

Contemporary Management of Comorbid Anxiety and Depression in Geriatric Patients

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Anxiety and depression in elderly people are major public health problems in the United States. Recognition and treatment of these conditions will likely gain more attention in the next 30 to 50 years because of the projected growth of the geriatric population. As in many younger patients, the most common presentation of anxiety in elderly patients is comorbid anxiety and depression. Although age is not a risk factor for either anxiety or depression, factors associated with aging—such as increased medical burdens and loss of independence—are substantial risk factors for development of these conditions. Moreover, there is a close association in older people between untreated mental illness and exacerbation of physical illness. Some of the newer antidepressants are more appropriate long-term options for the treatment of comorbid anxiety and depression than either benzodiazepines or tricyclic antidepressants. The newer antidepressants can decrease symptoms, improve quality of life, and potentially promote healthier outcomes in geriatric patients who have comorbid anxiety and depression and/or comorbid mental and physical illness. (*J Clin Psychiatry* 2001;62[suppl 12]:30–35)

Anxiety and depression in elderly people are major public health problems in the United States. Recognition and treatment of these conditions will likely gain more attention in the next 30 to 50 years because of the projected growth of the geriatric population. The management of anxiety and depression in older people may present special challenges to physicians. Elderly people have a high prevalence of comorbidity not only between anxiety and depression but also between mental and physical illness; thus, coprevalence of anxiety, depression, and physical illness is high in the geriatric population. Several factors contribute to the failure of clinicians to diagnose anxiety and depression in geriatric patients. A common cause for the underdiagnosis of geriatric anxiety and depression is the assumption that symptoms of these disorders are a normal reaction to aging or physical illness. Additionally, benzodiazepines and certain older antidepressants, such as tricyclic antidepressants (TCAs), are often used instead of newer selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and norepinephrine reuptake inhibitors (SNRIs). Treatment using the newer antidepressants can decrease symptoms, improve quality of life, and promote healthier outcomes in geriatric pa-

tients who have comorbid anxiety and depression and comorbid mental and physical illness.

ANXIETY AND DEPRESSION IN GERIATRIC PATIENTS

Anxiety disorders represent the most common psychiatric disorders in the United States, and epidemiologic surveys reveal that about 1 of 4 individuals will experience an anxiety disorder during his or her lifetime.¹ Anxiety disorders are less prevalent in older age groups than in younger age groups.² Older age per se does not appear to increase the risk for anxiety disorders, and, if anything, the prevalence of anxiety disorders in persons older than 85 years seems to be slightly lower than in elderly patients younger than 85 years. Most anxiety disorders in older persons appear to be a continuation or recurrence of early-onset anxiety; late-age onset of anxiety disorder is somewhat unusual. With the possible exception of agoraphobia (especially without panic disorder),² it is unusual for anxiety disorders to start late in life. In some studies, the mean duration of anxiety symptoms in elderly individuals is 10 years or longer, which suggests that the disorder started in adulthood. Common risk factors for anxiety in the elderly are listed in Table 1. Like anxiety in the younger age groups, anxiety in the elderly is more common in women. Late-age onset of anxiety can be precipitated by the death of a partner, declining health, or living alone. In general, the diagnostic criteria for anxiety are the same for elderly as for young patients. Chronicity is common. Individuals with a history of depression are at high risk for developing anxiety disorders. Either anxiety or depression can pre-

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Table 1. Risk Factors for Anxiety Disorder in the Elderly

Female gender
Depression
Death of a partner
Living alone
Overall declining health

precipitate the other illness and can alter response and compliance to medications used to treat the primary condition.

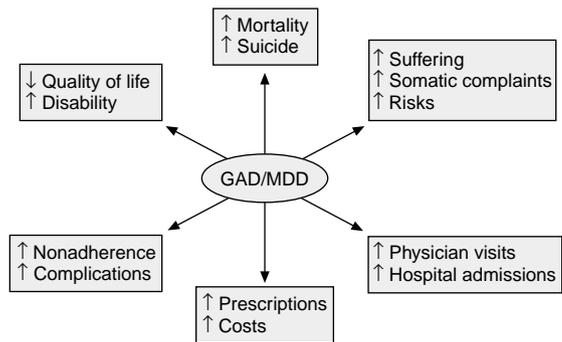
There are more epidemiologic data on the prevalence of depression than anxiety in the elderly. In a community-dwelling (noninstitutionalized) elderly population at large, the prevalence of depressive symptoms appeared to be approximately 15%, whereas the prevalence of a major depressive disorder (strictly defined according to standard DSM-IV criteria) appeared to be between 1% and 3%.³ Depression and anxiety—at levels of impairment sufficient to qualify as disorders—are not the usual response of older people to either aging or physical illness. Although age is not a risk factor for either anxiety or depression, factors associated with aging, such as increased medical burdens and loss of independence, are substantial risk factors for development of comorbid anxiety and depression.

Comorbid Anxiety and Depression

As in many younger patients, the most common presentation of anxiety in elderly patients is comorbid anxiety and depression. The National Comorbidity Survey⁴ reported that 39.5% of patients with a lifetime diagnosis of generalized anxiety disorder also had major depression. Clayton et al.⁵ reported that nearly two thirds of depressed patients also had symptoms of anxiety. Recent data show that 35% of older individuals who have major depressive disorders have at least one lifetime anxiety diagnosis, and 23% have a current anxiety diagnosis.⁶ In a community-based study⁷ of older respondents in the Netherlands, 36% of subjects with depression also had any anxiety disorder, while 13% of subjects with any anxiety disorder also had major depression. In a study⁸ of major and subthreshold disorders in 286 subjects aged 60 years and older, 4.9% had a lifetime diagnosis of major depression, 31.8% had either minor or recurrent brief depression, 6.6% had a major anxiety disorder, and 18.5% had a subthreshold anxiety disorder. In a primary care population prevalence study,⁹ the majority of patients were found to have mixed anxiety-depressive syndrome (42.3%) or depression with comorbid anxiety (19.2%), while only 12.8% of the population had anxiety only and 10.3% had depression only.

Diagnosis of Anxiety and Depression in Geriatric Patients With Physical Illness

There is a close association between untreated mental illness and exacerbation of physical illness in the elderly. Figure 1 is a schematization of the impact of untreated comorbid generalized anxiety disorder (GAD) and major de-

Figure 1. Impact of Comorbid Anxiety and Depression in the Elderly^a

^aAbbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder. Symbols: ↑ increased, ↓ = decreased.
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pressive disorder on the health of older individuals. Depression and anxiety are not only potential risk factors for new onset of medical diseases such as hypertension or coronary artery disease,¹⁰ but also can lead to adverse outcomes and increased mortality in these diseases.¹¹ Lack of early treatment can increase patients' somatic complaints, suffering, and health care utilization—the latter reflected by an increase in physician visits, number of prescriptions, hospital admissions, and overall costs to society. Lack of early treatment can also reduce medication compliance and increase complications in both the mental disorder and the comorbid medical illness. Complications can lead to a pervasive decrease in the quality of life and functioning and eventually to an increase in mortality rates from all causes, including suicide. From 1980 through 1992, the suicide rate among persons aged 65 years and older increased 9%; most striking was a 35% increase in rates for men and women aged 80 to 84 years.¹²

In older patients with apparent late-age onset of anxiety disorders, it is particularly important to look for potential medical causes that increase the risk for symptoms of anxiety (Table 2). Medical states that present with symptoms of anxiety include drug-induced anxiety, such as sympathomimetic toxicity; benzodiazepine and alcohol withdrawal; hypoglycemia and certain endocrine states; and certain neurologic, cardiac, and pulmonary conditions. The presentation of anxiety disorders and clusters of anxiety symptoms in the elderly is similar to that seen in younger patients except that neurovegetative or somatic symptoms may be more common in the elderly. Geriatric patients may be less likely to report subjective symptoms of depression or worry, even if excessive, because they believe that those feelings are normal for their situation. Thus, the clinician should inquire about somatic complaints such as a change in weight, unexplained aches and pains, sleep difficulties, low energy levels, and frequent health care utilization. A profound loss of interest, apathy, decreased concentration,

Table 2. Clinical Considerations in Evaluating Patients With Late-Age Onset of Anxiety Disorders

Types of presenting symptoms:
Somatic symptoms
Loss of interest
Decreased sleep, energy, concentration
Increased worry
Phobias
Panic
Check for contributing/complicating medical factors:
Cardiopulmonary: congestive heart failure, myocardial infarct, coronary artery disease, chronic obstructive pulmonary disease
Endocrine: thyroid, carcinoid, hypoglycemia
Cerebrovascular: stroke
Neurologic: dementia, temporal lobe epilepsy, multiple sclerosis, vestibular disorder
Sympathomimetic toxicity; alcohol, kava, valerian, or benzodiazepine withdrawal

and difficulty making decisions may also be common findings in elderly depressed patients.

There is no clear consensus as to the best way to diagnose anxiety disorders in medically ill older individuals. Attributing symptom causality is sometimes difficult in medically ill patients, because the symptoms of a medical illness may be difficult to distinguish from those of a primary mental disorder. One technique favored by researchers studying depression is the inclusive approach, in which all symptoms are considered, regardless of cause. For example, if an elderly cardiac patient presents with lower energy level and possible depression, the lower energy level should be considered as a symptom of depression. That is, depression should be ruled out—rather than ruled in—in elderly patients who have underlying chronic medical illness.¹³ The inclusive approach, however, may become somewhat more complicated in the diagnosis of anxiety disorders such as GAD, especially in the elderly. According to DSM-IV, the intensity, duration, or frequency of the anxiety and worry must be far out of proportion to the actual likelihood or impact of the feared event. Establishing whether the worry is in excess of what one would normally expect for an elderly person who has a medical illness can be subjective and difficult to determine. Further research is clearly needed to determine whether the same diagnostic criteria are equally applicable to elderly patients with medical illness as they are to younger patients without medical illness.

PHARMACOTHERAPY FOR ANXIETY AND DEPRESSION IN GERIATRIC PATIENTS

Although some trials may presently be underway, there are few published placebo-controlled studies of treatment with newer antidepressants for geriatric patients with anxiety disorders. Moreover, no published long-term, placebo-controlled data for GAD are available in older patients. Because of the lack of controlled data, clinicians must rely on clinical experience and randomized trial data

Table 3. Treatment Options for Comorbid Depression and Anxiety in the Elderly

Exposure therapy, cognitive-behavioral therapy, interpersonal therapy
Benzodiazepines, buspirone
Venlafaxine extended release
Selective serotonin reuptake inhibitors
Bupropion, nefazodone, mirtazapine
Herbals (eg, St. John's wort, kava, valerian)
Tricyclic antidepressants
Others (eg, electroconvulsive therapy, biofeedback, exercise)

from younger subjects to select drug therapy for elderly patients with comorbid depression and anxiety. Treatment for comorbid anxiety and depression is essentially the same for elderly as for young patients. Ideally, safe and effective pharmacotherapy should be selected when elderly patients first present with symptoms of these disorders. A combination of pharmacotherapy and certain types of psychotherapy appear to have a pronounced effect in maintaining depressed patients in remission and reducing the risk for relapse,¹² and the same may potentially be true for treatment of anxiety disorders in geriatric patients. Treatment options include antianxiety agents such as benzodiazepines and buspirone, and antidepressants such as venlafaxine extended release (XR), SSRIs, bupropion, and TCAs (Table 3).

Newer antidepressants are generally viewed as more appropriate longer term choices for the treatment of comorbid anxiety and depression than either benzodiazepines or TCAs. Most TCAs are inappropriate for use in older patients because of anticholinergic and cardiac side effects, but they may be useful in the treatment of sleep disturbances or somatic complaints. A patient profile (e.g., anxious, somatically impaired, anergic, cognitively impaired) can help to guide the selection of targeted treatment in geriatric patients. Prior response to treatment, as well as patient profile, should also be factored into therapy selection. Ideally, one drug should be used for treatment, although there are exceptions; multiple drugs increase the risk for interactions, side effects, and adverse pharmacokinetics. A drug should be selected that will improve somatic complaints and energy levels without adversely affecting cognitive functioning or medical status. Response rates may be somewhat slower in elderly patients, and treatment may be necessary for longer periods since both depression and anxiety can be chronic and recurring. Since chronicity is an issue, long-term agents should be selected when treatment is initiated. Medication should be given for an extended period of time after symptomatic improvement, and management should include frequent follow-ups for assessment of symptoms.

Antianxiety Agents

Many elderly patients who have symptoms of anxiety or comorbid anxiety and depression are administered benzodiazepines. In primary care, many are also treated with-

out a specific diagnosis. In a study of 1423 community-based older adults, the 12-month prevalence, standardized by age and gender to the Quebec population, of long-term continuous use of benzodiazepines was 19.8%.¹⁴ Benzodiazepines continue to be used 3 to 10 times more frequently than antidepressants in general practice. The risk of chronic benzodiazepine use seems to increase with advancing age; that is, the older the patient, the greater the risk that benzodiazepines—frequently long-acting or even 2 or more benzodiazepines in combination—will be used without adequate follow-up. Despite the overall decline in the use of sedative anxiolytics in the general population, a recent 10-year longitudinal study¹⁵ suggests that the frequency of benzodiazepine use in the elderly is not declining significantly and continues to remain greater than in the general population.

There may be a role for the judicious use of antianxiety agents as short-term treatment in combination with a newer antidepressant to hasten the onset of response and improve sleep disturbances. Common antianxiety agents include benzodiazepines—e.g., lorazepam and oxazepam—and buspirone. In general, benzodiazepines should be avoided or used for less than 1 month because of withdrawal, tolerance, or dependence problems. Clinicians should be familiar with the hepatic cytochrome P450 (CYP) metabolic activity of various drugs; agents that have intermediate half-lives are preferred. Lorazepam (0.5–2 mg/day) or oxazepam (10–30 mg/day) is preferable to diazepam for treatment of anxiety in geriatric patients. Lorazepam and oxazepam have a mean half-life in the plasma of about 12 to 15 hours, have no active metabolites, and have pharmacokinetics that remain relatively unaltered with advancing age.^{2,16} They also do not undergo oxidative metabolism in the liver, unlike drugs like diazepam.¹⁷ Persons with an apolipoprotein E4 allele may be particularly vulnerable to acute benzodiazepine-induced cognitive impairment.¹⁸ Additionally, benzodiazepines can adversely affect psychomotor functioning, equilibrium, respiratory drive, and coordination. Although buspirone is effective as treatment for patients who have GAD, it is less well accepted as a treatment for depression. Additional study is also needed to determine the long-term anxiolytic and antidepressant efficacy of buspirone in the elderly population. Herbal preparations such as kava and valerian are frequently used by the elderly to self-medicate anxiety symptoms but lack sufficient data to support their use as firstline. Abrupt withdrawal of valerian in a medically compromised elderly patient has been associated with delirium and withdrawal symptoms.¹⁹

Newer Antidepressants

Whereas traditional treatments for anxiety—such as the benzodiazepines and buspirone—have shown little efficacy in the treatment of depression, antidepressants have a long history of use in the treatment of anxiety disorders.

Despite the widespread use of the newer antidepressants, there is limited information on their effects in the anxious geriatric population; treatment recommendations for the elderly are often extrapolated from younger population data. However, many of the trials that determine the effectiveness of newer antidepressants in adults with depression, panic disorder, obsessive-compulsive disorder, and phobias also include elderly patients, albeit mostly those in their 60s. Although SSRIs are generally well-tolerated in older patients, geriatric depression trials²⁰ suggest that, compared with younger patients, effect sizes are somewhat smaller and response times are variable in elderly patients. Additionally, possible age-associated changes in hepatic oxidative metabolism may occur in older patients.²¹ The SSRIs—citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline—differ by their chemical structure and metabolism. The pharmacokinetics of these drugs may be modified in elderly patients at different levels of absorption, distribution, metabolism, and excretion.²² A double-blind comparison of sertraline and fluoxetine in 236 outpatients ages 60 years and older demonstrated a similarly positive response on the 24-item Hamilton Rating Scale for Depression and the Clinical Global Impressions scale ratings with 12-week responder rates of 73% for sertraline and 71% for fluoxetine.²³ Sertraline-treated patients showed greater cognitive improvement on several measures. Although bupropion sustained release is traditionally not viewed as a first-line antidepressant in anxious patients, a recent report²⁴ suggests that it may have similar efficacy as sertraline in treating anxiety symptoms secondary to major depression. However, neither bupropion nor any of the SSRIs have to date been proven to be effective in controlled trials of generalized anxiety disorder. Paroxetine has recently completed such trials although these data are not yet published.

Venlafaxine XR, an SNRI, has been found useful for both anxiety and depression and holds promise for use in the elderly population. Venlafaxine XR has been extensively evaluated for the treatment of GAD. The ability of venlafaxine to inhibit the reuptake of both norepinephrine and serotonin may represent a particular advantage in GAD, because evidence suggests that both of these neurotransmitters are dysregulated in the disorder.²⁵ As a result of the efficacy shown by venlafaxine XR in reducing the core feature (excessive worry) of GAD, as well as associated symptoms of depression and global anxiety, this agent was approved by the U.S. Food and Drug Administration for use in patients with the disorder.²⁶ In a post hoc pooled analysis²⁷ of 184 elderly patients (mean age = 66 years) with GAD, the response rates on the Clinical Global Impressions scale suggest that a greater percentage of patients taking venlafaxine (66%) improved than those taking placebo (41%). There is also evidence that venlafaxine is at least as efficacious and better tolerated than clomipramine in older patients with depression.²⁸

The effect of relatively low doses of venlafaxine on cognition has been studied in elderly depressed patients. In a 3-month open-label pilot study²⁹ of 36 elderly depressed patients taking venlafaxine 75 mg to 100 mg/daily, the mean Mini-Mental State Examination score improved by about 20% ($p < .052$) and the Cambridge Cognitive Examination score also improved to a similar extent ($p < .001$). In a randomized comparison³⁰ of venlafaxine and dothiepin in 86 elderly depressed patients, venlafaxine either improved or did not worsen cognition compared with dothiepin. Daytime sedation was greater in patients taking dothiepin than venlafaxine.

The side effect profile of venlafaxine is broadly similar in adults and geriatric patients; minimal changes have been noted in weight, blood pressure, and electrocardiograms. The key benefits of venlafaxine treatment in geriatric patients include effective treatment of both depression and anxiety, few side effects, and a minimal risk for cytochrome P450 inhibition or protein-binding-induced drug interactions. Pharmacokinetics of venlafaxine are not substantially affected by age,²⁰ and there is minimal risk for sedation or cognitive slowing. Adverse effects of venlafaxine include headache, gastrointestinal upset, restlessness, dry mouth, sleep disturbances, and (infrequent) increased blood pressure. The primary care provider and the patient's family should coordinate treatment, paying special attention to medication costs and trying to avoid polypharmacy. A multifaceted intervention consisting of collaborative management by the primary care physician and a consulting psychiatrist, patient education, and surveillance of antidepressant refills may improve compliance with treatment regimens in elderly patients.³¹

ANXIETY, DEPRESSION, AND FUNCTIONAL SYNDROMES IN GERIATRIC PATIENTS

Symptoms of anxiety disorder and functional syndromes often overlap in the geriatric population. For example, my colleagues and I are currently conducting a trial in subjects with atypical chest pain, which could easily have been diagnosed as true cardiac pain or as panic or anxiety disorders. O'Malley et al.³² conducted a meta-analysis of randomized, placebo-controlled trials in 6595 patients to determine the efficacy of antidepressant therapy for unexplained symptoms or symptom syndromes (Table 4). Most of the 94 trials that were included studied TCAs, SSRIs, or multiple agents for the treatment of the following syndromes: headache (50 studies), fibromyalgia (18 studies), functional gastrointestinal syndromes (13 studies), idiopathic pain (11 studies), tinnitus (2 studies), and chronic fatigue (2 studies). A majority (69%) of the studies demonstrated treatment benefits for antidepressants in these "functional" syndromes.

Evidence suggests that depression and chronic pain share common biological pathways, namely the serotoner-

Table 4. Randomized Controlled Antidepressant Trials in Patients With Idiopathic Symptoms or Symptom Syndromes (N = 6595)^a

Symptom/Syndrome	Total	% Trials Beneficial
Chronic headache	50	62
Fibromyalgia	18	80
Functional gastrointestinal illness	13	75
Idiopathic pain	11	66
Tinnitus	2	50
Chronic fatigue	2	50
All	94	69

^aAdapted from O'Malley et al.³²

gic and noradrenergic systems.³³ Depression is a common comorbidity associated with chronic pain, occurring in as many as 50% of patients who have chronic pain.³³ The lifetime prevalence of diabetic neuropathy is 50% and an estimated 2 to 3 million diabetics have more than 1 neuropathy. About 10% of them have severe pain. A randomized, placebo-controlled, 6-week trial³⁴ of venlafaxine XR was carried out in 244 nondepressed patients with at least 3 months' daily pain of at least moderate severity. The primary outcome measure of pain relief, the Visual Analog Scale for Pain Intensity, showed more improvement in patients taking venlafaxine XR (150–225 mg/day) than in patients taking venlafaxine (75 mg/day) or placebo. The optimal dose for efficacy and fewest side effects was venlafaxine XR at 150 mg/day. Animal studies³⁵ suggest that the analgesic effects of venlafaxine may in part be mediated through the adrenergic system.

The management of patients with chronic pain frequently requires a multidisciplinary approach.³³ Patients who have chronic pain and depression will benefit from treatment with antidepressants. Treatment should be selected based on a prior clinical response, the side effect profile, the dosing schedule, and the potential for drug interactions. Agents with dual serotonergic and noradrenergic activity appear to have the most consistent benefits in pain syndromes, based on available data. The analgesic effects of antidepressants can occur in the absence of depression and may result from improved mood and decreased anxiety in the patient. The fact that antidepressants can be effective in the treatment of functional syndromes has tremendous potential for reducing health care utilization in affected patients.

CONCLUSION

Comorbid anxiety and depression is the most common presentation of anxiety in geriatric patients. Elderly patients with comorbid anxiety and depression may be more chronically ill, have more past episodes of illness, show a poorer response to treatment, and be at higher risk for suicide than patients with either separate disorder. In the geriatric population, antidepressant therapy can ease the symptoms of depression and anxiety, improve quality of life, and

may also improve some physical illness outcomes. One limitation to interpreting available data about the newer agents is the paucity of prospective studies in geriatric anxiety disorders. Therefore, at present, clinical judgment must guide physicians in making individual pharmacotherapeutic decisions for elderly patients with comorbid anxiety and depression, especially those with medical illness. Medication tolerability, compliance, and costs must also be considered. Prospective randomized trials of the newer agents in "real world" geriatric patients with psychiatric and medical illness comorbidities are warranted. Such data will undoubtedly help physicians make evidence-based treatment decisions and improve outcomes for elderly patients with these debilitating disorders.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, bupropion, buspirone, citalopram, clomipramine, diazepam, fluoxetine, fluvoxamine, lorazepam, oxazepam, paroxetine, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for treatment of GAD in the elderly, comorbid GAD and depression in the elderly, depression in medically ill patients, anxiety in medically ill patients, chronic pain syndromes, and diabetic neuropathy.

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