more than double, with an estimated 8.9 million individuals by the year 2030.[1] Because of these changing demographic trends in the general population as well as greater sophistication in recognition and treatments for individuals with bipolar disorder, bipolar disorder in older adults has become a topic of increasing concern. Because the effects and impact of bipolar disorder are multidimensional, suffering and burden related to illness can be expected to affect not only the older adult with bipolar disorder but also his or her family and society at large. Clinicians struggling to meet the needs of geriatric patients with bipolar disorder have few evidence-based studies on which to base treatment decisions and often must contend with issues of psychiatric and medical comorbidity in these vulnerable individuals. While anxiety disorders are frequently comorbid among younger individuals with bipolar illness, the prevalence and impact of comorbid anxiety is far less understood among geriatric individuals with bipolar disorder. Examining bipolar disorder and anxiety separately in this population may yield insight into the comorbid condition.

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BIPOLAR DISORDER IN OLDER ADULTS

Prevalence

Currently, in individuals 65 years and older, prevalence rates of bipolar disorder range from 0.1% to 0.4%.[2] Hirschfeld and colleagues[3] reported that 1.6% of individuals aged 55 to 64 years screened positive for bipolar disorder using the Mood Disorder Questionnaire (MDQ), as did 0.5% of individuals 65 years and older. As is the case for bipolar disorder in younger individuals, bipolar disorder may be unrecognized or underrecognized among older adults. Additionally, since the majority of older individuals with mental illness live in the community, samples from research studies may overemphasize inpatient populations with mania and provide limited information on bipolar depression and interepisode functioning among geriatric populations with bipolar disorder.[4]

Presentation

Among older adults, bipolar illness may be first manifested in young adulthood, persisting into later life, or alternatively may be of later onset. The proportion of "new" or later-onset cases of bipolar disorder among older indi-

viduals with bipolar disorder has been reported to range from 6.1% to 11.0%.[5–8] It has been suggested that late-onset mania is a distinct subtype of bipolar disorder associated with medical and neurologic disorders.[6,9,10] A recent analysis[5] of a large database from the Veterans Health Administration (VHA) suggests that nearly one fourth of veterans with bipolar illness in the VHA are 60 years or older and that, of these, approximately 82.5% (N = 13,447) have early-onset illness.

Psychotic features occur in approximately 64% of older adults with bipolar disorder,[11] similar to what has been noted for mixed-age populations.[9] Additionally, among older adults, cognitive impairment is also a particular concern. Multiple reports have suggested that individuals with bipolar disorder develop dementia at a higher-than-expected rate,[12–14] but other data conflict with this finding.[15] Depp and colleagues[11] recently noted that elderly bipolar patients have more cognitive and functional impairment compared with younger patients. Kessing and Nilsson[14] found that the risk of dementia was significantly increased by the number of prior affective episodes. Finally, some older individuals may have bipolar symptoms that occur as a result of neurologic or medical pathology. The term *secondary mania* has been used to describe mania that occurs with identifiable medical or substance-related etiologies.[16]

Outcome

While outcomes of geriatric bipolar disorder seem to have improved significantly in the last several decades, primarily because of medication treatment advances,[2] geriatric bipolar disorder remains a condition associated with substantial morbidity and mortality. A recent study[17] noted that older adults with bipolar disorder treated under standardized pharmacotherapy protocols had associated low symptom levels; however, most did not experience sustained recovery. In contrast to elderly adults with unipolar depression, in whom maintenance antidepressant pharmacotherapy is associated with sustained recovery in the majority of individuals,[18] geriatric bipolar patients appear to have less stable outcomes and greater risk of relapse.[17]

With respect to longitudinal outcome, Angst and coworkers[19] reported that at long-term follow-up (34 to 38 years), older adults with mood disorders had elevated mortality rates, primarily from suicide and circulatory disorders. In addition, manic patients over 65 years of age were reported to have more psychosocial deficits and poorer outcomes than similarly aged depressed patients and control participants.[13] In a long-term Swiss study[20] of older bipolar patients (median age = 68 years), only 16% had fully recovered, 36% were still suffering from recurring episodes, and 7% had committed suicide.

In summary, geriatric bipolar disorder appears to have a pervasive effect on multiple domains of life functioning across the life span. In addition to mania and depression, cognitive impairment may affect functional status as well.

ANXIETY IN LATER LIFE

Prevalence

Although geriatric anxiety is common, it has received less attention than other disorders.[21] The reasons for this are several-fold: (1) despite their frequency in the community, primary anxiety disorders are not common in older patients seen in the mental health practice setting; (2) anxiety disorders seen in clinical practice are typically secondary to other disorders; (3) most older patients with anxiety do not meet criteria for specific disorders because existing diagnostic criteria may not adequately capture the quality of anxiety in the older patient; (4) primary anxiety disorders in the elderly generally have their onset in earlier adulthood and thus are usually chronic and have been present for decades; (5) given the absence of work or school responsibilities, older people may be more able to avoid anxiety-provoking situations than younger adults; and (6) ageist assumptions may hinder the detection and management of anxiety in later life (e.g., anxiety may be dismissed as "age-appropriate").[21,22]

Despite this lack of attention, anxiety disorders as a group are the most common psychiatric disorders in older adults.[23] The prevalence of anxiety disorders in older community populations ranges from 2% to 10%, and the prevalence among older adults in institutional settings is higher.[24] Rates of clinically significant anxiety are even higher than rates of anxiety disorders, ranging from 24% in community samples[25] to 40% in hospitalized elderly.[26] Among the anxiety disorders, generalized anxiety disorder (GAD) and phobic disorders are the most prevalent, estimated at 2% to 7%[27–29] and 3% to 10%,[28,30] respectively. Panic disorder (estimated prevalence < 1%)[27,28,30] and obsessive-compulsive disorder (OCD) (estimated prevalence < 2%)[28,30] are less common than other anxiety disorders among older adults.

Presentation

The clinical presentation of anxiety in later life is impacted by a number of factors including (1) the presence of comorbidity, (2) masked symptoms, and (3) age at onset. Among older adults, anxiety disorders are frequently comorbid with each other and with other psychiatric and physical disorders. Such comorbidity may overlap with anxiety symptoms and make differential diagnosis more difficult.

Many anxiety disorders rarely occur as new-onset primary disorders in late life; when these disorders emerge, they are often secondary to psychiatric or medical comorbidity. Late-onset panic disorder may be less severe with patients having less distress due to body sensations, cognitions, or emotions during panic attacks.[31] Early-onset post-

traumatic stress disorder (PTSD) may persist into late life, and new-onset PTSD may develop in older adults after traumatic events. Most older patients with GAD report an onset of symptoms in childhood or adolescence and appear to have a more severe course characterized by pathologic worry compared with those with a late onset of symptoms.[32] Late-life GAD is often concurrent with depression, though the onset and resolution of the 2 disorders may be distinct.[33]

Anxiety Comorbid with Mood Disorders

Symptoms of anxiety are seen in as many as 65% of older patients with depression.[34] The most common anxiety disorders in older depressed patients are phobias and GAD, although comorbid panic attacks can also occur with depression.[35] Most new-onset GAD in older adults is thought to be "masked depression," in which patients may emphasize anxiety symptoms or lack of pleasure without a sad mood[22,36] or have unexplained or amplified physical symptoms. Beekman et al.[34] found that 47% of depressed older adults had a concurrent anxiety disorder, while Lenze and colleagues[37] found that 28% of depressed elderly had GAD and 23% of depressed elderly had other anxiety disorders. Given the considerable symptomatic overlap between GAD and depression; the high rates of mixed GAD, depression, and other anxiety disorders; and the frequent progression of GAD to depression over time,[38] Flint[21] has noted that the usefulness of studying GAD as a discrete "pure" disorder in late life is questionable.

In older adult populations with depression, the presence of comorbid anxiety is associated with more severe depressive symptoms, more chronic medical illness, greater functional impairment, lower quality of life,[39] and greater suicidality.[35] Anxiety is also a risk factor for poor outcomes of late-life depression treatment, including nonadherence to treatment. In the recent PROSPECT study[40] using care management of late-life depression, the intervention was more effective than usual care in patients with low levels of anxiety but added little benefit for patients with higher anxiety severity. Older patients with anxious depression frequently misattribute somatic symptoms of anxiety to adverse medication effects,[41] which contributes to both dropout and poor response in antidepressant trials.[42] Additionally, older adults with an anxious/somatic focus may tend to discount psychological explanations for psychiatric symptoms and refuse treatment.[43]

PREVALENCE OF COMORBID ANXIETY IN LATE-LIFE BIPOLAR DISORDER

Earlier reports have suggested that some types of comorbid conditions seen in younger bipolar populations may be less common among bipolar elders. For example, the rate of lifetime substance abuse in individuals with bipolar disorder over the age of 60 years has been reported as 13% to 30%, compared with a rate of 61% in mixed-age populations.[4,5,44] Ponce et al.[45] reported that 29% of bipolar older adults had comorbid Axis I disorders; however, 2 recent and comprehensive publications that reviewed the current published literature on bipolar disorder in older adults[4,46] noted an absence of studies that examined the presence of anxiety disorder in older people with bipolar disorder.

Table 1. Anxiety Disorder Comorbidity in Older Adults (aged 60 years and older) With Bipolar Disorder (N = 3748): Results From the VA Psychosis Registry, Federal Fiscal Year 2001[a]

ICD-9 Code	Specific Anxiety Diagnosis	N	%
309.81	Prolonged posttraumatic stress disorder	1668	44.5
300.00	Anxiety state unspecified	1614	43.1
300.01	Panic disorder	220	5.9
300.02	Generalized anxiety disorder	867	23.1
300.09	Other anxiety states	145	3.9
300.10	Hysteria unspecified	5	0.1
300.20	Phobia unspecified	17	0.5
300.21	Agoraphobia with panic attacks	83	2.2
300.22	Agoraphobia without mention of panic attacks	17	0.5
300.23	Social phobia	20	0.5
300.29	Other isolated or simple phobias	9	0.2
300.3	Obsessive compulsive disorders	176	4.7

[a]Adapted with permission from Blow.[51]

In mixed-age samples, it has been found that anxiety frequently coexists with bipolar disorder. In the National Comorbidity Survey,[47] 92% of those who met criteria for lifetime bipolar I disorder also met criteria for a lifetime anxiety disorder. In the Epidemiologic Catchment Area (ECA)[48] survey, 21% of bipolar I and II patients had lifetime panic disorder, which was significantly greater than in patients with major depression (10%) and in the total population (1%). Other studies[49] have confirmed that panic disorder and GAD occur at significantly higher rates among patients with bipolar disorder than unipolar depression. Similarly, 21% of the patients in the ECA survey with bipolar disorder had a lifetime diagnosis of OCD, compared with 12% of those with major depression and 2% of the general population.[50] ECA data also indicate that bipolar disorder more than quadruples the risk of social phobia (odds ratio = 4.6).[50]

Research in older adults with bipolar disorder and comorbid anxiety disorders is needed to examine whether such disorders are epidemiologically comorbid with bipolar disorder. A recent analysis[51] examined the recorded rates of comorbid psychiatric illness in a population of 16,330 geriatric patients with bipolar disorder in a VHA administrative database. Patients were identified from case registry files during federal fiscal year 2001. Table 1 identifies recorded anxiety diagnoses seen among the 3748 older veterans (60 years and older) with bipolar disorder and comorbid anxiety (23% of the total bipolar sample). We suspect the reported rates of anxiety found

are an underestimate of the true prevalence of clinically significant comorbid anxiety for the following reasons: (1) underreporting of comorbid anxiety disorder diagnoses in patients with a serious mental disorder diagnosis (bipolar disorder); (2) limited diagnostic precision in the sample by the case registry methodology, which used clinical diagnoses rather than standardized diagnostic assessments; and (3) the fact that many providers might not code subsyndromal anxiety or anxiety thought to be secondary to a primary mood disorder. Additional limitations include the gender homogeneity of the VHA sample and the overrepresentation of PTSD due to high combat exposure of the sample.

TREATMENT OF THE OLDER ADULT WITH BIPOLAR DISORDER AND COMORBID ANXIETY

Assessment and Foundational Treatment of Bipolar Disorder

A key component of appropriate and effective treatment of bipolar disorder in mixed populations is accurate diagnosis of illness. Accurate identification of elderly individuals with bipolar disorder may be complicated by the long duration of time between first depressive episode and first manic episode, which may occur relatively late in life. Young and Klerman[52] reported that individuals with a history of major depression and family history of bipolar disorder (type V bipolar disorder) may develop type I or type II bipolar disorder with age. In a study[53] evaluating new-onset mania in older patients versus new-onset mania in younger patients, the older manic group had a longer latency from first depressive episode to first manic episode (17 years) compared with the younger manic group (3 years). McDonald and Nemeroff[54] have noted that late-onset mania may be associated with poor recognition of mood symptoms by providers, resulting in increased caregiver burden, premature nursing home placement, and a more rapid functional decline. In community settings, the MDQ has been demonstrated to be useful in identifying older adults with bipolar disorder.[3] Psychiatrists and other clinicians treating depressed elderly patients must be aware of the possibility of a bipolar disorder, particularly in individuals who experience apparently treatment-refractory illness, irritability, or new-onset mood lability.

No published, evidence-based treatment guidelines have been specifically developed for geriatric bipolar disorder. In the absence of prospective, controlled treatment trials in geriatric bipolar disorder, current treatment guidelines that refer to treatment of older adults with bipolar disorder largely rely on extrapolated findings from mixed-age populations.[46,55] A recent trial[17] of standardized treatment in bipolar disorder involving geriatric patients was modeled after the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[56] in which the goals of medication treatment were "to maximize the appropriate use of lithium or valproate (either singly or in combination), to achieve remission of acute mood episodes, maintain euthymia, and minimize adjunctive antipsychotic or antidepressant medications, except as judged clinically necessary."[17(p320)] As with younger individuals suffering from bipolar disorder, effective treatment of underlying mood disorder is critically important, and isolated treatment of anxiety symptoms without good control of mood symptoms is likely to be difficult and unlikely to be optimally effective.

The limited data on lithium and valproate treatment in geriatric populations suggest that both of these compounds may be effective[57–60]; however, tolerability issues may arise, particularly in frail or debilitated elders. Neurologic adverse effects have been reported in approximately 30% of older adults treated with lithium.[61–63] Abnormal serum levels of thyroid-stimulating hormone or need for thyroid replacement have been reported in 30% of older adults taking lithium as well.[64] Additional adverse effects that may be associated with taking lithium in older adults include polyuria, polydipsia, ECG abnormalities, edema, and weight gain.[65] Valproate has frequently replaced lithium as a treatment of choice for the elderly in some practice settings,[66] but valproate may have adverse effects in the elderly as well, such as sedation, tremor, and gait disturbance.[65] Research is underway to more clearly define efficacy and tolerability of lithium versus valproate in older adult populations.[67]

Current treatment choices should be informed by the safety and tolerability profiles of medication with respect to the unique profile of the individual patient.[46] Lamotrigine, a novel anticonvulsant that has demonstrated usefulness in bipolar depression, may also be effective and relatively well tolerated in older adult bipolar populations.[68] However, rigorous trials in bipolar elderly patients remain to be conducted. Carbamazepine may offer some advantage in individuals with atypical bipolar disorder[69] and may be of particular relevance in older adult populations in which bipolar symptoms secondary to neurologic illness are a greater concern.[70]

The anticonvulsants topiramate[71] and gabapentin[72] have shown some benefits in the management of mixed populations with bipolar disorder and comorbid anxiety, but it is not clear what role these agents may play in the treatment of geriatric patients with bipolar disorder and anxiety. Sethi and colleagues[73] reported on a small case series (N = 7) in which gabapentin appeared effective in geriatric mania, with excellent tolerability. Topiramate has minimal hepatic metabolism, low protein binding, and minimal drug interactions and is excreted mostly unchanged in the urine, all features that may be advantageous for some elderly patients. However, topiramate may also have a higher incidence of cognitive adverse effects compared with some other anticonvulsants, which may be particularly problematic for older adult patients.[74]

Atypical antipsychotics represent a potentially valuable treatment option for geriatric patients with bipolar disorder, particularly when compared with conventional antipsychotic agents, with which parkinsonism and tardive dyskinesia are major concerns. Secondary analyses of older bipolar adults treated with olanzapine[75] or quetiapine[76] suggest benefit and reasonably good tolerability. Case reports and retrospective studies also indicate improvement with risperidone in elderly bipolar patients,[77] and clozapine has been reported to be of benefit in refractory geriatric bipolar disorder.[66] Potential side effects of particular relevance to older adult populations include weight gain and metabolic abnormalities (particularly with clozapine and olanzapine), extrapyramidal symptoms (particularly with risperidone), anticholinergic effects (particularly with clozapine), and potential for QTc prolongation (particularly with ziprasidone).[78]

Recently, the U.S. Food and Drug Administration (FDA) issued a warning of an increased risk (1.6- to 1.7-fold) of death associated with all novel antipsychotics in elderly patients with dementia-related psychosis.[79] The FDA also indicated that typical antipsychotics may carry a similar risk. Because there are no reports of increased risk of mortality with atypical antipsychotics in patients with bipolar disorder, the relevance of the FDA findings with respect to older patients with bipolar disorder is not clear.

TREATMENT OF ANXIETY SYMPTOMS AMONG OLDER ADULTS WITH BIPOLAR DISORDER

There are no published studies to our knowledge that address the management of comorbid anxiety states in late-life bipolar disorder, but some lessons learned from the treatment of mixed-age patients with comorbid anxiety and from treatment of older patients with anxious depression are likely to be helpful.

Among mixed-age individuals with bipolar disorder, divalproex may decrease generalized anxiety and panic symptoms.[80] Carbamazepine was found to be ineffective for panic disorder in one trial.[81] Atypical antipsychotics have been found to be helpful for a number of anxiety disorders including PTSD, OCD, and as adjunctive treatment in GAD. Antidepressant medications, particularly selective serotonin reuptake inhibitors and other novel compounds, may be utilized for depressed bipolar patients, including older adults,[55] but issues of possible manic "switching" may be a potential complication. Among older adults with depression, tricyclic antidepressants have assumed a more limited role mainly because of relatively greater adverse effects.

A major concern for patients with anxious depression is the increased risk of early treatment withdrawal due to anxiety symptoms, leading to fear of medications, increased somatic symptoms, and rumination about mild adverse effects.[35] If appropriately identified, anxiety comorbid with mood symptoms can be effectively managed via a number of different strategies. First, a pretreatment account of the patient's physical symptoms of anxiety is often helpful for comparison with later symptoms that could be attributed to side effects.[82] Medications should be started at the lowest possible dosage but with the same target dosage as for nonanxious patients. Physicians should discuss such potential events with patients and assuage concerns by reassuring them that they will be monitored closely and that they can reach their provider if help is needed.[35,41] Cognitive-behavioral treatment strategies modified for anxious elderly patients[43,83] may also be useful. Such structured support of older patients with anxious depression can achieve outcomes similar to those in patients without anxiety.[84] Structured support is likely to be of benefit to those with anxiety and bipolar disorder as well, though this potential benefit remains to be studied.

CONCLUSION

Comorbid anxiety disorders are known to be common among mixed-age populations with bipolar illness, but little information is available on comorbid anxiety among geriatric individuals with bipolar illness. Anxiety disorders may be underreported among geriatric patients with serious mental illness, including bipolar disorder. It can be expected that comorbid anxiety among older individuals with bipolar disorder is likely to increase treatment complexity and may be associated with greater symptom severity, greater chronicity, and greater functional impairment than in younger patients. Preliminary and uncontrolled reports suggest that lithium, some anticonvulsants, and some atypical antipsychotics may be of benefit for geriatric patients with bipolar disorder and comorbid anxiety, but controlled studies are needed to provide the basis for evidence-based treatment decisions.

Drug names: carbamazepine (Epitol, Tegretol, and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, clozapine, gabapentin, and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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