Geriatric Depression

Stephen C. Cooke and Melissa L. Tucker

Depression in the elderly is more common than once thought, especially in nursing home settings, where as many as 25% of residents can exhibit signs and symptoms of depression. Depression in the elderly can have a significant impact on overall health and desired outcome. The depressed elderly patient has been shown to have worsened prognosis of concomitant medical conditions, increased use of health care, decreased recovery time, and more likelihood to experience accelerated physical deterioration. Suicide represents the most serious complication of depression of the older depressed individual. The elderly are at a disproportionate risk for suicide attempts and are more likely to be successful. Diagnosis should be made using *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (DSM-IV) criteria, and clinicians should use standardized rating scales such as the Geriatric Depression Scale to assist in monitoring the severity of depressive symptoms and the efficacy of antidepressant treatment. Several treatment options are available to the clinician and include psychotherapy, electroconvulsive therapy, older antidepressants such as the tricyclics, and newer more tolerable therapies such as the serotonin reuptake inhibitors. Drug therapy should be individualized and should take into account the pharmacokinetic and pharmacodynamic changes that are associated with normal aging.

KEY WORDS: depression, elderly, suicide, SSRI, pharmacokinetic, pharmacodynamic geriatric depression.

INTRODUCTION

DEPRESSION IN THE elderly population is more common than once previously thought. Recognition and treatment of this disorder can be confounded by physiologic and psychological changes that are part of the normal process of aging. Depression in the elderly is associated with increased mortality, decreased quality of life, and worsened prognosis of accompanying medical disorders.[1] Elderly depression is associated with an increased risk of completed suicide.[2] Although many physicians and patients view symptoms of depression as an inevitable consequence of late life, both evidence and experts agree that depression is not a normal condition of the elderly. Depression causes more social disability than many other common ailments of late life such as diabetes, arthritis, back pain, hypertension, and cardiovascular disease.[3] Adequate and efficacious antidepressant treatment strategies for late-life depression exist; however, recognition and assessment as well as provider education must be enhanced to improve the treatment of this disorder.

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EPIDEMIOLOGY

Studies analyzed by the National Institutes of Health Consensus Panel on Diagnosis and Treatment of Depression in Late Life show that 15% of elderly individuals in community samples showed evidence of depressive symptoms.

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Fully 3% met criteria for major depression.[4] Of particular note and concern was the finding that elderly residents of nursing homes are at a disproportionately high risk, with a prevalence of major depression between 15% and 25% and an incidence of approximately 13% of new cases each year.

ASSOCIATED DISORDERS

Medical comorbidity is common and is associated with worsened disease outcome, increased health care use, decreased recovery time, delayed resumption of normal activities, and interference with treatment compliance.[3] The relationship between cardiovascular disease and depression has been reported for over 60 years.[5] Up to 30% of patients recovering from stroke experience depression.[6] Almost 20% of patients who have had a recent myocardial infarction will meet criteria for major depression.[7] Rates of coexisting depression in patients with coronary artery disease have been reported as high as 18%.[8] In all of these groups, mortality is increased and overall prognosis is diminished as compared to patients who are not depressed.[7,9] The relationship between cardiovascular disease and depression is confounded by several factors. Patients with depression have a higher rate of cigarette smoking, a known modifiable risk factor for cardiovascular disease. These patients are also less likely to succeed in smoking cessation efforts.[10] However, several studies that controlled for smoking, as well as other cardiovascular risk factors, still showed an increase in ischemic heart disease in those study patients who were depressed.[11] Some researchers have also hypothesized that increased cardiovascular risk is secondary to the use of tricyclic antidepressants (TCAs), a class of medications that is associated with slowed cardiac conduction, orthostasis, and fatal ventricular arrhythmias in overdose. This idea, however, was refuted in a well-designed study that showed that cardiovascular death rate was actually lower after the tricyclics became available.[12]

Depression is common in patients with chronic pain syndromes such as cancer and rheumatoid arthritis. Up to 50% of patients with chronic pain will experience depression.[13] Pain and depression are so intertwined that adequate antidepressant therapy can itself reduce severity of chronic pain. Current recommendations suggest that depression screens be routinely used during chronic pain evaluation and treatment.

Several neurological and psychiatric disorders have also been shown to be associated with depression. As many as one-fourth of Alzheimer's patients will exhibit signs of depression.[14] Parkinson's patients appear to be at particular risk, with almost 50% experiencing depressive symptoms.[15] Depressive episodes are also common in patients who have also been diagnosed with anxiety or substance abuse or who are experiencing withdrawal from substances of abuse, particularly cocaine.

COMPLICATIONS

Depression has been shown to accelerate physical deterioration in the elderly. A large study of community residents that assessed physical function over a 4-year period showed that depressive symptoms were predictive of loss of physical skills and self-care.[16] This finding is especially important as individuals with declining self-care skills are at risk for nursing home placement. Adequate identification and treatment of these individuals may decrease subsequent admission to long-term care facilities.

The most severe and serious complication of depression, at any age, is suicide. Although they represent only 13% of the U.S. population, the elderly account for 25% of suicide attempts.[2] In fact, elderly individuals account for the highest suicide rate among all age groups. By age 85, the suicide rate is over twice that encountered in the general population.[17] Suicidal attempts in the depressed elderly patient are also more likely to be successful than in younger individuals.[2] Tragically, opportunities for

intervention prior to suicidal attempts are often missed. A retrospective study of completed suicide revealed that 75% had seen their primary care provider within 1 month of death, 40% were seen within 1 week, and 20% were seen within 1 day.[18] Simply put, failure to identify, diagnose, and adequately treat depression can have tragic consequences.

AGE CLASSIFICATION AND DEFINITIONS

Generally speaking, patients older than 65 have been traditionally defined as elderly. This nomenclature is, however, inadequate to describe the complete range of physiologic function encountered in a sample of older patients. Biologic variability in this population does not lend itself to precise numerical definitions of "elderly." Some patients appear and are indeed elderly several years prior to the age of 65. Conversely, some patients in their seventh decade of life are physiologically and functionally much younger than their stated age. New terminology has been devised to clarify these differences. "Young old" describes a person between the ages of 60 and 74. The terms "very old" and "old old" are being used to describe individuals over the age of 75. "Oldest-old" describes an individual that is greater than 90 years of age. The term "frail elderly" describes an individual who is functionally older than he or she actually is.

ETIOLOGY

The etiology of depression in the elderly is thought to be influenced by both biological and psychosocial components. Biologic factors in the elderly, such as hereditary influence and neurotransmitter abnormalities appear to be similar to younger individuals with depression.[19] Less similar to younger depressed patients, however, are the neuroendocrine and circadian rhythm changes that accompany normal aging. Dysregulation of the hypothalamic-pituitary-adrenal axis, long associated with the development of depression, increases with normal aging.[20] In addition, older individuals experience changes in their circadian rhythm that affect sleep architecture to a similar degree as that seen in those with depression. Older patients exhibit increased periods of nighttime wakefulness, have more difficulty initiating sleep, and also experience decreased stage 4 and rapid-eye-movement sleep.[21]

Many psychosocial causes of elderly depression have also been postulated. Although not clearly recognized as causative, these psychosocial factors should be identified and addressed in an effort to improve overall treatment and to possibly reduce or minimize future depressed episodes. According to one psychosocial theory, the development of a triad of negative beliefs regarding self-worth, current experiences, and a negative view of the future contribute to elderly depression.[19] Stressors can also contribute to the development and severity of elderly depression. Stressful life events such as the loss of a spouse, onset of a major medical illness, retirement, and nursing home placement can herald the onset of a depression or worsen a depressive episode already in place. Other stressors associated with elderly depression include loss of mobility, decrease in independent decision making, loss of defining roles ("head of family"), debits in mental acumen, and loss of support and peer groups.

DIAGNOSIS AND EVALUATION

The diagnosis of depression in the elderly should be made using the DSM-IV criteria mentioned elsewhere in this series of articles. The presentation of symptoms in an elderly depressed patient may be similar to or may differ from a younger depressed patient.[22] Elderly depressed patients may exhibit more cognitive impairment and social isolation and may complain less of dysphoric mood.[23] The elderly may also be more somatically focused, experience a higher level of fatigue and psychomotor retardation, and complain more about loss

of interest in usual activities.[4] Vegetative complaints such as decreased appetite and poor sleep may prompt initial contact with a clinician.

The elderly are at increased risk for comorbid medical conditions, and therefore, generally take more medications than younger patients. Many diseases and medications have been associated with causing or exacerbating depression. A comprehensive history regarding medical conditions and routine medications taken, including over-the-counter and herbal preparations, is invaluable at baseline to assist in differential diagnosis. As noted earlier, cardiovascular conditions such as stroke, coronary artery disease, and myocardial infarction have been closely tied to development of depression. Alzheimer's and other dementias are also commonly linked to depression. Other diseases that should be ruled out or evaluated at the time of initial evaluation include thyroid abnormalities, diabetes, cancer, vitamin deficiency, fibromyalgia, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis.[24] The exact relationship between these diseases and depression is unclear. Some clinicians have hypothesized a direct connection between disease and neurotransmitter dysregulation. Others suggest that stress secondary to chronic illness may precipitate depressive symptoms in a susceptible elderly patient.[25] Current treatment recommendations suggest treatment of both underlying illness and the depressive episode.

Medications that have been noted to worsen or cause depressive symptoms are numerous. Medications commonly used by the elderly such as steroids, diuretics, nonsteroidal anti-inflammatory agents, propranolol, methyldopa, and central nervous system depressants such as the benzodiazepines have been implicated in causing or worsening depressive symptoms.[26]

A common occurrence for the elderly is bereavement over the loss of close friends or other family members. The process of grief or bereavement can resemble a major depressive episode. Generally, if bereavement lasts for more than a few months or if depressive symptoms become debilitating or severe, antidepressant treatment (either pharmacotherapy or psychotherapy) should be initiated. Patients should be reassured that antidepressant therapy does not interfere with the grieving process.[27]

PHARMACOKINETICS

Pharmacokinetics is the study of a drug's action within the body over a period of time. The various components of pharmacokinetics include the absorption, distribution, metabolism, and excretion of drug substances. These processes may change substantially due to physiological transformations that occur as a part of the aging process. These age-related changes are often unpredictable and vary from patient to patient (Table 1). In addition to increasing age, other factors such as comorbid disease states, multiple drug regimens, and environmental changes may further influence pharmacokinetic processes.[28]

Alterations in pharmacokinetic processes in elderly patients are extremely important for clinicians to consider when prescribing agents for this population. Most antidepressant studies that have been conducted in the elderly population have only included healthy young-old patients. Therefore, the adverse effects reported in these studies have limited usefulness in patients who are elderly with multiple disease states and complex drug regimens. It is important for the clinician to individualize each patient's overall physiological status (i.e., nutrition, hydration, cardiac output) and subsequently recognize how this status may affect the pharmacokinetic aspects of various medications. By individualizing each patient's drug therapy, safer and more efficacious dosing regimens may be attained.[28]

Absorption of most drugs occurs primarily in the small intestine via passive diffusion. Alterations in gastric motility, gastric emptying, and gastric pH are just a few of the gastrointestinal changes that occur during aging. These physiologic changes may or may not affect how the patient absorbs a drug. For example, a de-

Table 1. Physiologic Changes Relevant to Drug Pharmacokinetics in the Elderly

Pharmacokinetic Process	Physiologic Change	Clinical Significance
Absorption	Altered gastrointestinal motility Decreased absorptive surface Decreased gastric emptying rate Decreased splanchnic blood flow Increased gastric pH	Little change in absorption with increasing age
Distribution	Altered protein binding Decreased serum albumin Increased α-acid glycoprotein	Increased or decreased unbound concentration of drugs in plasma
	Decreased lean body mass Decreased total body weight Increased adipose tissue	Higher concentration of drugs that distribute into body fluids; altered volume of distribution of some drugs often leads to a prolonged elimination half-life
Metabolism	Decreased phase I metabolism No change in phase II metabolism Decreased hepatic blood flow Decreased hepatic mass	Decreased hepatic clearance of drugs and metabolites with increased plasma concentrations
Elimination	Reduced glomerular filtration rate Reduced renal blood flow Decreased tubular secretion function	Decreased renal clearance of drugs and metabolites with increased plasma concentrations

Adapted from References 28, 29, and 34.

crease in an elderly patient's gastric motility can cause a nonsteroidal anti-inflammatory drug to remain in contact with the gastric mucosa for a longer period of time, potentially increasing the risk for ulceration.[28,29]

Active transport is decreased in the elderly population. Various nutrient drugs such as thiamine, folic acid, calcium, and iron are absorbed via this process.[30] Use of vitamin supplementation should be a consideration in these patients because vitamin deficiency has been postulated as a medical cause of depression.[24,29]

Distribution is generally variable in the elderly population. Elderly patients commonly have decreased availability of the plasma protein albumin, which is necessary for the binding of acidic drugs. When plasma albumin is decreased, more active and unbound drug is available to receptors, placing the patient at risk for toxicity.[31] Factors that may contribute to the decrease in albumin include malnutrition, immobility, and chronic illnesses.[32]

Conversely, α_1-acid glycoprotein (AAG) tends to be increased in the elderly population. AAG is an acute phase reactant protein to which many basic drugs bind. This protein is also increased during acute illnesses and inflammation. The increase in AAG may cause enhanced binding of basic drugs with subsequent decrement in unbound or free fraction of the drug leading to subtherapeutic levels and decreased pharmacologic effect.[33]

As a person ages, the ratio of lean body mass to fat as well as the total body water content of the person changes, which can affect drug distribution and thus pharmacologic response. A decrease in lean body mass with a subsequent increase in adipose tissue affects the volumes of distribution for hydrophilic as well as lipophilic medications. Between the ages of 20 and 80 years, total body water content is decreased approximately 10%–15%. Physical inactivity of the elderly population may also contribute to these changes that occur in body composition.[34]

Generally, the volumes of distribution as well as the half-lives for hydrophilic medications are decreased in the elderly.[28] Water-soluble drugs, such as lithium and morphine, are distributed primarily in lean body mass or body water, which is decreased in the elderly population.[29] Therefore, a lower dose of water-

soluble drugs is usually required for these patients to reach therapeutic plasma concentrations. In addition, shorter intervals between administration times may be required due to the decreased half-lives of these water-soluble medications.[35]

Conversely, lipophilic drugs have increased volumes of distribution as well as increased half-lives in the elderly population due to the accumulation of these agents in adipose tissue. Because of the physiologic alterations in this population, the duration of action and the process of eliminating the drug is delayed, potentially increasing the risk for adverse effects of the drug. For example, sedative-hypnotics and analgesics are given on an intermittent basis to decrease the incidence of adverse effects commonly associated with these agents. Diazepam, a long-acting benzodiazepine, has an almost 2-fold increase in the volume of distribution in elderly patients and a half-life of approximately 90 hours compared to 24 hours in young patients.[28]

Metabolism in the liver, excretion by the kidneys, or a combination of these processes are the primary mechanisms by which medications are eliminated from the body. Higher plasma drug concentrations with a subsequent increase in pharmacologic response can result due to a decrease in total body clearance that occurs as a person ages, placing the patient at risk for drug toxicity. With increasing age, physiologic changes regarding kidney function have a greater influence on drug elimination compared to physiologic changes in hepatic function.[29]

Age-related physiological changes that occur in the hepatic system, such as decreased liver mass, hepatic blood flow, and metabolizing activity, contribute to problems with the elimination of medications that are biotransformed in the liver. Other factors such as diet, gender, genetics, smoking, concomitant drugs, and diseases can also affect the process of drug metabolism.[29] Autopsy studies have shown that between the ages of 20 and 80 years, the size of the liver is decreased approximately 18%–25%, which has been associated with a decreased clearance of certain drugs.[34] In addition, the reduction in hepatic blood flow is the rate-limiting step for medications that are highly metabolized in the liver. As a result, the decline in hepatic blood flow, and thus hepatic clearance of the drug, could increase the plasma drug concentrations to potentially toxic levels.[29]

Age-related physiologic changes in hepatic metabolizing activity affect the ability of the liver to eliminate certain medications from the body through biotransformation reactions.[29] These reactions involve both microsomal and nonmicrosomal enzymes and are classified as either phase I or phase II reactions. Phase I reactions are normally reduced in the geriatric patient, while phase II reactions are generally unaffected by normal aging.[34]

Phase I reactions are associated with the cytochrome P-450 system and involve oxidation, reduction, and hydrolysis, typically producing compounds with pharmacologic activity. The key cytochrome P-450 isoenzymes responsible for the metabolism of certain psychotropic medications include CYP1A2, CYP2D6, CYP3A4, and the CYP2C subfamily.[36]

Phase II reactions involve glucuronidation, acetylation, and sulfation and usually produce inactive metabolites. For example, chlorazepate, diazepam, and prazepam are benzodiazepines that undergo biotransformation to active metabolites via oxidation, a phase I reaction. All of these agents demonstrate decreased clearance and prolonged elimination half-lives in the elderly population, increasing the risk of excessive sedation and other adverse effects. Alternately, the benzodiazepines lorazepam, oxazepam, and temazepam are metabolized to inactive metabolites by undergoing conjugation, a phase II reaction.[37] Overall, the cumulative effect of increased volumes of distribution and half-lives in conjunction with decreased hepatic metabolism in the elderly population may dramatically prolong the desired clinical effect of numerous medications.

Renal function progressively declines with age and provides the most consistent reflection of aging on pharmacokinetic variables.[34,35] Effects such as reduced renal blood flow, reduced

glomerular filtration rate (GFR), lack of glomeruli in the renal cortex, and diminished tubular secretion lead to renal impairment in the elderly population.[35] Generally, renal blood flow declines 1.9% every year. The GFR may decline as much as 50% as age increases, likely resulting in lesser elimination of drugs that are partially or completely cleared by the kidneys.[34] Drug elimination is associated with creatinine clearance. On average, the creatinine clearance of an individual declines by 50% from the ages of 25 to 85 years.[28] Common methods of estimating creatinine clearance, such as the ubiquitous Cockcroft and Gault formula, should be used with a certain degree of caution because some studies have suggested that the formula may not be accurate for residents of nursing homes.[38]

Decreased renal elimination may lead to prolonged half-lives of medications excreted by the kidneys, resulting in increased plasma concentrations. This is particularly important for medications with narrow therapeutic indices, as clinically significant adverse effects may occur in elderly patients if dosages are not adjusted accordingly.[28] In addition, elimination of hydroxy metabolites of tricyclic antidepressants, which are potentially cardiotoxic to elderly patients, is dependent on renal function.[39] Since renal function usually declines with age, accumulation of cardiotoxic metabolites may occur and can potentially lead to impaired cardiac conduction.[40]

TREATMENT

The overall goal of any antidepressant treatment modality is to improve and maximize quality of life, to maintain independent living skills in a community setting, and finally to avoid or delay placement in a long-term care facility or nursing home. In most treatment facilities, the older depressed individual is most likely to be evaluated and subsequently treated by a primary care practitioner. Psychiatric referral to a mental health specialist should be made in treatment refractory patients or in high-risk situations such as suicidality or in individuals with complex comorbidities.[24]

Baseline evaluations should include a complete physical exam including laboratory studies. Clinicians should also routinely make use of well-validated rating scales such as the patient-rated Geriatric Depression Scale[41] or the clinician-administered Hamilton Depression Rating Scale.[42] The use of these scales improves diagnostic reliability and can give the clinician a concrete mechanism to evaluate symptom progression, symptom severity, and antidepressant efficacy. A complete drug history, including past antidepressant treatment successes and failures, should be recorded at baseline.

Individualization of overall antidepressant treatment is key to the successful treatment of the elderly depressed patient. Symptom severity, disease comorbidity, economic means, expected tolerance to adverse effects, concurrent drug therapies, and patient attitude must be taken into consideration when developing an initial treatment plan. Psychotherapies may be used as the primary therapy in mild depression or may be combined with antidepressants in more moderate or severe depression.[43] Severe or treatment-resistant depression may respond to a course of electroconvulsive therapy (ECT). Clinicians that are presented with a clinical case involving a possible disease-induced depressive episode should generally treat both the depression and the underlying disease for maximal efficacy. Concurrent medications that are known to worsen depression should be evaluated for possible substitution.

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Psychotherapies for geriatric patients, such as group therapy, family therapy, and cognitive therapy, can aid in understanding and adapta-

tion to the inevitabilities of older age. These nonpharmacological therapies can improve self-esteem, reduce helplessness and anger, and can improve quality of life.[44] Common issues for the geriatric patient involve grief, family and peer losses, assumption of new roles, and acceptance of mortality. Group therapy is especially effective in that it can provide an opportunity for mutual support as well as provide a mechanism for new friendships at a time when many long-term friends may have died. Family therapy helps to increase familial understanding of the changes that an elderly person is undergoing. Involving family can reduce resentment, prevent elder abuse, and can provide the depressed individual with a sense of belonging and support. Cognitive therapy can minimize self-induced prejudices about growing older. Cognitive therapy can correct distortions in thinking, especially as relates to new skill acquisition, maintenance of sexual activity, learning, and helping others.[45]

ECT has been shown to be a safe and effective treatment for elderly depression, especially in the context of symptom severity, treatment resistance, or the presence of psychosis.[46] In fact, elderly individuals make up over one-half of patients who receive ECT in the United States.[47] Although most studies of ECT have included only young-old patients, a more recent study has concluded that ECT is safe and effective in the old-old patient. The overall conclusion of this most recent study was that despite a higher medical comorbidity and worsened cognitive functioning, ECT is tolerated as well as in younger patients and acute response was similar or better than seen in younger patients.[46]

Antidepressant selection, as in younger patients, should be based on past history of response, avoidance of adverse effects, presence of comorbidities, concurrent medications, and any known age-related physiological change that would impact pharmacodynamic or pharmacokinetic functioning. The lowest effective dose of any antidepressant should be used to minimize toxicity and enhance patient acceptance and compliance. The time-honored maxim to "start low and go slow" has particular significance and application in the elderly. Table 2 describes the usual dosage recommendations of commonly used antidepressants in elderly depression.

Table 2. Dosage Recommendations of Selected Antidepressants in the Elderly

Medication	Adult: Age < 65 (mg/day)	Geriatric: Age ≥ 65 (mg/day)
Amitriptyline[1]	75–300	25–150
Bupropion	225–450	50–100
Citalopram	20–40	20
Desipramine[2]	75–300	10–100
Doxepin	75–300	10–75
Fluoxetine	20–80	10–40
Fluvoxamine	50–300	N/A
Imipramine	75–300	10–150
Mirtazapine	15–45	N/A
Nefazodone	300–600	N/A
Nortriptyline[2]	75–300	10–75
Paroxetine[2]	20–50	10–30
Sertraline[2]	75–200	25–200
Trazodone	150–600	25–150
Venlafaxine	75–375	N/A

Adapted from References 29 and 57.
[N/A]Recommended dosage range presently unavailable in geriatric patients.
[1]Not recommended for use in geriatric patients.
[2]Preferred antidepressant in geriatric patients.

PHARMACOTHERAPY

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) are as efficacious as TCAs and have become the preferred medications for the treatment of depression in most elderly patients due to easier dosing schedules and more tolerable adverse effects.[39,48] Although all SSRIs appear to be effective for late-life depression, only paroxetine has been studied in patients older than 80 years of age.[39] The primary difference between the SSRIs involves pharmacokinetic parameters. The SSRIs are highly protein bound and undergo extensive metabolism. Paroxetine, sertraline, and fluvoxamine have relatively shorter half-lives compared to fluoxetine and citalopram. Norfluoxetine, the active metabolite of fluoxetine, has a 7 to 9 day half-life, possibly leading to accumulation in

the adipose tissue of elderly patients. Clinically, agents with longer half-lives have the advantage of increased compliance and stable blood concentrations if doses are missed, while agents with shorter half-lives possess the advantage of increased dosing flexibility. Drug interactions are also a concern due to hepatic metabolizing enzymes that are shared between SSRIs and other medications that are frequently prescribed in this population.[39]

Compared to the TCAs, the SSRIs reportedly cause more gastrointestinal (GI) adverse effects such as nausea and vomiting, especially during the first few weeks of therapy. To help alleviate or lessen GI irritation, the patient should consume food 20 to 30 minutes before taking these medications.[48] In addition, the elderly patient should also be monitored for weight loss, especially in the low-weight elderly. The SSRIs, especially fluoxetine, may cause agitation, anxiety, and/or insomnia in elderly patients. Decreasing the dose or switching to a less stimulating antidepressant may be helpful in these patients.[48,49]

Another adverse effect associated with the SSRIs is drug-induced parkinsonism. This syndrome is characterized by dystonias, akathisia, and potential exacerbation of symptoms in elderly patients suffering from idiopathic Parkinson's disease.[50,51] In addition, a rare adverse effect associated with both the TCAs and SSRIs is the syndrome of inappropriate antidiurectic hormone secretion (SIADH). Although both SIADH and parkinsonism have been primarily reported with fluoxetine, data regarding these adverse effects are limited.[52,53]

Recommended starting doses for the SSRIs in the elderly population are generally between one-third and one-half of the usual dose for young and middle-aged adults. Doses of SSRIs are usually administered in the morning due to the stimulating effects, but can be given at bedtime if the patient complains of sedation.[48]

Other Newer Antidepressants

The other newer antidepressants, bupropion, trazodone, nefazodone, venlafaxine, and mirtazapine, may also play a role for elderly patients suffering from depression. Compared to the TCAs and the SSRIs, these agents have been studied to a lesser extent in the elderly population. Although there are fewer studies in these patients, clinical experience indicates that these antidepressants are effective in the elderly. Similar to other antidepressants, these agents should be initiated with lower doses and slowly titrated to effect in elderly patients.

Bupropion is considered to be a favorable antidepressant in many elderly patients due to its minimal anticholinergic, sedative, orthostatic, and cardiovascular adverse profile. Bupropion is believed to inhibit the reuptake of dopamine, norepinephrine, and serotonin. The aspect of dopamine reuptake inhibition may be especially useful in patients suffering from depression who also have been diagnosed with Parkinson's disease. Common adverse effects include nausea, vomiting, agitation, and insomnia.[48] Because this medication tends to be activating for most patients, administration at bedtime should be avoided. Another adverse effect that limits dosing is the increased risk of seizure activity at single doses greater than 150 mg or total daily doses greater than 450 mg. Bupropion should be avoided in patients with seizures.[39,48] Elderly patients should be initiated with 75 mg twice daily with at least 6 to 8 hours between each dose.[48] The availability of a sustained-release (SR) formulation offers another option for elderly which may improve compliance. Approximately 6000 patients participated in clinical trials with the SR formulation in which 275 patients were 65 years and over and 47 were 75 years and older. There were no overall differences in the clinical effectiveness or safety profile between younger and older patients. With the SR formulation, elderly patients should be initiated with 150 mg SR daily, preferably as a morning dose.[54]

Trazodone is believed to inhibit the reuptake of serotonin as well as antagonize the serotonin-2 postsynaptic receptor, which may contribute to anti-anxiety effects reported with this medication. Trazodone also antagonizes alpha-1-adrenergic receptors, resulting in significant

orthostatic hypotension that commonly occurs 1 to 2 hours after administration. This adverse effect greatly limits its usefulness as a clinically effective antidepressant, especially in elderly patients. Trazodone also inhibits alpha-2-adrenergic receptors, which has been reported to rarely induce priapism in patients.[48] Although trazodone lacks significant anticholinergic adverse effects, the agent produces significant sedation in patients. For this reason, the most common use of trazodone in the geriatric population is as a sedative-hypnotic.[29] However, for elderly patients who have been resistant to other antidepressant therapy, trazodone may be considered as an alternative medication.[29,49]

Nefazodone is another atypical antidepressant that has been used in elderly patients. Like trazodone, this serotonergic agent is believed to inhibit the reuptake of serotonin as well as antagonize serotonin-2 postsynaptic receptors. Adverse effects frequently experienced with this medication include sedation, headache, and orthostasis.[48] This antidepressant has minimal to no anticholinergic effects, cardiac conduction abnormalities, or seizure risk and has been found to be safer than TCAs in overdose.[55] Nefazodone is metabolized to 3 active metabolites that have relatively shorter half-lives and therefore requires twice daily dosing. Due to sedation and orthostasis that may occur with this medication, doses as low as 50 mg twice daily are recommended for initiating drug therapy in elderly patients. Additionally, nefazodone inhibits the CYP3A4 enzyme which is responsible for metabolizing many other medications.[48] Because elderly patients are commonly prescribed multiple medications, it is important to monitor the patient's medication profile for potential drug interactions with nefazodone.

Venlafaxine is generally used as a second-line agent in elderly patients who have not responded to other antidepressant therapy. This antidepressant resembles the pharmacologic profile of the TCAs in that it selectively inhibits the reuptake of both norepinephrine and serotonin from the synaptic cleft.[48] However, venlafaxine lacks the anticholinergic effects that are commonly associated with the TCAs. Adverse effects associated with venlafaxine include nausea, headache, insomnia, confusion, and a possible elevation in blood pressure. The adverse effects of venlafaxine emphasize the need for caution with its use in the elderly population, especially those with brittle or severe hypertension.[39,48] This agent is metabolized to an active metabolite by the cytochrome P-450 system and is also excreted through the kidneys. Therefore, dosage adjustments may be required in elderly patients with renal impairment.[48]

Mirtazapine is a relatively new antidepressant that antagonizes alpha-2 receptors and is postulated to cause an increase in noradrenergic and serotonergic activity. This agent is also believed to antagonize 5-HT2 and 5-HT3 receptors. Adverse effects associated with mirtazapine include sedation, orthostasis, increased appetite, weight gain, and increases in triglycerides and total cholesterol. Because mirtazapine is substantially excreted by the kidney (75%), dosages must be adjusted in patients with decreased renal function. A majority of elderly patients have impaired renal function and consequently require a lower dose, especially on initiation of therapy. Due to the risk of oversedation and orthostasis with mirtazapine, this antidepressant should be reserved as second-line therapy in the elderly population.[56]

TCAs

TCAs are effective medications for elderly patients diagnosed with major depression but are more frequently used in lower doses for chronic pain syndromes. The TCA adverse effect profile of anticholinergic effects (dry mouth, blurred vision, constipation, confusion), inhibition of histamine-1 receptor activity (sedation), inhibition of alpha-1-adrenergic activity (orthostatic hypotension), and prolongation of cardiac repolarization (responsible for widening of the QT interval) reduce their utility in the elderly.[50] The cardiac effects can make TCAs contraindicated in many elderly

patients. The secondary amines (desipramine and nortriptyline) are the preferred TCAs for elderly patients due to decreased adverse effects and the availability of serum concentration monitoring.[48] However, significant adverse effects have been noted in patients who were within the therapeutic range for the medications. For this reason, geriatric patients should also be monitored for signs and symptoms of toxicity, whether mild (blurred vision, urinary retention, and confusion) or severe (arrhythmias and respiratory depression).[48]

Elderly patients with cardiovascular disease, benign prostatic hypertrophy, urinary retention, narrow-angle glaucoma, or a history of seizures should be closely supervised while using TCAs. Anticholinergic effects such as dry mouth and constipation may cause severe problems within the gastrointestinal system. Central nervous system anticholinergic effects of these agents are more pronounced in elderly patients and may cause difficulties with memory and attention, potentially escalating to severe cognitive impairment over time.[35] TCAs should be dosed at bedtime to decrease the incidence of falls, which can be serious or possibly fatal in these patients. Caution is also advised in elderly patients with suicidal ideation, given that an accidental or purposeful overdose of as little as a 2-week supply of TCAs can prove to be lethal.[48]

Before initiating TCA therapy in an elderly patient, the clinician should obtain a complete physical exam including an electrocardiogram (ECG). Use of the ECG aids the clinician in monitoring the patient for potential cardiotoxic effects of the TCAs. Starting doses should be especially low (e.g., amitriptyline equivalents 10–25 mg qd), and titrated upward to a dose that elicits the therapeutic response with the least amount of adverse effects.[49] See Table 2 for the usual dosage recommendations of the TCAs and other commonly used antidepressants in elderly depression.

Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitors (MAOIs), phenelzine and tranylcypromine, because of their adverse effects and drug-drug and drug-food interactions, have not been well studied in the geriatric population. These medications are not considered first-line agents used for major depression. However, the MAOIs may be effective for elderly patients suffering from atypical depression that is characterized by dysphoric mood accompanied by increases in vegetative symptoms such as sleep, appetite, and libido.[48]

MAOIs should only be prescribed to responsible, compliant elderly patients or to elderly patients whose medications are closely supervised.[49]

CONCLUSION

Depression in the elderly is underdiagnosed, undertreated, and associated with poor outcomes. Older depressed individuals are at risk for cardiovascular disease, poor quality of life, increased risk of suicide, and worsened prognosis of medical comorbidities. Treatment options are numerous, effective, and now more tolerable than in the past. The SSRIs are currently recognized as the preferred pharmacotherapy due to their improved adverse effect profile, ease of dosing, and documented efficacy across all geriatric age groups. Other treatment options, in the case of treatment failure or treatment intolerance, include bupropion, venlafaxine, and the secondary TCAs, nortriptyline and desipramine. Failure to recognize and treat depression in the elderly has economic, psychosocial, and ethical consequences. As the "baby boomer" generation ages, increased focus and attention on depression in the older patient will become even more of a priority.

MAOIs may be effective for elderly patients suffering from atypical depression.

REFERENCES

1. Montano CB. Primary care issues related to the treatment of depression in elderly patients. *J Clin Psychiatry.* 1999; 60(suppl 20):45–51.
2. Conwell Y. Management of suicidal behavior in the elderly. *Psychiatr Clin North Am.* 1997; 20:667–83.
3. Hays RD, Wells KB, Sherbourne CD, et al. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. *Arch Gen Psychiatry.* 1995; 52:11–19.
4. National Institutes of Health Consensus Development Panel on Depression in Late Life. Diagnosis and treatment of depression in late life. *JAMA.* 1992; 268:1018–24.
5. Malzberg B. Mortality among patients with involutional melancholia. *Am J Psychiatry.* 1937; 93:1231–8.
6. Hermann N, Black SE, Lawrence J, et al. The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. *Stroke.* 1998; 29:618–24.
7. Schleifer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. *Arch Intern Med.* 1989; 149:1785–9.
8. Carney RM, Rich MW, Freedland KE. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med.* 1988; 50:627–33.
9. Wells KB, Rogers W, Burnam MA, et al. Course of depression in patients with hypertension, myocardial infarction, or insulin-dependent diabetes. *Am J Psychiatry.* 1993; 150:632–38.
10. Glassman AH, Helzer JE, Covey LS. Smoking, smoking cessation, and major depression. *JAMA.* 1990; 264:1546–9.
11. Roose SP, Spatz E. Treatment of depression in patients with heart disease. *J Clin Psychiatry.* 1999; 60(suppl 20):34–37.
12. Weeke A, Vaeth M. Excess mortality of bipolar and unipolar manic-depressive patients. *J Affect Disord.* 1986; 11:227–34.
13. Ruoff GE. Depression in the patient with chronic pain. *J Fam Pract.* 1996; 43:S25–S34.
14. Reifler BV, Larson E, Hanley R. Coexistence of cognitive impairment and depression in geriatric outpatients. *Am J Psychiatry.* 1982; 139:623–6.
15. Dooneief G, Mirabello E, Bell K, et al. An estimate of the incidence of depression in idiopathic Parkinson's disease. *Arch Neurol.* 1992; 49:305–7.
16. Penninx BW, Guralnik JM, Ferrucci L, et al. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA.* 1998; 279:1720–6.
17. NIH Consensus Development Conference. Diagnosis and treatment of depression in late life. NIH Consensus Development Conference Consensus Statement. 1991; 9(3,Nov):4–6.
18. Clark RC. "Rational" suicide and people with terminal conditions or disabilities. *Issues Law Med.* 1992; 8:147–66.
19. Blazer D. Depression and the older man. *Med Clin North Am.* 1999; 83(5):1305–16.
20. Veith R, Raskin M. The neurobiology of aging: does it predispose to depression? *Neurobiol Aging.* 1988; 9:101–17.
21. Prinz P, Vitello M, Raskind M. Geriatrics: sleep disorders and aging. *N Engl J Med.* 1990; 323:520–6.
22. Donner DL. An overview of paroxetine in the elderly. *Gerontology.* 1994; 40(suppl 1):21–27.
23. American Psychiatric Association. Practice guideline for major depressive disorder in adults. *Am J Psychiatry.* 1993; 150(suppl 4):1–26.
24. Mulsant BH, Ganguli MD. Epidemiology and diagnosis of depression in late life. *J Clin Psychiatry.* 1999; 60(suppl 20):9–15.
25. Bruce ML, Seeman TE, Merrill SS, et al. The impact of depressive symptomatology on physical disability: MacArthur Studies of Successful Aging. *Am J Public Health.* 1994; 84:1796–9.
26. Pies RW, Shader RI. Approaches to the treatment of depression. In: Shader RI, ed. *Manual of Psychiatric Therapeutics*. 2nd ed. Boston: Little, Brown and Company: 1994; 22:217–46.
27. Pasternak RE, Reynolds CF, Schlernitzauer M, et al. Acute open-trial nortriptyline therapy of bereavement-related depression in late life. *J Clin Psychiatry.* 1991; 52:307–10.
28. Beyth RJ, Shorr RI. Medication use. In: Duthie EH, Katz PR, eds. *Practice of Geriatrics*. 3rd ed. Philadelphia: W.B. Saunders Company: 1998; 38–47.
29. Miller SW. Geriatric drug therapy. In *Textbook of Therapeutics: Drug and Disease Management*. 7th ed. Philadelphia: Lippincott Williams & Wilkins: 2000; 2063–76.
30. Bhanthumnavin K, Schuster MM. Aging and gastrointestinal function. In: Finch CE, Hayflick L, eds. *Handbook of the Biology of Aging*. New York: Van Nostrand Reinhold: 1977; 709–23.
31. Hayes MJ, Langman, MS, Short AH. Changes in drug metabolism with increasing age. *Br J Clin Pharmacol.* 1975; 2:73–9.
32. Greenblatt DJ, Sellers EM, Koch-Weser J. Importance of protein binding for the interpretation of serum or plasma drug concentrations. *J Clin Pharmacol.* 1982; 22:259–63.
33. Davis D, Grossman SH, Kitchell BB, et al. Age related changes in the plasma protein binding of lidocaine and diazepam. *Clin Res.* 1980; 28:234A.
34. Vestal RE, Gurwitz JH. Geriatric pharmacology. In: Carruthers SG, Hoffman BB, Melmon, KL, Nierenberg DW, eds. *Clinical Pharmacology: Basic Principles in Therapeutics*. 4th ed. New York: McGraw-Hill: 2000:1151–77.
35. Devane CL, Pollock BG. Pharmacokinetic considerations of antidepressant use in the elderly. *J Clin Psychiatry.* 1999; 60(suppl 20):38–44.

36. Devine B. Gantamycin therapy. *Drug Intel Clin Pharm.* 1974; 8:650–5.
37. Bellantuono C, Reggi V, Tognoni G, et al. Benzodiazepines: clinical pharmacology and therapeutic use. *Drugs.* 1980; 19:195–219.
38. Drusano GL, Munice HL, et al. Commonly used methods of estimating creatinine clearance are inadequate for elderly debilitated nursing home patients. *J Am Geriatr Soc.* 1988; 36:437–41.
39. Salzman, Carl. Practical considerations for the treatment of depression in elderly and very elderly long-term care patients. *J Clin Psychiatry.* 1999; 60 (suppl 20):30–33.
40. Kutcher SP, Reid K, et al. Electrocardiogram changes and therapeutic desipramine and 2-hydroxydesipramine concentrations in elderly depressives. *Br J Psychiatry.* 1986; 148:676–9.
41. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1983; 17:1737–49.
42. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56–62.
43. Reynolds CF, Frank E, Kupfer DJ, et al. Treatment outcome in recurent major depression: a post hoc comparison of elderly ("young-old") and midlife patients. *Am J Psychiatry.* 1996; 153:1288–92.
44. Weiss LJ, Lazarus LW. Psychosocial treatment of the geropsychiatric patient. *Int J Geriatr Psychiatry.* 1993; 8:95–106.
45. Geriatric Psychiatry. In: Kaplan HI, Sadock BJ, eds. *Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*, 8th ed. Baltimore: Williams and Wilkins 1998; 54:1289–1304.
46. Tew JD, Mulsant BH, Haskett RF, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. *Am J Psychiatry.* 1999; 156(12):1865–70.
47. Olfson M, Marcus M, Sackheim HA, et al. Use of ECT for the inpatient treatment of recurrent major depression. *Am J Psychiatry.* 1998; 155:22–29.
48. Hay DP, Franson KL, Hay L, Grossberg GT. Depression. In: Duthie EH, Katz PR, eds. *Practice of Geriatrics*, 3rd ed. Philadelphia: W.B. Saunders Company: 1998; 286–94.
49. Salzman C, Satlin A, Burrows AB. Geriatric psychopharmacology. In: Schatzberg AF, Nemeroff CB, eds. *The American Psychiatric Press Textbook of Psychopharmacology*. Washington, DC: American Psychiatric Press: 1995; 803–21.
50. Steur E. Increase of Parkinson disability after fluoxetine medication. *Neurology.* 1993; 43:211–3.
51. Caley CF, Friedman JH. Does fluoxetine exacerbate Parkinson's disease? *J Clin Psychiatry.* 1996; 57:278–82.
52. Sharma H, Pompei P. Antidepressant-induced hyponatremia in the aged: avoidance and management strategies. *Drugs Aging.* 1996; 8:430–5.
53. Woo MH, Smythe MA. Association of SIADH with selective serotonin reuptake inhibitors. *Ann Pharmacotherapy.* 1997; 31:108–9.
54. Bupropion package insert. Greenville, NC: GlaxoWellcome; 1999 Sept.
55. Preskorn SH. Recent pharmacologic advances in antidepressant therapy for the elderly. *Am J Med.* 1993; 94(suppl 5A):2S–12S.
56. Mirtazapine package insert. West Orange, NJ: Organon; 1999 Mar.
57. Citalopram package insert. St. Louis, MO: Forest Laboratories; 2000 May.