GERIATRIC PSYCHIATRY

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Learning Objectives

1. Demonstrate an understanding of the prevalence and manifestations of psychotic, depressive, bipolar, anxiety, and sleep disorders in elderly patients.
2. Distinguish between the courses and outcomes of psychotic, depressive, schizophrenic, bipolar, anxiety, and sleep disorders in older versus younger patients.
3. Design a rational pharmacotherapeutic regimen for an elderly patient with a psychotic, depressive, bipolar, anxiety, or sleep disorder.
4. Account for physiological, pharmacokinetic, and pharmacodynamic differences between older and younger patients when recommending, implementing, or monitoring a pharmacotherapeutic regimen.
5. Distinguish among the various commonly used psychometric rating scales used in clinical research and medical care of elderly patients with psychiatric disorders.
6. Discuss the potential adverse effects seen with psychotropic agents and their impact on pharmacotherapy of the geriatric patient.

Introduction

The average age of the United States population is steadily rising because of increasing longevity and a currently low birth rate. With the aging of the baby boomer population, born between 1945 and 1964, the nation is on the threshold of an unprecedented increase in the number of individuals older than 65 years of age. Overall, the percentage of the total population in this age group is expected to increase from 12.4% in 2000 to 19.6% in 2030 and will double in the next 75 years. This "graying of America" will lead to significant changes in the health care needs of our country's population. Older adults have unique medical, functional, and psychological needs that extensively impact health care use, quality of life, and eventual place of residence.

Importance of Geriatric Psychiatry

Although most common psychiatric illnesses present earlier in life, the specialty area of geriatric psychiatry is becoming an increasingly important discipline. One reason for an expanded focus in this area is the increase in average life span, meaning that patients are carrying psychiatric issues developed earlier into their old age. Second, the growing number of elderly patients in our society is leading to increasing psychiatric issues specific to this population, particularly dementia and other neurological disease-related mental illness. It is estimated that about 10% of geriatric people suffer from dementia, usually of the Alzheimer's type, whereas the prevalence of other psychiatric disorders is about 25%. With the increasing numbers of elderly patients with psychiatric disorders, the need for clinicians with knowledge and experience in geriatric psychiatry will continue to expand. Unfortunately, many experts predict an emerging national crisis in geriatric mental health care. The current pool of mental health professionals, research infrastructure, and delivery systems are inadequate to meet the needs of the growing number of geriatric patients with mental illnesses. In addition, older adults with severe mental illness continue to be moved from state hospitals to long-term care facilities (LTCFs), where access to mental health services is reduced, or into the community, where such services may be nonexistent. Therefore, it is incumbent on pharmacists, whether employed in the community setting, hospital, assisted-living facilities, or LTCFs, to possess the knowledge, skills, and abilities to provide comprehensive pharmaceutical care to this growing and often neglected population.

Abbreviations in this Chapter

5-HT	Serotonin
AD	Alzheimer's disease
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADHD	Attention-deficit hyperactivity disorder
ADL	Activities of daily living
AIMS	Abnormal Involuntary Movement Scale
AIP	Antipsychotic-induced parkinsonism
BDI	Beck Depression Inventory
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease
BPRS	Brief Psychiatric Rating Scale
BPSD	Behavioral and psychological symptoms of dementia
CES-D	Center for Epidemiological Studies-Depression (scale)
CGI	Clinical Global Impressions (scale)
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central nervous system
CSDD	Cornell Scale for Depression in Dementia
CT	Computed tomography
CVAE	Cerebrovascular adverse event
CYP	Cytochrome P450
D_2	Dopamine type 2
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
GDS	Geriatric Depression Scale
GFR	Glomerular filtration rate
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
ICU	Intensive care unit
LBD	Lewy body dementia
LTCF	Long-term care facility
MAOI	Monoamine oxidase inhibitor
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NPI	Neuropsychiatric Inventory
OCD	Obsessive-compulsive disorder
PD	Parkinson's disease
PET	Positron emission tomography
SPECT	Single photon emission-computed tomography
SSRI	Selective serotonin reuptake inhibitor
STMS	Short Test of Mental Status
TCA	Tricyclic antidepressant
TD	Tardive dyskinesia
V_d	Volume of distribution

Definitions

For our purposes, "elderly" or "geriatric" is defined as people 65 years of age or older. The term "very old" often is used to describe patients 85 years of age or older, but unfortunately, little pharmacotherapy research exists in this population. This is especially true regarding psychiatric issues, and many important questions remain unanswered.

Chronic Illnesses and Comorbidities

Drugs are a centrally important aspect of the care of the geriatric patient, and typically are the most common therapeutic intervention regardless of disease state. The goal of optimal drug prescribing is to maintain patient function and quality of life. However, a major difficulty in the pharmacotherapeutic management of these patients is the substantial burden of chronic illness and comorbidities. Because age is a major risk factor for virtually all of the major chronic, debilitating diseases, patients tend to accumulate diagnoses as they get older. With these added comorbidities, the number of chronic drugs taken also rises, leading to an increase in the risk of significant drug-drug interactions and the potential for decreased adherence to prescribed regimens. Adherence can be worsened by cognitive changes or alterations in sensation (e.g., poor eyesight) brought on by aging. In addition, a substantial percentage of the elderly do not have an outpatient prescription drug benefit and live on fixed incomes, making the acquisition costs of drug regimens a critical part of the pharmacotherapy decision-making process.

Further complicating the diagnosis and treatment of psychiatric disorders of the elderly is the need to differentiate between normal age-related changes and illness. Drugs often are prescribed without examining the current regimen and making necessary adjustments to minimize the risk of interactions. When an adverse effect does appear, it may be misconstrued by the patient or caregiver as a new illness or dismissed as part of "getting old". Adverse drug effects, such as confusion, gait instability, parkinsonian symptoms, incontinence, or epigastric pain, may trigger the addition of another drug to the regimen, an emergency department or hospital admission, or in severe cases, such significant morbidity as hip fracture or subdural hemorrhage. The presence of one or more chronic psychiatric disorders, not uncommonly coupled with socioeconomic issues, may further confuse the treatment plan. For example, individuals may lose cognitive function with age, and distinguishing normal changes from a disease process can be difficult. Often, the difference is simply the degree of impairment and its effects on the patient's functional ability. Likewise, differentiating a normal grief reaction after the loss of loved ones from symptoms of clinical depression can be complicated. Because of the efficacy and relatively good tolerability of the newer drugs used in geriatric psychiatry, most experts recommend a relatively low threshold for treating mental illness in this age group. The observation that geriatric

patients are more likely than younger patients to receive inappropriate or inadequate treatment for mental health issues underscores the dramatic need for improvement in this area.

This chapter focuses on geriatric psychiatric disorders, including their prevalence and presentation and the drugs used to treat them. In addition, basic principles of pharmacokinetics, pharmacodynamics, and adherence promotion in geriatric patients are reviewed.

Age-related Changes

Geriatric Brain Function

With age, brain mass and cerebral blood flow decrease. Gray matter decreases continuously in volume, whereas white matter remains relatively unchanged. The blood-brain barrier may become more permeable and sensory conduction is prolonged through a loss of nerve cells. These changes affect motor coordination, reaction time, and short-term memory. Primary memory, or the act of immediate recall, appears to change little with age. However, secondary memory, the function of daily adjustments and learning, may be diminished. Information retrieval also is affected negatively, especially when the individual is under stress and in unfamiliar surroundings. Vocabulary, information, and comprehension remain relatively intact at least until 75 years of age. The brain may process information more slowly after 60 years of age, but the ability to solve problems is less affected. These declines in learning, information retrieval, and processing speed may lead to significant short-term memory difficulties often referred to as a "normal" part of aging. Cognitive performance is affected by the aging process itself, but also may decline based on individual mental and physical health. A positive correlation exists between intellectual capacity and survival. Cognitive changes also may significantly result from poor genetics and a decline in neurotransmitter levels, such as serotonin (5-HT) and dopamine. The results of the changes in neurotransmission are discussed later in the Pharmacodynamics section.

Drug Handling: Pharmacokinetics

Absorption

Difficulties with swallowing are somewhat common among geriatric patients with psychiatric disorders, especially in those who have experienced a cerebrovascular incident or a neurodegenerative process. Dysphagia complicates drug administration, often requiring changes or omissions in the dosing schedule and necessitating coadministration with food, thereby potentially altering absorption. With increasing age, the surface area of the intestinal epithelium, gastrointestinal motor function, splanchnic blood flow, and gastric acid secretion all decrease. Limited studies suggest no clinically significant changes are likely to occur in the absorption of most drugs that permeate the gastrointestinal epithelium by diffusion. An age-related reduction in the rate or extent of absorption has only been shown for a limited number of drugs, including digoxin. Agents that slow gut motility, such as tricyclic antidepressants (TCAs), inhibit intestinal absorption to a greater extent than aging. Compounds that permeate the intestinal epithelium by carrier-mediated transport mechanisms, such as gabapentin, may be absorbed at a lower rate in the elderly, but again the clinical significance of this process is questionable.

Absorption from transdermal drug delivery systems is variable in the geriatric patient. Atrophy of the epidermis and dermis, coupled with a reduction in barrier function of the skin, may result in an increased rate of transdermal drug absorption. On the other hand, reduced tissue blood perfusion may result in decreased absorption. These factors also are important when administering subcutaneous and intramuscular injections. The latter dosage form typically should be avoided in this age group.

Distribution

The plasma concentration of a drug is inversely related to its volume of distribution (V_d). Age-related changes in V_d may occur with alterations in either body composition (e.g., body fat) or proteins associated with drug binding. Lean body mass, especially skeletal muscle mass, declines with age. Similarly, total body water content falls by 10–15% until 80 years of age. In general, the percentage of body fat increases with age, from 18% to 36% of total body weight in men, and from 33% to 48% in women. Although the fat content typically is higher in women, the relative change in the V_d for lipophilic drugs is more significant in men. Body composition changes result in an increased V_d for lipophilic agents, such as diazepam, and a decreased V_d for hydrophilic drugs, such as lithium.

The plasma half-life of a drug changes directly with its V_d. Therefore, a higher V_d may result in a longer half-life and an increase in the time necessary to reach a steady-state serum concentration. It is not uncommon for very old individuals to lose weight and become frail. As the proportion of body fat decreases, the V_d for lipophilic drugs decreases, leading to greater serum concentrations. However, it is common for the frailty of these patients to be overlooked. On average, low weight patients receive higher doses per unit body weight than do heavier patients.

Renal Clearance

With increasing age comes a reduction in both kidney mass and nephron size and number. It is estimated that after 40 years of age, these physiological changes result in a 10% decrease per decade in renal blood flow, tubular secretion, and glomerular filtration rate (GFR). Therefore, the GFR may be reduced by up to 35% in the geriatric patient compared to a younger adult. Because creatinine is filtered through the glomerulus, the serum creatinine is used to estimate creatinine clearance, which is directly proportional to the GFR. However, reduced GFR often is difficult to recognize in the presence of normal to low serum creatinine,

Charney DS, Reynolds CF 3rd, Lewis L, et al; Depression and Bipolar Support Alliance. Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. Arch Gen Psychiatry 2003;60:664–72.

which commonly is encountered in the geriatric patient as a result of reduced muscle mass. A 24-hour urine collection is limited by such patient variables as compliance and diet, whereas being restrictive because of inconvenience and cost. Therefore, it is recommended that creatinine clearance be calculated by using a simple formula that takes into account age, weight, and gender, such as the Cockroft-Gault equation. The disadvantage of this formula is that it may result in up to a 40% overestimation of creatinine clearance in the geriatric patient with muscle atrophy. As a consequence, dosing drugs that depend on renal excretion is a challenge in these patients because overestimation of renal function could result in overdosage and additional complications.

Hepatic Clearance

Most psychotherapeutic drugs other than lithium are cleared by hepatic metabolism. Although the effects of aging on the liver are minor compared to the effects of smoking, chronic alcohol ingestion, and specific disease states, several different pharmacokinetic processes are at work that may alter drug metabolism in the liver. Similar to that seen with the kidneys, a decrease in hepatic mass and blood flow has been demonstrated with increasing age. Age-related diseases, such as congestive heart failure, may further reduce hepatic metabolism by reducing hepatic blood flow. In the frail, elderly, nutritionally at-risk patient, drug metabolism is decreased to a greater extent than in a average weight individual of similar age. Decreased liver mass results in a decrease in hepatic metabolic capacity for drugs metabolized by cytochrome P450 (CYP) pathways. Studies of the plasma clearance of the CYP isoenzyme marker, antipyrine, have clearly demonstrated age-related decreases in metabolism. In one study, antipyrine plasma clearance correlated with liver volume and was about 50% lower in a group of geriatric patients compared to that of younger adults. Because of this decreased metabolism, elderly patients have higher peak and steady-state plasma drug concentrations than do younger patients receiving the same dosing regimen. Drugs, such as diazepam, which are metabolized through phase I oxidation reactions, are likely to have prolonged half-lives. Metabolism by phase II conjugation with glucuronic acid appears to be relatively spared with increasing age, so that metabolism of drugs through this pathway (e.g., lorazepam), are not as likely to be affected. Because the majority of geriatric patients take multiple drugs, they also are at risk for interactions that arise from inhibition of one or more of the CYP isoenzymes. Examples of drugs with high potential for such interactions include the selective serotonin reuptake inhibitors (SSRIs), paroxetine and fluoxetine, which both inhibit CYP2D6. They would be expected to increase the steady-state plasma concentrations of TCAs in patients taking stable doses of the TCAs. The reader is encouraged to consult a drug interactions text for a complete list of psychotropic drug interactions. However, caution also is recommended in extrapolating these reports to the geriatric patient.

Unfortunately, common liver function tests (e.g., alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transpeptidase) are not reliable indicators of hepatic drug metabolism, and there are no established pharmacokinetic relationships between changes in these tests and the pharmacokinetics of psychotropic drugs.

Drug Responsiveness: Pharmacodynamics

The pharmacodynamic effects of aging are, at least in part, because of the related changes in homeostatic mechanisms. Changes in specific receptor and target organ responses have been described but have been studied far less extensively than pharmacokinetic changes. Theoretically, increased drug sensitivity in the elderly results in increased serum concentrations and adverse reactions. Reported in the literature are numerous examples of psychotropic drugs causing adverse sequelae in the geriatric patient, including:

- Central nervous system (CNS) effects—sedation, confusion, disorientation, memory impairment, and delirium
- Peripheral anticholinergic effects—constipation, dry mouth, blurred vision, and urinary retention
- Motor effects—extrapyramidal symptoms (EPS), tremor, impaired gait, increased body sway, and falling
- Cardiovascular effects—hypotension and cardiac conduction delay
- Other effects—agitation, mood and perceptual disturbances, headache, sweating, sexual dysfunction, gastrointestinal disturbances, and hyponatremia

Receptor Influence

It is difficult to demonstrate that changes in receptor sites are because of aging alone as receptor function and numbers are influenced by many other factors. However, a reduction of several receptor sites and a decrease in responsiveness has been demonstrated. For example, in the CNS, the number of dopamine neurons and dopamine type 2 (D_2) receptors decrease in the elderly, leading to EPS when a certain threshold of neuronal loss is reached. Ascending dopamine neurons, as well as postsynaptic dopamine receptors degenerate with age. This degeneration is associated with as much as a 50% decline in dopamine content in the striatum by 65 years of age. Similarly, the decreased number of cholinergic neurons and receptors results in older patients being more susceptible to the anticholinergic effects of antipsychotic drugs, TCAs, and antihistamines. Age-dependent changes in the γ-aminobutyric acid (GABA) type A benzodiazepine receptor complex are known to be decreased both in number and in composition. Geriatric patients are sensitive to the effects of the benzodiazepines, which may result in additional sedation. Benzodiazepine use also may predispose them to confusion, ataxia, memory disturbances, cognitive impairment, and immobility.

Homeostatic Mechanisms

After a pharmacological agent has exerted its effect on the geriatric physiology, more time is required to return to

Zubenko GS, Sunderland T. Geriatric psychopharmacology: why does age matter? Harv Rev Psychiatry 2000;7:311–33.

the original steady-state level of functioning. Therefore, drug effects are prolonged, the actions may be stronger, and the incidence of adverse effects may be higher than is routinely seen in a younger individual. One example is the incidence of syncope in the elderly, which is thought to be drug-induced in 11% of cases. Drug-induced orthostatic reactions are estimated to occur in 5–33% of the elderly and contribute to significant morbidity through falls.

Adherence Issues

Compliance or adherence with prescribed drug regimens continues to be one of the great challenges of modern medicine. Estimated rates of nonadherence with prescribed therapeutic regimens range from 30% to 60%. In psychiatry, as in other disciplines, a correct diagnosis and prescribed treatment does not guarantee that the patient will follow the treatment plan. Psychotic and mood disorders may be especially affected by adherence issues because of the frequent presence of poor judgment and insight. Adherence to long-term and complex drug regimens appears to be the most difficult for geriatric psychiatric patients who live symptom-laden, highly stressful, and disorganized lives. Consequences of nonadherence include poor psychosocial outcome, chronic hospital admissions, and increased suicide rates. Direct hospital costs attributed to this problem exceed $800 million annually. Given these sobering facts, it is interesting that there has been such an increase in health care expenditures to ensure appropriate diagnosis and pharmacological treatment selection, yet there has been little effort to improve adherence. Few clinical trials in this area have had industry sponsorship. However, progress has been made in measuring or "policing" adherence through processes, such as pill counts, patient and family reports, pharmacy records, electronic devices, and plasma drug concentrations. Perhaps the most significant advance in this area has been the development of drugs with fewer adverse effects, such as the atypical antipsychotic drugs and SSRIs, which have improved adherence significantly. Discount programs offered by many pharmaceutical companies also have helped provide necessary drugs to seniors on fixed incomes who otherwise could not afford therapy.

What can clinicians do to improve adherence? The answer to this question depends on the underlying reason for nonadherence. Studies have shown that geriatric patients who choose to take their drugs do so based on scheduled activities, social needs, and concern about possible adverse reactions. The most frequently cited reason for nonadherence to psychiatric drug regimens is the nature of the disorder and the need for mood-altering drugs. Many patients experience guilt about their disease, whereas others remain in denial and refuse to accept the diagnosis and treatment. Substance abuse may play a part, as can the loss of autonomy. Research indicates that the quality of social interactions between patients and their health care providers appears to influence whether patients will adhere to therapy. Understanding illness and reasons for treatment are the cornerstones of drug adherence. Clear explanations and positive communication are musts. Thirty-one percent of psychiatric nurses surveyed indicated that drug education was the most effective adherence strategy. Encouraging the use of drug cassettes, scheduling regular clinic appointments, and supplying dose calendars and reminder signs are other strategies. Given that short-term memory disturbances are experienced by many geriatric patients, drugs that require multiple doses daily should be discouraged in favor of agents whose pharmacokinetics allow for dosing 1 time/day or at most 2 times/day. Nonadherence may result from the family's attitude toward the illness, lack of family care, observed side effects, and lack of resources. Therefore, it is imperative to involve family members and caregivers in decisions if they are available and interested. Home health care agency visits by psychiatric nurses also decreased early recidivism among geriatric patients. Finally, patient associations and self-help groups are important in providing support and information that might lead to improved adherence. With the goal being to improve patient outcome, pharmacy providers should focus on developing educational programs, using somatic and behavioral strategies, and assist in identifying both the cause and consequences of nonadherence.

Disordered Behaviors

Disordered behaviors (psychosis and agitation) are common symptoms in geriatric people living in the community or in LTCFs. Psychosis refers to an inability to properly assess reality. Symptoms of psychosis may include delusional thought content, such as paranoia or hallucinations. Disordered behavior most commonly manifests as agitation, which is defined as any verbal, vocal, or motor behavior that is disruptive, unsafe, distressing to the patient, and interferes with care and is not due to patient needs that is unexplained by apparent needs or confusion. Behavioral disturbances may manifest as a result of delirium, environmental factors, drugs, and the direct effects of neurodegenerative diseases.

Delirium

Delirium (acute confusional state) is a condition of cerebral insufficiency, resulting from widespread disruption of brain metabolism, most likely a reflection of a failure at the interneuronal or intraneuronal level of cerebral organization. It is a multifactorial syndrome that develops when a vulnerable patient, for whatever reason, is subjected to hospital-related insults (e.g., drugs or procedures). Delirium often is unrecognized and in the older adult, is frequently diagnosed as dementia, depression, or simply attributed to the aging process. In addition to behavioral disturbances and psychotic symptoms, the patient may experience a reduction in the clarity of awareness of the environment, which usually is of rapid onset and brief duration.

During acute hospitalization, 14–56% of geriatric patients become delirious. This number does not include the about 20% of patients who are already delirious when admitted. More than 2 million elderly people experience delirium each year, at a cost to Medicare of more than $4 billion. Postoperative delirium is common, occurring in

40–60% of orthopedic surgery patients. Delirium has several potentially serious outcomes, including the need for restraints and psychoactive drugs; the development of decubitus ulcers because of bed confinement; and the predisposition of the patient to falls, infections, and incontinence. The mortality rate from any disorder can double when delirium is present and may be as high as 76% in patients who develop severe delirium during a hospitalization. Patients who become delirious when hospitalized are likely to remain in the hospital almost twice as long as those who do not, and there is a substantially greater risk for the patient to require institutionalization after discharge.

Risk factors for delirium in the hospital and LTCFs include immobility, drugs, iatrogenic events (e.g., acute urinary tract infection), concurrent illnesses (especially dementia), sensory deprivation, impaired vision and hearing, dehydration, and social isolation. Many authors have indicated that "virtually any" drug can cause drug-induced delirium. Table 1-1 lists categories of drugs considered common offenders responsible for delirium. These agents can be recalled by using the mnemonic ACUTE CHANGE IN MS. The updated Beers Criteria of Potentially Inappropriate Medications for the Elderly also is a good reference. Many of these potentially inappropriate drugs have anticholinergic properties. Anticholinergic agents should be used with great caution in the geriatric patient because of their significant side effect profile, which includes tachycardia, mydriasis, urinary retention, constipation, confusion, and memory impairment.

An association between delirium and visual and hearing impairment has been shown, suggesting a role for reduced environmental stimuli. For example, patients placed in windowless hospital rooms have higher rates of delirium. In one study, 40% of patients placed in an intensive care unit (ICU) without windows developed delirium compared with 18% in an ICU with windows. In another study, behaviors were monitored in patients who were randomly assigned to either a private or semiprivate room. Sixty-four percent of those assigned to private rooms experienced one or more disturbances (visual, auditory, body-touch, smell, taste, and cognitive disturbances and noncompliant behavior) compared with 34% of patients in semiprivate rooms. Environmental factors associated with confusion in older surgical patients include fewer interactions with family and, contrary to expectations, the presence of more orienting objects (e.g., television or radio on). Obviously, sensory overload (too much noise and activity) may have a negative effect on a patient's cognitive state. A recent study determined modifiable environmental variables significantly related to an increase in confusion. These include confinement in an ICU or long-term care bed, an increased number of room changes, the absence of a clock or watch and reading glasses, the use of restraints, and the presence of a family member, who may make the situation worse when visiting the confused patient.

Table 1-1. Categories of Drugs That can Cause Acute Change in Mental Status

Antiparkinsonian drugs (levodopa, amantadine, selegiline, and catechol-O-methyltransferase inhibitors)
Corticosteroids (prednisone)
Urinary incontinence drugs (oxybutinin, flavoxate)
Theophylline
Emptying, gastrointestinal (metoclopramide)
Cardiovascular drugs (digoxin, methyldopa, β-blockers, angiotensin-converting enzyme inhibitors, and amiodarone)
Histamine type 2 receptor blockers (cimetidine and famotidine)
Antimicrobials
Nonsteroidal anti-inflammatory
Geropsychiatry drugs (TCAs, BNZs, and antipsychotics)
ENT drugs (decongestants, antihistamines, expectorants, and antitussives)
Insomnia drugs (BNZs and diphenhydramine)
Narcotics
Muscle relaxants (cyclobenzaprine, methocarbamol, and carisoprodol)
Seizure drugs (phenytoin and phenobarbital)

BNZ = benzodiazepine; ENT = ear, nose, and throat; TCA = tricyclic antidepressant.

The course of delirium may extend beyond hospital discharge, with some patients displaying symptoms for months. Older patients with preexisting dementia or any prior cognitive deficit are at greatest risk for prolonged delirium. This is thought to be, in part, because of the cholinergic deficit that is believed to occur during dementia, which acutely worsens during delirium. Many other pathological mechanisms occur as well, including an increase in serum cortisol concentrations and dysregulation of β-endorphin-, 5-HT-, norepinephrine-, and glutamate-mediated neuronal networks.

Establishing the diagnosis of delirium includes a history from a reliable information source regarding the patient's prior baseline level of functioning and mental status. Physical, neurological, and mental status evaluations and laboratory studies are then conducted to determine any treatable cause of the acute confusion. Neuroimaging studies and an electroencephalogram are performed routinely to determine the existence of a neurological condition, such as stroke or brain neoplasm. In addition, the patient's drug regimen must be examined to determine a correlation, if any, with the onset of symptoms.

The treatment of delirium is aimed at identifying underlying medical causes and providing symptomatic relief

Flaherty JH. Commonly prescribed and over the counter medications: causes of confusion. Clin Geriatr Med 1998;14:101–27.

Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med 2003;163:2716–24.

McCusker J, Cole M, Abrahamowicz M, Han L, Podoba JE, Ramman-Haddad L. Environmental risk factors for delirium in hospitalized older people. J Am Geriatr Soc 2001;49:1327–34.

as well as supportive care. The use of psychotropic drugs (discussed in the Dementia section) should always be judicious and should help alleviate overt psychiatric symptoms; such treatment also should reduce behaviors that may cause harm to the patient or others, or interfere with the delivery of medical and nursing care. The goals of symptomatic treatment include use of the lowest possible effective dose for the shortest time period while instituting supportive measures to calm and redirect the patient.

Dementia

Behavioral changes also may result from neurodegenerative diseases, such as dementia of the Alzheimer's type (Alzheimer's disease [AD]), stroke, vascular dementia, Lewy body dementia (LBD), and frontal lobe dementia. About 83% of patients with dementia demonstrate some psychopathology. The most common of dementias, AD involves both cognitive and a heterogeneous group of behavioral disturbances known as behavioral and psychological symptoms of dementia (BPSD), shown in Table 1-2. The International Psychogeriatric Association describes these symptoms as disturbed perception, thought content, mood, and behavior. Psychotic symptoms are assessed through interviews with either the patient or family members, whereas agitated behaviors are identified on the basis of observation of patient behavior. The most common BPSD resulting in institutionalization are paranoid delusions and aggression. Sleep disorders commonly trigger BPSD, likely leading to agitated behavior during the day. The patient also may experience other neurological symptoms that correlate with the presence of BPSD, such as EPS. For example, Parkinson-like rigidity and bradykinesia occur in 64% of patients with AD. Agitation and aggressive symptoms also may occur in patients with untreated pain. It is estimated that 25–50% of community-dwelling elderly live with untreated pain.

Table 1-2. Behavioral and Psychological Symptoms of Dementia

Psychosis	Agitation
Delusions (including paranoia)	Aggression
Hallucinations	Combativeness
	Hyperactivity (including wandering)
	Hypervocalization
	Disinhibition

Agitation is perhaps the most troubling BPSD. The term refers to "inappropriate verbal, vocal, or motor activity unexplained by apparent needs or confusion." The prevalence of agitation in AD begins to rise early in the course of the disease, with 20–40% of patients experiencing symptoms after 1 year of onset, and 50–60% of patients having agitation after 2 years. Once agitation is present, it is likely to persist in 60–80% of patients. Symptoms peak about 6–8 years after onset. As a result, patients with AD display agitation when their disease reaches a moderate to severe level of impairment. This persistence of symptoms suggests that agitation may reflect an underlying neuropathology. As the disease continues to progress and the patient becomes more cognitively impaired and less behaviorally capable, agitative symptoms decrease. Aggressive behaviors tend to occur in later stages of dementia, when verbal communication is severely compromised. Aggressive behaviors usually are a response to actions by others, when the patient with dementia does not comprehend and is not able to articulate his or her needs. At the point in the disease process when symptoms are no longer apparent, the need for drug therapy must be reevaluated. Therapy duration is discussed further in the Antipsychotic Drugs section.

The BPSD reduce the well-being of the patient while substantially increasing caregiver burden. Behaviors often result from the exposure of a patient with a vulnerable brain to an unhealthy environment (e.g., placing the patient in a home with relatives who do not understand the disease). Caregivers commonly report that behavioral and psychiatric symptoms of AD are more distressing than the cognitive impairment component. Physical aggression against caregivers is a known risk factor for elder abuse, whereas nonaggressive behaviors can increase caregiver distress because of the demands made on that individual's time and attention. Caregiver burnout is the most common cause of institutionalization of a patient with dementia. Early intervention, whether through pharmacological or non-pharmacological methods, has delayed LTCF placement, and improved the quality of life for both patients and caregivers. For example, taking advantage of an AD caregiver support program, including counseling sessions and support group functions, was shown in one study to delay placement an average of 329 days.

Diagnosis

Correct and early diagnosis is the key to appropriate and improved care for patients with BPSD. However, the number of comorbidities routinely experienced by this patient population may make diagnosis challenging. Differential diagnostic criteria include the following:

- Primary dementing disorder (e.g., AD)
- Primary psychiatric illness (e.g., schizophrenia, depression, and bipolar disorder)
- Delirium
- Physical discomfort (e.g., acute or chronic pain)
- Environmental or psychosocial triggers and precipitants

Multiple brain and neurotransmitter deficits are thought to be partially responsible for BPSD. Patients with dementia, as with other patients suffering from symptoms of aggression, have a 5-HT deficit and a loss of 5-HT-receptors in cerebrospinal fluid and the raphe nuclei. For example, common 5-HT_{2A}- and 5-HT_{2C}-receptor polymorphisms have been associated with visual hallucinations in patients with AD. In addition, studies have shown that a hyperresponsive 5-HT system also may contribute to aggressive behavior. This relationship provides a rationale for using 5-HT-antagonists to manage BPSD.

Neuroimaging studies are just beginning to shed light on the neuroanatomical changes associated with BPSD. Positron emission tomography (PET) studies have found that psychosis is associated with decreased glucose metabolism in the frontal lobe. Agitation correlates with changes in both the frontal and temporal lobes. Delusions

and hallucinations also are associated with specific regional impairments seen by single photon emission-computed tomography (SPECT). Delusions are found with frontal lobe hypoperfusion, whereas hallucinations are seen with parietal lobe hypoperfusion.

Screening Tools

Several researchers have developed behavioral screening tools specifically to evaluate patients with dementia. The Neuropsychiatric Inventory (NPI) is based on clinical observation and experience and has defined 10 domains of interest: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, disinhibition, irritability/lability, apathy, euphoria, and aberrant motor behavior. There are two versions of the NPI: one to be used when the patient is a resident of a LTCF, and the standard version to be used when the patient is in the home environment. In both cases, the caregiver provides a rating that evaluates the burden or increased work the symptoms may cause. The NPI was used in the first population-based study of neuropsychiatric disturbances in AD, and since then is used routinely to evaluate BPSD treatment approaches.

The Brief Psychiatric Rating Scale (BPRS) is a widely used, well-researched, relatively brief scale that measures major psychotic and nonpsychotic symptoms in patients with a major psychiatric disorder, namely schizophrenia. The ratings are based on observations made by the clinician during an interview. Items measured on the 18-item scale include emotional withdrawal, tension, mannerisms and posturing, uncooperativeness, unusual thought content, guilty feelings, and anxiety. The BPRS is used in clinical trials to evaluate baseline psychopathology, clinical outcome, and treatment response.

The Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) is a 25-item scale used to evaluate the behavioral symptoms of AD. In BEHAVE-AD, all assessment measures are largely independent of the cognitive symptoms of dementia. This allows the researcher to evaluate the effects of psychotropic drugs strictly on BPSD. The assessments are based on the information obtained from the caregiver and are structured into two parts: symptomatology and global rating. Symptoms assessed include delusions, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxiety and phobias. Global questions ask the caregiver to rate the symptoms as they apply to care (e.g., "Which is the most troubling symptom?").

The Cohen-Mansfield Agitation Inventory (CMAI) is a 29-item caregiver rating questionnaire used to assess agitation. Twenty-nine behaviors are each rated on a 7-point scale of frequency.

The Mini-Mental State Examination (MMSE) was developed in 1975 as a screening tool to assess an individual's orientation to time and place, recall ability, short-term memory, and arithmetic ability. The 11-item scale is divided into two sections. The first section requires verbal responses; the second section asks the patient to read a passage, write a sentence, and copy a geometric figure. Although 30 is a perfect score, scores of 23–25 indicate some degree of cognitive impairment. The MMSE is not used alone to diagnosis dementia but is used as a quick, simple bedside instrument to assess the cognitive function of the patient.

The Short Test of Mental Status (STMS) is a screening tool used in dementia assessment and is intended to be more sensitive to problems of learning and mental agility that are seen in patients with mild cognitive impairment (MCI). Mild cognitive impairment can be described as a transitional stage between "normal aging" and dementia. About 48% of patients with MCI will develop AD within 4 years of diagnosis. The STMS recently was compared with the MMSE in more than 1300 patients with either normal cognition, MCI, or mild AD. The STMS was superior in detecting patients likely to develop MCI or AD. Although the study had limitations of potential bias, it suggested that the STMS may have equally effective value to that seen with the MMSE.

Treatment

In assessing and treating BPSD, clinicians ideally proceed through several consecutive steps. First, symptoms are identified and prioritized. Total remission usually is not a realistic goal; however, reduction of symptoms is achievable. Second, any reversible medical, psychiatric, or psychological condition is determined. Finally, an appropriate therapy is chosen. Treatment of BPSD traditionally has been managed by using physical restraints. When restrained, residents in LTCFs exhibit either equal or higher levels of agitation. In fact, restraining may contribute to the manifestation of agitated behavior. Therefore, drugs are now considered more effective in controlling BPSD. However, if the symptoms are mild, non-pharmacological intervention may prevent the need for drugs, or may allow use of a lower drug dose.

Non-pharmacological Intervention Strategies

Various non-pharmacological intervention strategies should be attempted until one is found that fits the patient's needs. Reassurance and distraction often suffice. Light exercise, music, decrease in nighttime interruptions, and increasing access to outdoor areas may be effective. Two studies have demonstrated the positive relationship between patients being fitted with hearing aids and a significant decrease in the number of inappropriate behaviors. Evaluation and removal of environmental triggers is another approach. For example, if agitation occurs regularly at a certain time of day or is precipitated by an event or person, it may be advantageous to decrease or eliminate the trigger. Finally, improved eating and drinking have been demonstrated with the use of enhanced lighting during meal times. Light therapy improved depression in people with seasonal affective disorder and relieved sleep problems in people with jet lag and other body rhythm disturbances.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gombein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.

Similarly, timed exposure to bright light at the correct intensity (usually 2–3 hours at intensity levels greater than 2500 lux) may be helpful in promoting sleep and reducing agitation in patients with dementia. A randomized, single-blind, dose-comparison, crossover study currently is under way to evaluate high-intensity light therapy in residents in LTCFs who have AD and related dementias. Because people with AD often will not remain still in front of a fluorescent light panel, this study renovated areas of the LTCFs by installing even regulated high-intensity light. Researchers anticipate recruiting 180 residents.

Establishing a psychological relationship with the patient can be helpful in improving therapeutic outcomes (i.e., maintaining cognitive and verbal skills as long as possible and preserving quality of life). Verbal and nonverbal communication, touching, empathy, and listening are all effective techniques to use with patients well into the middle and later stages of AD. Videotapes of family members, contact with animals, massage therapy, and telephone tapes of family caregivers are all ways to reduce patient loneliness when one-on-one interactions are not possible.

Although most non-pharmacological interventions have been studied in the LTCF setting, studies involving caregivers in the home setting also are under way. The Bathing persons with Alzheimer's disease aT Home study evaluates the effectiveness of a 3-week reminiscence intervention applied during a patient's bathing time. In this 9-week study, 100 patient/caregiver couples will be recruited either into a reminiscence with coaching group or a control group. Reminiscence provides an intervention that draws on preserved individuality and memories of the patient, easily implemented by the caregivers. By using these techniques, the researchers hope to achieve less resistance to care, relieve patient discomfort, and improve caregiver appraisals of burden, capabilities, and confidence.

Pharmacological Treatment Strategies

Antipsychotic Drugs

When non-pharmacological approaches are not sufficient to alleviate the patient's symptoms, pharmacological agents may be indicated. No drugs are uniformly accepted or specifically Food and Drug Administration (FDA)-approved for labeling as treatment for BPSD. Often, trials with various drug classes are required for symptom control; however, evidence-based recommendations suggest that antipsychotic drugs be used initially. Results of seven double-blind trials comparing antipsychotic drugs to placebo in BPSD indicate that antipsychotic drugs are significantly more effective. Therefore, it is not surprising that 35% of residents of LTCFs with dementia receive prescriptions for antipsychotic drugs. Conventional or first-generation antipsychotic drugs include low-potency agents, such as thioridazine and chlorpromazine, and high-potency agents, such as haloperidol. First-generation agents are specific D_2-antagonists in the mesolimbic system, which reduce positive symptoms of psychosis (e.g., delusions, hallucinations, and loss in touch with reality), but have little effect on negative symptoms (e.g., social withdrawal, lack of motivation, and blunted affect). All of the conventional antipsychotic drugs have been used with modest success in this population. A meta-analysis of clinical trials using these agents for BPSD showed a response of 61% compared to 34% for placebo. Because of their ability to block D_2-receptors in the nigrostriatal pathway, and muscarinic, α_1-adrenergic, and histamine receptors, these drugs carry the possibility of significant adverse effects, including the risk of EPS, anticholinergic toxicity, cardiac toxicity, sedation, and irreversible movement disorders. Tardive dyskinesia (TD) is seen in roughly 63% of geriatric patients after receiving 3 years of conventional antipsychotic agents. For these reasons, the older, first-generation agents typically have been supplanted by the atypical antipsychotic drugs risperidone, clozapine, olanzapine, quetiapine, and aripiprazole, all of which have shown positive results in double-blind, placebo-controlled, clinical trials of BPSD. Ziprasidone has been used in geriatric patients with schizophrenia; however, there are few data available on its use for treatment of BPSD. Comparative studies suggest that these agents may have similar efficacy to the conventional antipsychotic drugs but are better tolerated. Another benefit of the atypical agents is that they block both the D_2- and 5-HT_{2A}-receptors, allowing these drugs to effectively treat both psychosis and aggression in patients with dementia. Despite these findings, the conventional agent haloperidol continues to be used routinely in many geriatric patients, particularly in the hospital setting. The growing number of available atypical agents, followed by reports of their safe and effective use in the elderly population, should help reduce the inappropriate use of conventional agents, especially haloperidol, in this vulnerable population.

Clozapine. Clozapine was the first atypical antipsychotic drug FDA-labeled for use in treating schizophrenia. Initial open-label studies of clozapine use in the elderly described efficacy; however, adverse effects were disabling in about 50% of patients. The American Academy of Neurology states that clozapine appears to be the most effective agent to treat psychosis associated with Parkinson's disease (PD) or LBD, especially in patients unable to tolerate other agents. The drug's D_2-receptor binding is significantly lower than the conventional agents, explaining its low incidence of EPS. A recent randomized, double-blind, placebo-controlled trial by the Parkinson Study Group found that low doses of clozapine (6.25–12.5 mg at bedtime) significantly improved drug-induced psychosis without worsening motor symptoms. However, because of its side effect profile, clozapine is not recommended as a first-line agent in elderly patients with dementia. The most notable side effect is agranulocytosis, which requires weekly monitoring of a complete blood cell count. Other side effects include sedation, orthostatic hypotension, seizures, myocarditis, and

Mintzer JE. Managing behavioral dyscontrol related to dementia. J Clin Psychiatry 2003;5(suppl 6):14–21.

anticholinergic effects similar to low-potency conventional antipsychotic drugs. Hypersalivation also is a troublesome adverse effect, thought to be due to clozapine's inhibition of muscarinic type 4 receptors as well as α_2-adrenergic receptors. Anticholinergic agents or α_2-agonists have been used successfully to treat the hypersalivation but are not appropriate strategies in the geriatric patient. Instead, non-pharmacological approaches should be attempted (e.g., chewing gum and using towels to prevent soaking of bed linens and clothes).

Risperidone. To date, the largest pool of patient data has been reported with the atypical agent risperidone. Efficacy of this agent over placebo was seen in controlled studies of more than 1200 geriatric patients with BPSD; however, it has been less effective than clozapine in controlling psychosis in PD. In a recent 12-week, double-blind study, 305 residents in LTCFs were randomized to receive either flexible-dose risperidone (mean dose = 0.95 mg/day) or placebo. After 4 weeks, 8 weeks, and at the end point, there was a significant improvement in agitation with risperidone. Risperidone was associated with a slightly higher incidence of somnolence and EPS compared with placebo, although this difference was not statistically significant.

When risperidone was compared to the traditional antipsychotic haloperidol, risperidone was superior in safety and efficacy. In one study, risperidone was compared to haloperidol in 344 patients with dementia. Patients treated with risperidone had significantly greater improvement on BEHAVE-AD aggressiveness scores, as well as on the CMAI total and verbal aggressive scores. Based on changes in MMSE scores, there was no cognitive deterioration with risperidone, whereas deterioration was seen in the patients treated with haloperidol.

Risperidone is the preferred agent in more than 75% of LTCFs, largely because of its ability to reduce the severity and frequency of BPSD symptoms, particularly aggression. There also have been preliminary suggestions of cognitive improvement with risperidone, given its affinity with α_2-adrenergic receptors. Blockade of this receptor disinhibits adrenergic transmission and may contribute to enhanced cognition and antidepressant effects, whereas peripheral blockade may result in increased cardiac output. Although dosages up to 6 mg/day were used in early clinical trials, experience has shown that doses of 0.5–2.0 mg/day are efficacious for BPSD and carry a low risk of adverse events. When risperidone is used for symptoms of delirium, experts recommend slightly lower than maximum doses: 0.75–1.75 mg/day. Risperidone causes EPS in a dose-dependent manner, so doses of more than 2 mg/day should be avoided in the geriatric patient. Its D_2-receptor binding is intermediate compared to that of haloperidol, and its affinity is 20 times less than its binding affinity for 5-HT_{2A}. Orthostatic hypotension, a result of α_1-adrenergic receptor blockade, is more frequent at the beginning of treatment and is characterized by the onset of dizziness, sinus tachycardia, or syncope. Therefore, the drug should be titrated slowly, beginning at 0.25–0.5 mg/day given at bedtime.

Olanzapine. Olanzapine is an atypical agent similar to clozapine in chemical structure and mechanism of action. It has a low to moderate affinity for the D_2-receptor, but has a high affinity for histamine and anticholinergic receptors, similar to that seen with clozapine. It currently is considered a second-line treatment for delirium and BPSD after risperidone. An early uncontrolled, clinical trial indicated that olanzapine was effective in inducing complete remission of delirium in about 76% of 79 hospitalized cancer patients. History of dementia, delirium due to CNS metastases and hypoxia, severe delirious symptoms, and age 70 years or older were predictors of poor response to olanzapine. More recently, olanzapine was compared to placebo in a 6-week, multicenter, double-blind, placebo-controlled trial of 206 residents in LTCFs. Olanzapine at doses of 5 mg/day and 10 mg/day produced significant improvement in the combined agitation, delusions, and hallucinations items of the NPI nursing home version. With 15 mg/day, there was no difference versus placebo at any symptom measurement. Measures of acute EPS were not significantly different among groups treated with olanzapine and placebo. However, there was a significantly increased dose-dependent incidence of somnolence and gait disturbances in patients treated with olanzapine. Weight changes were similar between olanzapine and placebo groups, whereas anticholinergic effects were significantly higher for patients treated with 15 mg/day compared to placebo.

Olanzapine exhibits significant anticholinergic receptor affinity compared with risperidone. This fact has led to concern that olanzapine may have a more substantial side effect profile in elderly patients compared to risperidone. However, the data from clinical trials are conflicting on this point. One small trial of 19 elderly patients with BPSD compared olanzapine with risperidone. Although both drugs improved social functioning in all patients, the adverse effect profile differed, with olanzapine demonstrating comparatively more adverse effects. Another larger trial of 206 patients did not show an increase in anticholinergic side effects with olanzapine compared to placebo. An intramuscular formulation of olanzapine currently is available for treating acutely agitated patients with dementia. Although absorption in the elderly may be erratic, pharmacokinetic studies have shown that intramuscular olanzapine reaches maximum concentrations at about 5 times those attained after oral dosing and reaches peak concentrations within 15–45 minutes. For treating BPSD, both the oral and intramuscular formulations are recommended to be initiated at 2.5–5 mg/day.

Quetiapine. Quetiapine also is structurally related to clozapine and has shown promise in treating BPSD and PD psychosis. Its low incidence of EPS is expected, given its

Brodaty H, Ames D, Snowden J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:34–43.

Alexopoulos GS, Streim J, Carpenter D, Docherty JP; Expert Consensus Panel for Using Antipsychotic Agents in Older Patients. Using antipsychotic agents in older patients. J Clin Psychiatry 2004;65(suppl 2):1–105.

D_2-receptor binding, which is significantly lower than the conventional agents. Because quetiapine improves psychosis without exacerbating movement disorders, it is considered by many experts to be first-line treatment for PD. However, more research involving efficacy in the geriatric population is needed. A 52-week, open-label, multicenter trial involving 151 geriatric patients with a variety of diagnoses (e.g., AD, vascular dementia, and PD-associated dementia) evaluated quetiapine at a dose of 25 mg/day and titrated to a median dose of 100 mg/day. Total BPRS and Clinical Global Impressions (CGI) scale showed improvements from baseline. Quetiapine was well tolerated with adverse effects including somnolence, dizziness, postural hypotension, and agitation.

A 10-week, prospective, double-blind, placebo-controlled study compared quetiapine to haloperidol and placebo in 284 residents in LTCFs suffering from BPSD. Findings suggested a better functional status with quetiapine compared to placebo and haloperidol, a statistically significant decrease in the incidence of EPS with quetiapine versus haloperidol, and fewer falls or fractures with quetiapine. Rates of somnolence were higher with quetiapine than with placebo. A lingering concern with quetiapine is whether the lens opacification that develops in laboratory animals administered the drug is species-specific or if humans also are at high risk for developing cataracts. Quetiapine also may cause orthostatic hypotension (because of α_1-adrenergic blockade) with associated symptoms of dizziness, tachycardia and, in rare cases, syncope. For treating BPSD, quetiapine dosing is initially recommended at 25 mg 2 times/day.

The Treatment of Agitation and/or Psychosis in Dementia with Parkinsonism trial is currently under way. The goal of this study is to determine the safety, tolerability, and efficacy of quetiapine when used to treat BPSD in patients with dementia with a comorbidity of PD and who are taking a cholinesterase inhibitor. A secondary aim of the study is to determine the influence of quetiapine on parkinsonism. About 60 patients will be randomized in a multicenter, double-blind, placebo-controlled trial. The patients will either receive quetiapine 25 mg 2 times/day, titrated to a maximum of 150 mg 2 times/day, or placebo. The trial will be 10 weeks in duration and will evaluate behavior, motor function, cognition, adverse events, and other outcomes at baseline and at 6 and 10 weeks.

Ziprasidone. Although a paucity of data related to the use of ziprasidone in the elderly exists, this drug may offer some advantages. It has a favorable profile on cognitive function compared to the conventional agents, given its weak anticholinergic effects. Unlike the other atypical agents, it does not appear to be associated with weight gain in most patients and it has a low risk of neurological and neuroendocrinological adverse effects. It also causes no change in glucose utilization and seems to bring about a reduction in cholesterol and triglyceride levels. However, it may increase the QTc interval in a dose-dependent fashion. Recommended dosages in elderly patients are 20–40 mg/day.

Aripiprazole. Aripiprazole is considered a representative of the next generation of atypical antipsychotic agents because it offers high partial agonist binding affinity for D_2- and 5-HT_{1A}-receptors, but functions as an antagonist at the 5-HT_{2A}-receptors. Two 10-week trials have been completed which used aripiprazole in BPSD, and another is ongoing. Only one of the completed trials has reported results. It was a double-blind, placebo-controlled trial, and it examined the use of aripiprazole in 208 outpatients with psychosis of AD. Efficacy measures included the NPI and the BPRS psychosis subscale. Doses ranged from 2 mg/day to 15 mg/day, with a mean dose of 10 mg/day. Analysis showed no significant difference in NPI scores; however, mean changes in the BPRS total scores were significant compared to placebo at week 6. The drug was well tolerated with mild to moderate somnolence reported in 8% of patients. More clinical trials are needed before aripiprazole can be recommended for BPSD.

When examining atypical agents based on safety, the clinician should take into account the baseline frailty of the patient, the presence of comorbid conditions (e.g., disease states, pain, bowel status, sensory status, and sleep deprivation), and previous response, if any, to a particular drug. Although atypical agents share the same general mechanism of action, subtle differences in their impact on a combination of neuroreceptors may contribute to variations among these drugs in terms of safety and efficacy. Adverse effects, discussed in the following sections, can be predicted, in part, based on the drug's potency in blocking a specific receptor. Safety concerns include, but are not limited to, movement disorders, anticholinergic and antihistaminic effects, weight gain, risk of diabetes, and falls.

Adverse Effects and Concerns with Antipsychotic Drugs

Movement Disorders. Antipsychotic-induced movement disorders, including EPS and TD, have historically represented the greatest concern in geriatric psychiatry. In the future, as the need for antipsychotic drug therapy in the elderly population increases, the incidence of movement disorders is expected to increase. Movement disorders are associated with incoordination, feeding problems, disfigurement, social isolation, falls, and fractures. As previously discussed, loss of dopamine neurotransmission is an age-related change that has the ability to impact the pharmacodynamics of the antipsychotic agents. Neuroimaging and postmortem brain studies also have shown an age-dependent decrease in D_2-receptors. These neurotransmitter and receptor changes may be related to antipsychotic-induced movement disorders. The disorders may be grouped into acute and chronic conditions. Dystonia, parkinsonism and akathisia are acute conditions that develop within minutes to months after an antipsychotic drug is started. Although antipsychotic drugs are the drug class most often associated with EPS, movement disorders also may result from other psychiatric drugs, including

Caligiuri MP, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly. Drugs Aging 2000;17:363–84.

SSRIs and lithium. Acute disorders are thought not to persist as the patient may develop a tolerance to the offending agent. However, in most cases, continuing the agent is not an option because of the extreme distress experienced by the patient with EPS. Chronic, tardive conditions such as TD do not appear early in treatment, but have a delayed onset, sometimes months to years. Unlike acute symptoms, tardive disorders have the potential to be persistent.

Dystonia. Dystonia is characterized by sustained muscle contractions. Common symptom presentation includes one of the following: facial grimacing, tongue protrusion, throat constriction, torticollis, sustained open posture of the jaw, and abnormal posturing of the trunk and limbs. In severe cases, the patient may experience rolling of the eyes upward or to the side, a symptom called oculogyric crisis. Dystonia is rare among older patients; there is a strong inverse linear relationship between age and incidence of drug-induced dystonia. It is estimated that the incidence of dystonia decreases from more than 60% in patients younger than 20 years of age to less than 5% among patients older than 50 years of age. Treatment of acute dystonia consists of immediate withdrawal of the offending agent and administration of an antihistamine or anticholinergic (e.g., benztropine 2 mg parenterally, repeated within 30 minutes if necessary). Typically, patients are maintained on the benztropine or equivalent for 48 hours or longer if there is a history of dystonic reactions. Preventive measures should be considered in patients with a history of dystonia. Guidelines published by the American Psychiatric Association state that the prophylactic use of anticholinergic agents should be considered only in patients taking high-potency antipsychotic drugs who have a history of experiencing EPS, for patients who are at risk of nonadherence because the drugs are poorly tolerated, or for patients who request prophylaxis to avoid discomfort or distress. Prescribing these agents to treat acute dystonia in geriatric patients should be undertaken with caution, for reasons discussed in the Delirium section. For patients with a history of acute dystonia, atypical antipsychotic drugs should be considered first-line therapy, although there are no published studies on preventing dystonia in the at-risk elderly patient.

Akathisia. Akathisia remains one of the most common antipsychotic-induced EPS. It is seen with both conventional, and less commonly, with atypical agents, and it has an equal prevalence in younger patients and geriatric patients. It is considered by patients to be more distressing than parkinsonian symptoms or TD. Akathisia is characterized as a subjective feeling of restlessness or the urge to move, and an objective motor component expressed as a semipurposeful movement most often involving the lower extremities. In patients with dementia treated with an antipsychotic, akathisia often is confused with an exacerbation of agitation or restless behavior. In this instance, increasing the antipsychotic drug will only make the akathisia symptoms worsen. Although the majority of research on risk factors in akathisia does not show age as significant, data suggest that the elderly may be more prone to developing persistent or chronic akathisia. Two studies indicated that elderly women are more likely to exhibit akathisia than men of all ages. Other risk factors include the presence of severe TD or parkinsonism, higher average daily antipsychotic drug dosages, more severe psychopathology, and presence of depression. When reducing dosages, discontinuing the offending agent or switching to an atypical agent is not an option, specific classes of agents may be tried. β-Adrenergic blockers, such as propranolol, have been used with mixed success. There is a risk of hypotension and such CNS effects as confusion, hallucinations, emotional liability, and slowed cognition with propranolol use in the elderly. Benzodiazepines are an option for treating younger patients (younger than 65 years of age), and clonazepam, lorazepam and diazepam are equally effective. There are no studies involving benzodiazepines in older patients with akathisia; therefore, the drugs should be used with caution in this population.

Parkinsonism. One of the most concerning forms of EPS in the frail geriatric patient is antipsychotic-induced parkinsonism (AIP) because the characteristic muscle rigidity, course tremor, and bradykinesia may predispose the patient to falls. Many patients, particularly the elderly, also may exhibit masked facies and postural instability. Parkinsonian tremor differs from other drug-induced tremors or essential tremor by having a lower frequency and higher amplitude. In addition to resting tremors, antipsychotic drug use also results in postural or action tremors. When symptoms are unilateral, they are more likely to be associated with idiopathic PD, whereas bilateral symptoms are more likely to be AIP. Parkinsonism usually has an onset within the first 2–3 months of starting the drug. If AIP is left untreated, it typically remits within 2–3 months in the majority of patients, without having to discontinue the antipsychotic. However, in older patients, it is not uncommon for the symptoms to continue for several months or years after drug discontinuation. It could be that geriatric patients are more sensitive to antipsychotic drugs than younger patients, or that the patients had subclinical PD that manifested with addition of the antipsychotic.

Among patients greater than 60 years, the incidence of AIP exceeds 50%. If the patient also has AD, the incidence rises to 67%. Preexisting AD with EPS (tremor or bradykinesia) also increases the risk for developing AIP. It is likely that patients who exhibit motor disturbances before receiving antipsychotic drug treatment already have a diminished capacity for dopamine neurotransmission within the basal ganglia. The introduction of a dopamine antagonist may further enhance this deficit. Incidence rates for AIP with atypical antipsychotic drugs are low, even in the elderly. Women were twice as likely to develop AIP in some studies, whereas other studies found no difference between genders. Treatment of AIP consists of reducing the dose or discontinuing the offending drug. Antiparkinsonian agents should be used sparingly in older patients as discussed in the Delirium section. In fact, some clinicians consider prophylactic anticholinergic agents to be contraindicated in geriatric patients. If the patient is taking a conventional antipsychotic drug, switching to an atypical agent is indicated, the choice of which was previously discussed.

Tardive Dyskinesia. Tardive dyskinesia is a syndrome manifested by unsightly and irritating abnormal movements

that can reduce function and frequently are irreversible. The patient exhibits involuntary choreoathetoid movements of the mouth, face, limbs, and trunk. These movements may be rapid, jerky, and nonrepetitive (choreiform), or slow, sinuous, and continual (stereotypic) in nature. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), the movements must be present for more than 4 weeks to be considered persistent. The DSM-IV also states that TD may develop in the elderly after antipsychotic use for at least 1 month. About 3–5% of older patients will develop abnormal movements after 1 year of continuous therapy with conventional agents. Prevalence of TD varies among ethnic groups. For example, Europeans have a higher incidence compared to Chinese, Malays, or Indians. Several researchers have found higher incidence rates in African Americans compared with Caucasians. Female gender was once thought to be an important risk factor for TD; however, more recent large-scale studies of older patients have not found that gender influenced the risk. The development of acute EPS significantly increases the likelihood of subsequent TD, especially in the elderly. Patients who develop AIP, especially tremor, develop TD at a significantly faster rate than patients who do not develop AIP.

As a class, atypical agents are associated with a significantly decreased incidence of both EPS and TD compared with conventional agents. Researchers have examined the link between TD and haloperidol or risperidone used in geriatric patients at mean doses of 1 mg/day. They found the incidence of TD among those receiving risperidone to be about one-fifth that with haloperidol. The literature suggests that these agents may be effective as treatment for drug-induced movement disorders. Clozapine, risperidone, olanzapine, and quetiapine have shown improvement in patients with TD. It has been proposed that patients with TD lose their symptoms and dopaminergic hypersensitivity with long-term clozapine treatment. Recently, researchers have found that risperidone, in doses of 6 mg/day, showed significant improvement in TD symptoms of the orofacial areas. Yet, all of the atypical agents have been reported to induce TD. Therefore, long-term studies are required to further elucidate the place of atypical agents for treating TD.

Managing TD requires cooperation from both the patient and family. It is not uncommon for a patient who develops significant EPS to become nonadherent, discontinue drugs, and, subsequently, decompensate because of fear of developing TD. Cooperation can be fostered early in the patient's care through proper informed consent. At the present time, there is no consistently effective treatment of TD. As such, attention should be paid to its prevention and close monitoring. Frequent assessment using standard rating scales, such as the Abnormal Involuntary Movement Scale (AIMS), will alert the clinician to the emergence of TD. Biweekly assessments for the first few months of treatment and then monthly assessment are indicated in the elderly. Because the likelihood of withdrawal-emergent dyskinesia increases with age, assessment for TD should continue for several months after an antipsychotic drug is discontinued. Proactive strategies have been used successfully in some patients, including adjunctive therapy with tocopherol, GABAergic agents (e.g., valproic acid, β-adrenergic antagonists (e.g., propranolol), and α-adrenergic agonists (e.g., clonidine).

Orthostasis and Falls. Residents in LTCFs fall 3 times more often than geriatric people living in the community. Orthostatic hypotension increases in frequency with age and commonly is thought to be the cause of many falls. However, gait instability because of sedation or untreated psychosis also may be a significant contributor to the patient's risk. Gait disturbances related to the sedating effects of certain psychotropics have long been identified as a significant risk factor for falls in elderly patients. In 2001, the American Geriatrics Society Panel on Falls in Older Persons noted that there was a consistent association between psychotropic drugs (antipsychotic drugs, benzodiazepines, and antidepressants) and falls. For this reason, low-potency conventional antipsychotic drugs and some of the atypical agents (e.g., clozapine) should be avoided in the elderly. Choosing an antipsychotic drug with less anticholinergic properties is an important consideration. The link between psychotic symptoms and falls in the elderly was highlighted in one study in which researchers examined the incidence of several adverse events, including falls, in patients with dementia who received placebo or risperidone at various dosages. Those taking 1 mg/day of risperidone had a significantly lower risk of falling (12.8%) than those receiving placebo (20.2%), suggesting that the incidence of falls can be reduced by appropriately treating the patient's underlying BPSD.

Several studies have looked at frequency of falls and the relationship to antipsychotic drug therapy. Research comparing fall frequency of patients with dementia taking either risperidone or placebo to treat agitation and psychosis found that those taking a therapeutic dose of risperidone fell almost half as many times: 22.3% in the placebo group versus 12.7% in the risperidone 1 mg/day group. A 6-month observational study compared risperidone, up to 2 mg/day, and olanzapine 10 mg/day in 360 patients with dementia without PD. At the 3-month midpoint, researchers found that 6.9% of patients treated with risperidone experienced a fall compared to 17.9% of the olanzapine group. As previously discussed, reports of greater adverse effects, such as somnolence and gait disturbances, may limit the use of olanzapine in these patients.

Anticholinergic and Antihistaminic Effects. Both peripheral and central anticholinergic effects can result in significant morbidity among older adults, most notably because of the increased risk of memory impairment and delirium. The antihistamine effects include sedation and weight gain. Although clinicians sometimes use these side effects to their advantage to improve sleep and lessen weight loss, the cost may be excessive daytime somnolence, dizziness, increased fall risk, and masking the underlying reasons for weight loss, such as dental problems, dysphagia, or gastrointestinal disease. Compared to risperidone and quetiapine, both clozapine and olanzapine demonstrate greater antihistaminic and anticholinergic effects.

Weight Gain. Weight gain in the elderly, such as that seen with the antidepressant mirtazapine, often is a desired adverse effect of a drug. However, antipsychotic drug-induced weight gain may serve as a risk factor for

increases in multiple medical comorbidities, including hypertension, type 2 diabetes mellitus, coronary artery disease, osteoarthritis, and gallbladder disease. In younger patients (younger than 65 years of age), antipsychotic agent-induced weight gain varies, depending on the atypical agent used. Clozapine and olanzapine cause the greatest degree of weight gain, with significantly less seen with quetiapine and risperidone, and negligible weight gain associated with aripiprazole an ziprazidone use. Unfortunately, there is a paucity of data on the prevalence of weight gain in the elderly with dementia. A recent study found no increase in weight in older patients with schizophrenia after 1 year of risperidone therapy. The mechanism of atypical agent-induced weight gain is not well understood and is only partially explained by such factors as increase in appetite, antihistamine effect, α_1-adrenergic antagonism, and increased leptin concentrations.

Type 2 Diabetes Mellitus. The risk of new-onset type 2 diabetes mellitus, diabetic ketoacidosis, or exacerbation of underlying diabetes mellitus has emerged as an important factor associated with several atypical antipsychotic drugs. This concern is highlighted by the fact that many cases of diabetes go undiagnosed for extended time periods despite the increased associated risks of myocardial infarction, stroke, retinopathy, neuropathy, and nephropathy. Case reports in the literature have discussed significantly greater numbers of cases of antipsychotic-induced diabetes mellitus with clozapine and olanzapine compared with risperidone and quetiapine. However, in a recent retrospective, cohort study, 2984 geriatric residents in LTCFs were examined for diabetes mellitus and concurrent atypical antipsychotic drug use, including risperidone, quetiapine, and olanzapine. The study suggested that older adults receiving these particular atypical antipsychotic agents were not at a greater risk of developing diabetes mellitus than patients who receive benzodiazepines, a drug class not associated with the development of diabetes. In addition, within the atypical antipsychotic drug class, the incidence of those who developed diabetes mellitus was similar among the three agents. The study was limited by only identifying patients receiving antidiabetic drug therapy and not those who were diet-controlled only.

Cerebrovascular Events. The risk of stroke increases significantly with age, to more than 12% among patients 80 years of age and older. However, results of four placebo-controlled, clinical trials examining the use of risperidone versus placebo in BPSD showed that patients experienced cerebrovascular adverse events (CVAEs) twice as often with risperidone (4%) compared to placebo (2%). The trials included 1200 patients with AD and vascular dementia who received treatment for 1–3 months.

Similarly, an analysis of five placebo-controlled, clinical trials in 1184 elderly patients with dementia showed a significantly higher incidence of stroke in patients treated with olanzapine than patients who received placebo (1.3% vs. 0.4%). Patients treated with olanzapine also had a significantly higher incidence of death of all types than the placebo group. Patients took a mean daily dosage of 4.4 mg/day for a total of 328 patient-years of exposure. Vascular/mixed dementia was the only risk factor identified as a statistically significant contributor to the risk of CVAEs in the patients treated with olanzapine.

In two randomized, comparative trials involving olanzapine, risperidone, and conventional agents, the incidence of CVAEs was similar in all groups. All patients reporting CVAEs in the olanzapine groups presented with one or more predisposing condition or characteristics known to be risk factors for CVAEs. Similar risk factors were observed in the other treatment groups as well.

Although these findings are interesting, they require replication. None of these studies was designed to determine the incidence or risk factors for strokes or CVAEs, and patient randomization in trials was not adjusted for preexisting risk factors for cerebrovascular disease, such as uncontrolled hypertension and atrial fibrillation.

Ongoing BPSD Clinical Trials with Antipsychotic Drugs

To address the limitations of clinical trials evaluating antipsychotic drugs (e.g., poor design, short treatment duration, and ideal conditions), a multicenter study has been designed and implemented to evaluate the effectiveness of antipsychotic drugs in broad patient populations and "real world" settings. The Clinical Antipsychotic Trial of Intervention Effectiveness was 36 weeks in duration and enrolled 450 outpatients with AD who are not residents of LTCFs, and who have a caregiver who lived with or visited the patient at least 8 hours/week. Enrollment ended in December 2003; however, results have not yet been presented.

The Clinical Antipsychotic Trial of Intervention Effectiveness, a controlled, randomized, efficacy trial, has features from both health services and effectiveness research studies. It evaluated tolerability and compliance, quality of life, functional activities, caregiver indices, service use, and costs. Assessments of overall effectiveness of the antipsychotic drugs were made using rating scales, such as the BPRS and NPI. This trial was unique in that physicians could adjust, switch, or discontinue drugs as they might have done in a clinical setting. Patients were followed over the course of the trial whether or not they were complying with the protocol. The corresponding data provided further follow-up and outcomes information and allow for intent-to-treat analyses.

In Phase I of this trial (lasting 12 weeks), patients were randomized to flexible-dose olanzapine, quetiapine, risperidone, or placebo. Patients were kept in Phase I for a minimum of 2 weeks to determine whether the drug is having an effect. Patients with successful treatment response were maintained in this phase for the duration of the study. Patients with unsuccessful treatment response to Phase I proceed to Phase II, where they are randomized to one of the other treatment drugs or citalopram. Treatment responders may be maintained in this phase for the duration of the study. Patients whose symptoms do not respond well in Phase II or do not wish to continue in a double-blinded trial any longer could proceed to Phase III of the trial, in which they are randomly assigned in an open-label fashion to one of the study drugs that they have not yet taken. There also was a Phase IV, in which clinicians treated patients with whichever psychotropic drug they felt was necessary.

Clinicians also can choose to discontinue psychotropic drugs entirely and monitor symptoms. The primary outcome was measured by the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). The ADCS-CGIS is a tool for obtaining an assessment of meaningful clinical change over time. It focuses on the clinician's observations of change in the patient's cognitive, functional, and behavioral performance from the beginning of the trial.

Antipsychotic Drug Discontinuation

Placebo-controlled trials of antipsychotic drugs show modest benefit of dementia symptoms over periods of 6–12 weeks, but there are no studies of longer duration. Several preliminary studies have reported that the level of behavioral symptoms remains the same or improves after antipsychotic drug discontinuation. Quality of life also is a key outcome parameter to consider because a cross-sectional study showed that the use of antipsychotic drugs was associated with a significant reduction in patient well-being. A retrospective study in a LTCF found that residents with appropriate indications for antipsychotic drug use, according to federal regulations, were significantly less likely to have their antipsychotic agent stopped. Among those individuals who had their antipsychotic drug discontinued or reduced in dose, only 20% had the agent subsequently resumed or the dose increased. A recent study involving 100 patients with dementia found that 67% of patients with stable behavior (NPI scores less than 14) who had been receiving more than 3 months of low-dose drug treatment (i.e., thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) experienced no deterioration of their behavioral symptoms when the antipsychotic drugs were abruptly discontinued. No evidence of improved quality of life was seen after antipsychotic drug discontinuation.

In the patient with delirium, the Expert Consensus Panel for Using Antipsychotic Agents in Older Patients guidelines suggest tapering the antipsychotic drug after 1 week. In the agitated individual with dementia, tapering should start after 3–6 months of treatment to determine the lowest effective maintenance dose. A patient with schizophrenia should be continued at the lowest effective dose indefinitely.

Alternatives to Antipsychotic Drugs

Benzodiazepines. Alternatives to the antipsychotic drugs include the use of benzodiazepines; SSRIs; β-adrenergic blocking agents; buspirone; cholinesterase inhibitors; and the anticonvulsants/mood stabilizers carbamazepine, valproic acid, and gabapentin. Data supporting the use of benzodiazepines for managing BPSD are limited, and adverse effects are of great concern. Benzodiazepine use in older adults carries the risk of further cognitive impairment, sedation, falls, and paradoxical behavioral disinhibition and withdrawal symptoms. Benzodiazepines should be reserved for patients with prominent features of anxiety, and antidepressants should be used in patients with a significant depressive component to their agitation. If used, benzodiazepines should be given at the lowest effective dose, and for a short time period until the primary pharmacotherapy begins to show effect. Intermediate-acting agents, such as lorazepam and oxazepam, are preferred, although clonazepam improved BPSD in a retrospective, consecutive case series of hospitalized patients with dementia who received a mean dosage of 1.2 mg/day for 2 weeks.

Buspirone. There is modest evidence in the literature supporting the use of buspirone, a nonbenzodiazepine anxiolytic with partial 5-HT_{1A}-agonist effects. In two open trials of 26 patients with BPSD, buspirone in doses of 15–60 mg/day was given along with psychotropics, if necessary. About one-half of the patients showed improvement.

Mood Stabilizers. Mood stabilizers have been used for BPSD since the 1980s, when case reports indicated that they were effective for behavioral dyscontrol across a wide variety of disorders, from traumatic brain injury to dementia. It is estimated that 50–67% of patients with dementia may benefit from mood stabilizers. This drug class may be particularly effective in treating symptoms of lability, impulsivity, and aggression. They have been used both as monotherapy and as augmentation to an antipsychotic drug if psychosis is present.

Carbamazepine. Both in uncontrolled and two placebo-controlled studies carbamazepine decreased target symptoms and total BPRS scores when given at doses of about 300 mg/day. In one study, researchers found that patients treated with carbamazepine experienced a dramatic decrease in agitation and hostility as well as a decrease in demand on staff time because of agitation. This was a 6-week, randomized, multisite, parallel-group study where 51 patients with possible or probable AD were given carbamazepine 100 mg/day. The dosage was increased until a serum concentration of 5–8 mcg/ml was achieved. Primary outcome measures were the BPRS and CGI scale, and researchers reported that in both measures, 75% of patients showed significant improvement compared to 25% of patients who received placebo. An acceptable target plasma concentration, about 5 mcg/ml, is lower than that for seizure disorders. Carbamazepine carries the risk of drug-drug interactions and an adverse effect profile that includes rash, ataxia, sedation, hematological abnormalities, electrolyte disturbances, and hepatic dysfunction.

Divalproex Sodium. Divalproex sodium (valproate and valproic acid) was shown in several clinical trials to decrease agitation compared to placebo. To date, there have been 16 case reports, chart reviews, or case series in patients with dementia. These reports led to two placebo-controlled studies. In one of these, the efficacy, tolerability, and safety of divalproex sodium (mean dosage = 826 mg/day) was assessed in a 6-week, randomized, double-blind, placebo-controlled study of 56 patients with probable or possible AD, vascular dementia, or mixed dementia. Results indicated that 68% of patients experienced reduced agitation compared with 52% of patients given placebo. Although there was a large placebo effect in this study, divalproex sodium's effect was thought to be equivalent to that of carbamazepine. The most common adverse effects of divalproex sodium are somnolence and falls. Other effects include weight gain, alopecia, hepatic dysfunction, thrombocytopenia, hyperammonemia, and pancreatitis. As with carbamazepine, therapeutic concentrations often do not

correlate with those used for epilepsy, and the older patient may experience intolerable adverse effects if the dose is pushed upward. Trials have shown the usual dose range for dementia to be 375 to 1500 mg/day, with a target serum concentration of 40–80 mcg/ml. One option to reduce adverse effects and improve adherence is to use the extended-release forms of both carbamazepine and divalproex sodium. With regard to the latter agent, this dosage form was safe and tolerable in a 10-week, randomized, double-blind, outpatient study involving patients with AD.

Another potentially exciting benefit of divalproex sodium is its neuroprotective mechanism of action. In 1995, researchers first proposed the theory that treatment with this agent might reduce neuronal injury and the rate of disease progression in patients with AD. They suggested that divalproex sodium may achieve this effect by its ability to indirectly regulate many factors involved in cell survival pathways. Consequently, its potential neuroprotective mechanism currently is undergoing evaluation in clinical trials involving patients with dementia.

The ADCS is a 2-year, multicenter trial examining whether treatment with divalproex sodium can delay, attenuate, or prevent the emergence of agitation in patients who lack these features at baseline, before therapy.

A similar Phase III study currently recruiting patients is Valproate in Dementia, which is a randomized, placebo-controlled, double-blind, multicenter, 26-month trial of valproate therapy at a target dose of 10–12 mg/kg/day in 300 outpatients with mild to moderate AD. The purpose of this study is to determine whether valproate therapy delays the emergence of BPSD psychosis in outpatients with probable AD who have had no BPSD since the onset of illness. A secondary aim is to determine whether valproate therapy delays the progression of cognitive and functional measures of illness. If either of these trials demonstrates that the drug delays onset of psychopathology, treatment with valproate conceivably may delay institutionalization and have far-reaching implications in treating AD.

Gabapentin. The literature suggests that gabapentin also may have limited efficacy in treating BPSD. Case reports and open-label case series suggest mean effective dosages of 900 mg/day. The drug has a favorable adverse effect profile in the elderly and has other advantages over the other anticonvulsants, including lack of drug interactions and no need for serum concentration monitoring. Research currently is under way that will examine the effectiveness of gabapentin compared with risperidone therapy in BPSD. In a 12-week, randomized, double-blind, controlled trial, about 130 patients with AD will be randomized to either gabapentin or risperidone. The researchers hypothesize that patients in both treatment groups will manifest different overall decreases in ratings of BPSD. They anticipate that patients with higher psychosis ratings will manifest greater response to risperidone, whereas patients with high levels of affective lability will have greater response to gabapentin.

Cholinesterase Inhibitors. Cholinesterase inhibitors appear to inhibit BPSD in patients with AD either alone or in combination with antipsychotic drugs. In a double-blind, placebo-controlled trial, researchers determined the efficacy of donepezil on BPSD in 290 patients with moderate to severe AD. Patients received either 5 mg or 10 mg/day. The primary outcome measure was the NPI. At the end of 24 weeks, significant treatment improvements were noted in depression/dysphoria, anxiety, apathy/indifference, and irritability/lability in patients treated with donepezil compared with those treated with placebo. When patients who did not receive psychoactive drugs at baseline were analyzed separately, the NPI scores for the group treated with donepezil remained significantly improved.

The effects of rivastigmine on BPSD were assessed in 92 patients with LBD. The NPI was the primary outcome measure in a randomized, prospective, double-blind, placebo-controlled, exploratory study. Participants received rivastigmine for 20 weeks. Results revealed significant improvements in NPI scores in the patients treated with rivastigmine that lasted the duration of the study.

Galantamine also has provided behavioral benefit in patients with AD. A 5-month, placebo-controlled, double-blind study involving 978 patients with mild to moderate disease found significant benefit from galantamine as measured by the NPI. Patients received galantamine in a slow dose-escalation schedule of up to 8 weeks. Doses of 16 mg and 24 mg/day showed improvement, whereas doses of 8 mg/day showed no improvement.

Antidepressants. There is accumulating evidence that antidepressants are effective in reducing BPSD. Several case reports and open-label studies have reported antiagitation efficacy with trazodone, a serotonergic antidepressant with α_2-adrenergic blocking activity. Trazodone in doses of 150–400 mg/day has been associated with improvement in agitation and aggression in more than half the patients studied. Trazodone is equally as effective as haloperidol in reducing BPSD and has been shown to be superior to haloperidol in improving verbally aggressive behaviors.

In a randomized, double-blind, placebo-controlled trial involving 85 patients, citalopram 20 mg/day and perphenazine (mean dose = 6.5 mg/day) were equivalent in efficacy and better than placebo in reducing BPSD. Patients who were hospitalized acutely received either active drug or placebo for 17 days. The NPI measured changes in behavior and noted significant improvement with citalopram.

A Phase II, randomized, double-blind, parallel trial in which the safety and efficacy of citalopram is compared to that of risperidone in patients with BPSD currently is ongoing. About 100 patients will receive either citalopram or risperidone for up to 12 weeks. During the first 2 weeks of the study, participants are hospitalized to have their symptoms stabilized. After hospital discharge, they are transferred to a LTCF or a residential home and will continue the study drugs for up to 10 weeks. Side effects

Tariot PN, Loy R, Ryan JM, Porsteinsson A, Ismail S. Mood stabilizers in Alzheimer's disease: symptomatic and neuroprotective rationales. Adv Drug Deliv Rev 2002;54:1567–77.

and improvement will be assessed weekly for 6 weeks, then every 2 weeks for the remainder of the study.

Schizophrenia

Early-onset Versus Late-onset Disease

Currently, only 0.5% of patients older than 65 years of age have schizophrenia, although this number is expected to double throughout the next 30 years as the senior population increases in size. Historically, patients with schizophrenia had their life span shortened by institutionalization, drugs, suicide, and other factors such as lack of personal hygiene or self-care. Today's generation of people with schizophrenia have superior treatments available to them, are living in the community and must negotiate through a health care system that is not well suited to address their complex needs. Although most patients with schizophrenia develop the disease in the second or third decade of life, a minority of patients will have the disease first emerge during their middle or later years. The late onset occurs in 15–20% of older adults with the disease. Both early- and late-onset disease have similar risk factors and both sets of patients experience delusions, hallucinations, bizarre behavior, and thought disorder. About 10–15% of patients with early- and late-onset schizophrenia have first-degree relatives who have been diagnosed with the disorder. Both groups show the presence of gross structural abnormalities on cerebral magnetic resonance imaging (MRI), an overall pattern of neuropsychological deficits, and a positive response to antipsychotic drugs. However, several important distinctions have been seen between patients who are diagnosed with early-onset disease and late-onset disease. Some researchers hypothesize that these differences suggest that the latter type is a distinct subtype of schizophrenia. For example, men are more likely to be afflicted early in life, whereas women predominate among those who are diagnosed later. One theory for this finding is that estrogen may help delay the onset of psychosis until after menopause. Estrogen may act like an endogenous antipsychotic, masking symptoms of schizophrenia in women who are otherwise predisposed to the disorder. Although the paranoid subtype of schizophrenia is more common among patients with late-onset disease, these patients are likely to experience milder negative symptoms, may do better on neuropsychological tests, are manageable on lower doses of antipsychotic drugs, and have a better prognosis than those who were diagnosed at a younger age.

Behavioral and Psychological Symptoms of Dementia Versus Schizophrenia Symptoms

Symptoms of psychosis in AD contrast with those of schizophrenia in many ways. Psychosis in AD is much more common, with symptoms usually manifesting as delusions and hallucinations. The delusions in AD typically are paranoid in type, not bizarre, and simple in scope, whereas the hallucinations are more frequently visual than auditory. Delusions in schizophrenia, on the other hand, usually are complex and bizarre, and hallucinations are auditory rather than visual. Schneiderian first rank symptoms, such as hearing multiple voices talking to one another or running a commentary on the patient's actions, are common occurrences in schizophrenia but rare in patients with AD. Studies demonstrate that computed tomography (CT) scans or MRIs of the brains of patients with late-onset disease do not demonstrate the presence of strokes, tumors, or other abnormalities that could account for the development of psychosis. Caregiver agnosia is frequent in psychosis of AD but uncommon or rare with schizophrenia. Although psychosis and depression may coexist in a patient with AD, active suicidal ideation is rare. About 50% of patients with schizophrenia attempt suicide, with 10% being successful. Past history of psychotic episodes is rare with AD but common in geriatric patients with schizophrenia. Unlike the prognosis of AD, the long-term course of schizophrenia typically is stable, and although complete symptomatic remission is rare, it may occur. One researcher has described schizophrenia as being a form of static encephalopathy rather than a dementing disorder. Long-term studies found that 50–67% of patients with schizophrenia show improvement in functioning and psychopathology after living with the disorder for 20 years or more. In one study, 30% of older outpatients had been employed at least part time since the onset of psychosis, and 73% were living in the community setting. However, about 20% of patients with schizophrenia have poor outcomes with respect to cognitive deficits and psychopathology. This neurodegenerative process contrasts with early-onset schizophrenia in that the latter disorder is characterized by neurodevelopmental origins. By the sixth decade of life, these patients may have cognitive deficits equivalent to those caused by moderate or severe dementia. Even among higher functioning patients with schizophrenia, about two-thirds will have some level of cognitive deficits early in the disorder. With age, these deficits worsen, resulting in impairment equivalent to that seen with mild dementia. Geriatric patients with schizophrenia who develop a progressive dementia and patients with neurodegenerative disease who become psychotic are at high risk for poor outcomes and permanent institutionalization.

Treatment Issues

Antipsychotic drugs offer the most effective treatment for patients of all ages with schizophrenia. Similar to treatment of BPSD, the atypical agents are considered first-line therapy. Treatment regimens are relatively similar to those seen with BPSD, with a few distinctions. In AD, as previously discussed, psychotic symptoms tend to disappear as the underlying neuropathology advances. As a result, the overall duration of necessary antipsychotic drug therapy to control and prevent relapses is much shorter in patients with AD than in those with schizophrenia. Maintenance doses of antipsychotic drugs required for patients with AD with BPSD are considerably lower than those prescribed for geriatric patients with schizophrenia. The average optimal daily dose of an antipsychotic drug in geriatric patients with

Palmer BW, McClure FS, Jeste DV. Schizophrenia in late life: findings challenge traditional concepts. Harv Rev Psychiatry 2001;9:51–8.

schizophrenia is 40–60% of the dose used for younger adults with schizophrenia; patients with AD require 15–25% of the dose used for a younger adult. Trial-based evidence to guide treatment of late-onset schizophrenia is extremely limited; therefore, recommendations are made based on clinical judgment. Expert Consensus Panel for Using Antipsychotic Agents in Older Patients guidelines recommend risperidone 1.25–3.5 mg/day, olanzapine 7.5–15 mg/day, quetiapine 100–300 mg/day, and aripiprazole 15–30 mg/day. True antipsychotic drug effects are obtained after weeks of treatment, during which signs of hallucinations, delusions, and thought disorders may subside. If the expected remission of symptoms does not start within 6 weeks and there are no disturbing adverse effects, higher doses can be used for a limited time, even though the proportion of responders decreases with increasing doses. Maintenance treatment administered at a dose lower than the acutely effective dose markedly reduces relapse rate.

There are several challenges commonly encountered when managing the geriatric patient with schizophrenia. For example, movement disorders are more common in older patients with schizophrenia as opposed to their younger counterparts. Movement disorders are associated with impairments in various activities of daily living (ADL); thus, it is important to treat any drug-induced movement disorder as soon as it arises. In most cases, the cause is a conventional antipsychotic agent. The reasonable option is to discontinue the offending drug and treat with an atypical agent.

Several medical conditions (e.g., diabetes mellitus, cardiovascular disease, and some cancers) are more common in patients with schizophrenia than in patients without the disorder. A cascading effect of risk factors in older patients with schizophrenia engendered by their mental disorder, its treatment, and their lifestyles (e.g., smoking, unhealthy diet, and sedentary behavior) make them especially vulnerable to comorbid medical diseases. Still, the access to health care of the older patient with schizophrenia is comparable to the elderly patient without schizophrenia. This scenario differs from younger patients with schizophrenia, whose physical health is substantially worse than that of their peers without schizophrenia. Older patients with schizophrenia have access to more services than younger patients because they typically receive coverage from government programs. But older patients still face a multitude of impediments to health care, such as clinicians and health systems ill-prepared to deal with individuals who have a mixture of schizophrenia, cognitive deficits, advanced age, numerous physical problems, and a paucity of economic and social support.

Psychosocial therapy is a useful adjunct to antipsychotic drugs. Cognitive therapy, training in social skills, and supportive psychotherapy also are valuable to the patient and family. Cognitive behavior therapy and social skills can improve functioning, disease management, and mood disorder symptoms. Research also suggests that environmental modifications may alleviate stress. Structured activities and social contact, such as outings and exercise sessions, may benefit older patients with psychosis. Health care providers may assist in helping family members become involved with support or advocacy organizations.

Bipolar Disorder

The overall prevalence of bipolar disorder is difficult to determine in the geriatric population because it is an especially neglected and understudied area. Some researchers found that 5–10% of patients presenting with mood disorders had manic or hypomanic symptoms. Others found that the prevalence of bipolar disorder in older patients admitted to state facilities was between 4% and 5%. Late-onset bipolar disorder can occur after 50 years of age, and is more likely to be associated with comorbid medical conditions, drugs, and neurological disorders, such as cerebrovascular events. Older geriatric patients experiencing mania typically do not have a personal or family history of affective disorders. In addition, they seldom display the euphoria or elated mood characteristic of younger adults. Instead, there is a clear symptom overlap between dementia and mania, with patients likely to appear irritable, angry, paranoid, impulsive, disorganized, and psychotic. Bipolar disorder affects men and women equally in early life, but by late life, mania is more common in women. When a geriatric patient with bipolar disorder becomes agitated, it significantly increases the caregiver burden and often is the main reason for long-term care placement. Bipolar disorder also is associated with an increased mortality in this population, partially because of a higher suicide rate.

It is believed that as patients mature, so does their bipolar disorder, in that, they experience more depressions and fewer manias. However, older patients often have more frequent episodes of mania and depression, with a longer duration of symptoms than their younger counterparts. Episodes may become more refractory to treatment. The geriatric patient with bipolar disorder who develops increasing medical problems may become less stable, less adherent with drug therapy, and more prone to episodes of rapid cycling or mixed states of both mania and depression.

Treatment

As in younger patients, pharmacotherapy is the mainstay of treatment. However, because evidence-based strategies for managing mania in late life are lacking, current recommendations originate from controlled trials involving younger patients and uncontrolled studies and case reports involving older patients. The limited available data suggest that there are age-related modifying factors that significantly impact treatment. These factors are represented clearly when discussing the use of lithium in this population.

Sajatovic M. Treatment of bipolar disorder in older adults. Int J Geriatr Psychiatry 2002;17:865–73.

Lithium

Geriatric patients are much more susceptible to dehydration, renal impairment and the adverse effects associated with lithium (e.g., mental slowing, ataxia, tremor, renal dysfunction, and edema). As discussed in the Drug Handling section, lithium pharmacokinetics are significantly altered with aging. The frequency of acute lithium toxicity appears to be about 11–23% for geriatric patients. Lithium toxicity may occur not only at the time of drug initiation, but also in geriatric patients who have apparently tolerated lithium well for many years. Factors that may predispose to the sudden onset of toxicity in lithium-maintained patients include addition of new drugs or changes in medical status, such as dehydration. When lithium is used in a geriatric patient, the general consensus is that the usual starting dose should be reduced by 33–50%, depending on age and health status. Typical starting dosages are 150–300 mg/day with gradual titration to maintenance serum concentrations over 1 week. Target concentrations remain controversial, with some clinicians suggesting a range of 0.4 mEq/L to 0.7 mEq/L, whereas others report optimal outcomes occurring with maintenance serum concentrations greater than 0.8 mEq/L and less than 1 mEq/L. Concentrations above 1 mEq/L are associated with toxicity which manifests as nausea, apathy, lethargy, muscle weakness, and irritability and, therefore, should be avoided. Slow-release lithium may be preferred for elderly patients because of lower peak concentrations and decreased gastrointestinal upset. The decision to use lithium depends on the individual patient. Geriatric patients with classic mania and minimal neurological impairment may receive better results from lithium than anticonvulsant drugs. Elderly patients with mixed mania appear to do equally well on lithium or valproic acid. Bipolar disorder because of dementing factors is considered less responsive to lithium.

Anticonvulsants

Anticonvulsants, such as carbamazepine and divalproex sodium, are increasingly being considered as first-line treatment in geriatric bipolar disorder, but they are used at lower initial doses and titrated at slower increments to reach the target dose. Divalproex sodium response has been correlated with older age, increased severity of manic symptoms, neurological impairment, dysphoria, and history of lithium nonresponsiveness. Typical starting doses are 125–250 mg/day with gradual increases every 2–5 days to achieve maintenance serum concentrations. The suggested therapeutic range for divalproex sodium treatment of mania is about 60–90 mcg/ml.

In the elderly, carbamazepine is initiated at 100 mg 1–2 times/day and titrated to a typical dosing range of 400 to 800 mg/day. Target serum concentrations typically are 6–12 mcg/ml but are not tolerated by some elderly patients. The side effect and drug-drug interaction profile of carbamazepine limits its use in this disorder. Newer anticonvulsants (e.g., lamotrigine) have not been systematically studied in geriatric patients.

Antipsychotic Drugs

Antipsychotic drugs have been used to treat acute mania to help stabilize symptoms, and to reduce concurrent psychotic features. Information on the use of atypical drugs to manage bipolar disorder is accumulating rapidly, but data specific to older adults remain limited. Studies have been open-label or retrospective in design. In general, the atypical drug is dosed at 50–70% of the total daily dose typically used in younger patients. Dosing must take into account age and medical comorbidities. Data suggest that geriatric patients with bipolar disorder receive a mean dose of 1.6–3.8 mg/day of risperidone, 16 mg/day of olanzapine, 100 mg/day of quetiapine, and 25–112.5 mg/day of clozapine. Similar to that seen in patients with dementia, geriatric patients with bipolar disorder are at greater risk for side effects from these drugs than younger patients. For example, data suggest that the elderly are at greater risk for agranulocytosis from clozapine than the younger patient.

Antidepressants

When antidepressants are required to treat more severe bipolar depression, general recommendations are to use the newer agents, such as SSRIs, bupropion, and venlafaxine. Some elderly will obtain antidepressant effects from lithium, as well as the anticonvulsant lamotrigine. Stimulants, such as methylphenidate, also may have modest efficacy in geriatric mood disorder, but precipitation of mania and psychosis is always a concern.

Combination Therapy

Combination treatment with two or more drugs is more common in the clinical treatment of bipolar disorder than is monotherapy. In the geriatric patient with bipolar disorder, polypharmacy is common, as it is in younger patients. Drugs may have synergistic effects and superior outcomes than are possible with monotherapy have been reported with the use of multiple drugs. One example is the use of low-dose lithium (serum concentrations of about 0.43 mEq/L) with divalproex sodium that has led to a dramatic improvement in clinical course. Still, the use of combination therapy has not been well studied, and data are especially lacking for the elderly population.

Other

Benzodiazepines, as previously discussed, should be used with caution and only for a limited time in the elderly. For patients not responding to drug therapy, electroconvulsive therapy (ECT) has been highly effective in treating acute mania. An advantage of ECT is rapid response, particularly in patients with acute mania. The rapid effect of ECT may offer particular advantages for elderly people whose behavioral symptoms jeopardize physical state. An important issue for elderly patients with bipolar disorder is determination of the optimal ECT method. Although bilateral electrode placement may be more effective in mania, unilateral placement may be associated with less acute cognitive disturbance.

Psychosocial Therapy

Psychosocial treatment and support is underused for treating geriatric patients with bipolar disorder, but can greatly benefit them. Often, older people have exhausted their resources and have minimal family support. Compared

to geriatric patients with depression, geriatric patients with bipolar disorder use more hospital-based mental health support services and fewer psychotherapy services. It has been suggested that specialized services and interventions may be necessary to effectively treat geriatric patients with bipolar disorder. Referrals to services for older adults offer significant chances for stability and reduce the need for hospitalization.

Alcohol Abuse

Substance abuse in the elderly involves mainly alcohol and tobacco. Abuse of street drugs such as cocaine is rare in this age group, but all patients should be questioned about illicit drug use. In community samples, alcoholism affects up to 17% of elderly individuals. Many of these are covert drinkers, who drink small amounts on a daily basis, but do not receive attention because they do not work, do not drive, and live alone. The alcohol-abusing geriatric patient most likely presents as an unmarried man with no close friends, a lifelong drinking history, and a positive tobacco use history. Given the age-associated pharmacokinetics and pharmacodynamic changes previously discussed, even a small daily amount of alcohol consumption can have significant implications, especially when combined with other CNS depressants. Elderly alcoholics often suffer from numerous comorbidities, including hypertension, cardiomyopathy, liver disease, pancreatitis, dementia, peripheral neuropathy, gastrointestinal bleeding, anxiety disorder, and major depression. In addition, they are predisposed to falls, hip fractures, and motor vehicle accidents.

Screening for alcoholism in this population is easily accomplished by asking two simple questions, “When was your last drink?” and “Have you ever had a drinking problem?” Positive responses of “less than 24 hours ago” and “yes” have been found to have a 92% sensitivity.

Treatment of geriatric alcohol dependence, while striving for complete abstinence, is often an unattainable goal, especially given the extended drinking history of these patients. However, simple interventions, such as physician counseling, have been associated with a significant decrease in alcohol consumption among hospitalized and clinic geriatric patients. Other useful non-pharmacological interventions include recovery group meetings, such as Alcoholics Anonymous. Regular attendance, difficult for the geriatric patient with transportation issues, usually is required to maintain abstinence. Another effective intervention involves an ongoing one-on-one relationship with a supportive family member, friend, or sponsor. There is limited evidence that biofeedback may reduce alcohol consumption in detoxified alcohol abusers. Other behavioral and cognitive therapies also may be used as adjuncts.

Pharmacological therapies for alcohol dependence include naltrexone, disulfiram, the SSRIs, and possibly ondansetron and buspirone. Consensus statements and general literature reviews provide little evidence for the effectiveness of pharmacological interventions for geriatric alcohol abuse. Naltrexone and disulfiram are limited by low patient acceptance and compliance. The SSRIs may reduce cravings during the first few weeks of treatment, but these effects may not be sustained. Ondansetron and buspirone have reduced consumption and cravings in younger patients; however, they have not been studied in those older than 65 years. If these drugs are used, they should always be administered in conjunction with an appropriate non-pharmacological intervention.

Attention-deficit Hyperactivity Disorder

For many years, attention-deficit hyperactivity disorder (ADHD) was known as a disorder of childhood and adolescence. It is now widely acknowledged that ADHD persists well into adulthood, causing the patient to experience continuing distress and impairment in social and occupational functioning. It has been estimated that 3–4% of the adult population suffers some ADHD symptoms, with a men to women ratio of 3:1. The major characteristics of the disorder, even into later life, include poor attention, impulsivity, and hyperactivity. Family relationships may have been damaged by the behaviors, often attributed to being willful or spiteful. The learning problems associated with the disorder create significant distress and disruption, and the associated features of poor self-esteem, feelings of failure, and inability to complete tasks may have lifelong consequences. Today’s geriatric patients were raised and educated in an era when ADHD was largely unrecognized. Consequently, the prevalence of ADHD in adulthood is difficult to establish. The geriatric patient with ADHD also may have spent years treated with multiple courses of drugs and therapies. An older adult with ADHD is likely to have suffered from difficulties in employment, maintaining relationships, and in performing tasks that require constant attention, such as driving a car. Comorbid psychiatric disorders, such as mood disorders, anxiety disorders, and substance abuse and dependence, are common.

Treatment strategies for adult ADHD have focused on drug management, including stimulants, antidepressants, and antihypertensive drugs. Stimulants are safe and effective. Antidepressants, such as bupropion, venlafaxine, and TCAs, also have been used successfully. Atomoxetine, a presynaptic norepinephrine inhibitor with antidepressant properties, also has had positive results in adult ADHD. Antihypertensive drugs, such as clonidine and guanfacine, have been used in younger patients but are poorly tolerated in the geriatric population. Other forms of therapy include psychotherapy, marital and family therapy, and cognitive behavioral therapy.

Depression

Epidemiology

Depression is among the most common mental illnesses affecting the elderly and accounts for about one-half of all psychiatric hospitalizations in this age group. The prevalence of diagnosable major depression in community-dwelling patients is estimated at about 1–3%,

which is lower than that of younger patients. However, about one-third of elderly patients have depressive symptoms that do not qualify for a diagnosis of major depressive disorder. The prevalence of major depression in LTCFs and acute care settings is significantly higher, with about 15% and 35% of patients, respectively, experiencing diagnosable depression. The highest risk group seems to be those older than 85 years of age.

It is perhaps surprising that the rates of depression are not higher in geriatric patients. In addition to experiencing the physiological changes related to aging, the elderly often are facing medical illness or even end-of-life issues; a loss of independence; dwindling financial resources; and the deaths of spouses, siblings, friends, and even their children. Similar to younger age groups, depression is more common in elderly women than men, but the gap is narrower. Other identified risk factors include poor social support systems and cognitive impairment.

Depression and Outcomes

Depression in the elderly is associated with increased morbidity and mortality, decreased quality of life, and increased use of health care services. Of particular concern is the high suicide rate in elderly patients with depression, which is about twice that of younger groups. About 75% of elderly people visited a primary care physician in the month before they committed suicide, which indicates that these people could have been treated. Suicide risk is greatest in patients with concomitant medical illness and alcohol users. Men account for about 80% of suicides in the elderly; Caucasian men in particular are at high risk.

Diagnosis

General Issues and Symptomatology

Despite increased awareness and availability of effective treatment, it is estimated that only one in three geriatric depression sufferers is accurately diagnosed. The DSM-IV does not establish specific diagnostic criteria for depression in the elderly; thus, this group is diagnosed the same as younger patients. This is unfortunate as the symptomatology and clinical presentation can be considerably different in older patients with depression. Specifically, to be diagnosed with major depression according to DSM-IV criteria, patients must experience a depressed mood or a loss of interest in activities. The depressed mood in particular is less common in the elderly, who often present with nonspecific symptoms, including decreased self-care, anhedonia, irritability, psychomotor retardation, social withdrawal, insomnia or hypersomnia, loss of appetite, and weight loss. Somatic complaints and anxiety also are common and deserve further discussion.

Because of the greater likelihood of medical illness in elderly patients, physical complaints are common and may lead to lengthy diagnostic workups when in actuality depression is the true cause. Patients with numerous somatic complaints, such as unexplained pain or fatigue, or who experience an increased use of health services should receive more intensive screening for depression. Even if depression is not the cause of the symptoms, treating concomitant depression in medically ill patients often leads to improved outcomes. Furthermore, up to 80% of older patients with anxiety symptoms also have signs and symptoms of depression, so screening this group for depressive symptoms is critically important.

Although patients with anxiety symptoms or many somatic complaints deserve closer attention, most experts recommend routine screening of all elderly patients for depression. This recommendation is because spontaneous reporting of mood disturbances is less common than in younger populations. Men tend to be more reluctant to report a depressed mood than women. However, despite the fact that depressed elderly patients are less likely to report symptoms than depressed younger patients, a one-item screening test consisting of the question, “Do you often feel sad or depressed?” has been almost as sensitive and specific as much more involved screening tools.

Screening and Diagnostic Tools

A commonly used screening tool and rating scale is the Geriatric Depression Scale (GDS). This validated, self-administered instrument contains 30 questions requiring “yes” or “no” answers and takes about 5–10 minutes for patients to complete. It was developed specifically for use in the elderly and purposefully contains fewer questions about somatic symptoms than the more general screening tools. This increases the tool’s specificity, as somatic complaints because of concomitant illness are quite common in the elderly. Although the widely used score of 6 or more depressive symptoms is not diagnostic for depression, it suggests mood problems severe enough to warrant further investigation and management. A shorter version (five questions) of the GDS was developed in 1986 and it has been as effective as the 30-item GDS, with a marked reduction in administrative time. One limitation to using the GDS is in the patient with dementia, where its sensitivity is questionable.

Other depression scales relevant to the geriatric population are the Beck Depression Inventory (BDI) and the Center for Epidemiological Studies-Depression (CES-D) scale. Both contain more items regarding somatic complaints than the GDS and are, therefore, less favored for use in the elderly. However, the BDI and CES-D often are quicker to administer. In addition to assisting with diagnosis, depression assessment tools are useful in tracking response to therapy over time and monitoring for relapse.

Diagnostic Issues: Life Events and Underdiagnosis

Major depression should never be considered a part of normal aging. Although it is sometimes difficult to differentiate between normal grief reactions and depression, as a general rule, clinicians should have a fairly low threshold for initiating therapy in patients with depressive symptoms. Antidepressant therapy alone or in combination with interpersonal therapy reduces depressive signs and symptoms in patients with “reactive depression” after a traumatic life event, such as a death of a loved one or loss of a home because of diminished abilities to perform ADL.

Despite their high prevalence, depressive symptoms often are underdiagnosed and undertreated in elderly patients. Many reasons for this exist, including blaming concomitant medical conditions for symptoms of depression and the false assumption that depression is a normal part of

aging. Of interest, some evidence exists that underdiagnosis may be more prevalent in institutional settings than in the community.

Depression and Dementia

Diagnostic Issues

Patients with decreased cognitive function present a special problem in depression screening and diagnosis. The validity of the previously discussed screening tools becomes questionable when a patient has an MMSE score of less than 15. Interviewer-administered tools, such as the Cornell Scale for Depression in Dementia (CSDD), a 19-item scale including input from both the patient and the primary caregiver, and the Hamilton Rating Scale for Depression (HAM-D), are useful in this situation. The CSDD appears to be more reliable than HAM-D, and each takes about 20–30 minutes to complete as opposed to the 5–10 minutes typically required for the GDS.

Pseudodementia

Clinicians often see patients whose cognitive decline is felt to be because of, rather than a cause of, their depressive symptoms. This has been termed pseudodementia, and intensive neuropsychiatric testing often is useful for differentiating between dementia and depression. These patients often reply to MMSE questions by saying, "I do not know" or "I cannot remember," rather than giving an incorrect response. Recent studies have shown that as a group, elderly depressed patients show a small improvement in overall cognitive functioning after antidepressant treatment. However, if the patients are depressed and cognitively impaired at baseline, they remain mildly impaired despite treatment with antidepressant therapy. Up to 20% of patients with pseudodementia develop dementia later in life. Thus, it appears that in most patients, cognitive loss and depression should be treated as two separate entities rather than one and that pseudodementia may be in reality predementia.

Depression in Established Dementia

Depressive symptoms also are common in patients with an established diagnosis of dementia, with up to 50% of those with AD being affected. Rates of depression in vascular dementia and LBD are at least as high. Comorbidity leads to increased likelihood of long-term care admission, excess disability, increased caregiver burden, and increased mortality. Though no data exist specifically concerning mood, the acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, have had small but measurable beneficial effects on noncognitive symptoms in patients with AD.

Drug-induced Depression

The elderly use significantly more drugs than younger patients and are more likely to experience adverse reactions from them. Therefore, it is crucial that elderly patients who exhibit signs and symptoms of depression undergo a thorough review of their drug regimens to identify possible drug-related depression.

Unfortunately, the literature is unclear on the drugs that are most likely to cause depression and the frequency of drug-induced depression. The β-adrenergic antagonists were long blamed for depression, but a recent literature review did not support the association. Furthermore, this review found that the more lipid-soluble agents, such as propranolol, that easily penetrate the blood-brain barrier, were no more likely to lead to depression than water-soluble drugs, such as atenolol. Other antihypertensive drugs that have been associated with depression include calcium channel blockers, angiotensin-converting enzyme inhibitors, methyldopa, reserpine, and clonidine.

Other agents that have been associated with depression include tamoxifen, interferon alfa, progesterone, corticosteroids, digoxin, and benzodiazepines. When assessing for drug-induced depression, it seems reasonable to assess the temporal relationship between drug initiation and the onset of symptoms, though a delayed presentation is not uncommon. The risk versus benefit of stopping or adjusting any particular agent must be determined on an individual patient basis.

Depression and Functioning

Depression is associated with decreased functional ability in elderly patients. The loss of functional ability over time in depressed elderly patients is comparable to that of patients with coronary heart disease, diabetes mellitus, or arthritis. Depression also has been associated with poorer outcomes in rehabilitation settings. Because the main goal in caring for the older patient is to maintain functional ability and patient independence as long as possible, appropriate depression management has the potential to result in significant improvements in these areas.

Depression and Medical Illness

Because of the high rate of both medical illness and depression in the elderly population, the two frequently coexist. Historically, the high burden of disease was thought to be a cause of depression, but increasingly it is being realized that the opposite also is true; namely, depression leads to medical illness or at least to poorer outcomes in patients with preexisting medical illnesses. For example, the presence of depression has been identified as an independent risk factor for death after myocardial infarction or stroke. Therefore, identifying and treating

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depression in this population could significantly improve outcomes.

The elderly frequently experience diseases that can present with symptoms similar to depression, such as hypothyroidism, anemia, or electrolyte disorders. In addition, depression is common in many medical conditions, affecting up to one-half of those with PD or AD, 30% of those with cancer, and about 15% of those with myocardial infarction, rheumatoid arthritis, or diabetes mellitus.

Finally, the presence of concomitant medical illness makes pharmacotherapy for depression more difficult. Treatment of depression increases the complexity of therapy because of the potential for drug-drug and drug-disease interactions and adherence issues for patients already taking complex drug regimens.

Treatment of Geriatric Depression

General Points

Depression in geriatric patients usually is treated by generalist providers in primary care settings. Therefore, a great potential exists for pharmacists to positively influence the choice and monitoring of pharmacotherapeutic regimens. Maximizing the treatment of concomitant medical illness and discontinuing drugs that could be causing or worsening depression are rational first steps. Non-pharmacological methods, such as cognitive-behavioral or interpersonal therapy, alone or in combination with pharmacotherapy, are effective in elderly patients. Electroconvulsive therapy also is safe and effective, and may be of particular use in nonresponders to multiple drugs or those with severe or psychotic depression.

Most treatment studies have involved medically stable geriatric outpatients who do not have dementia and who are less than 80 years of age. There have been few studies involving very old people, patients with significant medical illnesses, or patients with dementia or other neurological problems. The findings of studies involving relatively healthy "young" elderly patients cannot necessarily be extrapolated to these special groups.

As in younger patients, the initial antidepressant drug chosen will result in a positive response in about one-half to two-thirds of geriatric patients. Little evidence exists that any drug or drug class is superior in efficacy. The choice of initial therapy often is made based on the patient's previous response to the drug, potential for drug-drug or drug-disease interactions, possible adverse events, adherence issues, and cost.

Because of changes in drug pharmacokinetics and pharmacodynamics often seen in the elderly, antidepressants usually should be started at one-half the recommended dose used in younger patients and increased slowly based on effectiveness and tolerance. The lower starting dose combined with the fact that elderly patients often respond to antidepressants more slowly than younger patients means it can take up to 8–12 weeks to see a therapeutic response. Underdosing is a common cause of treatment failure in geriatric depression, so pharmacists should help to monitor response to therapy and recommend dosage increases for patients who are tolerating a drug but have not experienced the desired response.

Adherence issues also are important in this age group. As previously discussed, complicated drug regimens, decreased sensation, loss of cognitive function, and financial burdens can contribute to poor adherence to prescribed therapy. Fortunately, most commonly used antidepressants are dosed once daily making adherence relatively straightforward.

Heterocyclic Antidepressants

Tricyclic Antidepressants

Tricyclic antidepressants, such as amitriptyline, doxepin, nortriptyline, and desipramine, have long been the standards of care for managing depression. The past 2 decades have seen the replacement of these agents as first-line therapy with newer, better tolerated classes of drugs. However, TCAs remain among the most well-studied antidepressant classes in the elderly. The secondary amine TCAs, nortriptyline and desipramine, have less anticholinergic, sedative, and orthostatic properties and, thus, are preferred in the elderly over the tertiary amines, amitriptyline, imipramine, and doxepin. Tricyclics are best avoided in patients with dementia because of the possibility that their anticholinergic effects may adversely affect cognition.

When used for their antidepressant effects, both nortriptyline and desipramine should be started at a dose of 10 mg/day and gradually increased to a maximum of 200 mg/day. Because they typically cause sedation, nighttime dosing is preferred; however, a minority of patients will experience activation with these agents. These agents could be considered for patients with severe melancholic depression and those with urge incontinence who would not be adversely affected by the central anticholinergic effects. An advantage of the TCAs is that serum concentration monitoring is feasible and can help assess adherence, determine the cause of somatic complaints after starting therapies, and ensure adequate dosing. The goal serum concentrations for nortriptyline and desipramine are 50 ng/ml or higher and 100 ng/ml or higher, respectively.

In addition to the risk of anticholinergic adverse effects, sedation, and orthostasis, other safety issues exist for the TCAs. Some have questioned their safety in patients with underlying cardiovascular disease because of the agents Vaughn-Williams class I antiarrhythmic properties. The TCAs also have a high potential for lethality in overdose, which is of concern given the high suicide rates in older patients. Despite these issues, the secondary amine TCAs are reasonable choices when multiple other drug classes have been ineffective.

Venlafaxine

Venlafaxine, a heterocyclic antidepressant, inhibits the reuptake of both norepinephrine and 5-HT. It typically is well tolerated by elderly patients and can be dosed once daily using the sustained-release form. The dose should be

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initiated at 37.5 mg/day and increased gradually to a target dose of 75–225 mg/day. This drug's main adverse effects are in the gastrointestinal tract and usually manifest as nausea or diarrhea. Sexual dysfunction, particularly anorgasmia, is sometimes observed. The agent also increases blood pressure in a dose-dependent manner, so caution should be used when the drug is given to patients with preexisting hypertension. The clinical significance of this phenomenon has been debated.

However, venlafaxine can be either activating or sedating. Because of its effects on norepinephrine, activation (insomnia and nervousness) is more common than sedation. Its FDA-approved labeling does not include the indication as treatment for generalized anxiety disorder (GAD).

Monoamine Oxidase Inhibitors

Because of the strict dietary requirements and potential drug-drug interactions of the monoamine oxidase inhibitors (MAOIs), such as tranylcypromine and phenelzine, their routine use in geriatric patients is discouraged. Their main place in therapy is for patients in whom treatment with other drug classes has not been successful. In most cases, however, even interventions such as ECT are preferred over MAOIs. An advantage of MAOIs is that they appear to have greater efficacy in treating depression with atypical symptom patterns such as overeating or oversleeping. Most generalists should defer the use of these agents to practitioners experienced and skilled in their use.

Selective Serotonin Reuptake Inhibitors

General Points. The SSRIs have become the mainstays of depression therapy in older patients. All SSRIs can be administered once daily and typically are well tolerated. Choice of drug usually is based on clinician preference and adverse drug effects, which as a class include headache, nausea, diarrhea, weight loss, nervousness or insomnia, tremor, sedation, sexual dysfunction (particularly anorgasmia), and discontinuation syndrome. An infrequent but potentially dangerous side effect is the syndrome of inappropriate secretion of antidiuretic hormone and hyponatremia. Virtually all cases of SSRI-induced hyponatremia have occurred in elderly people, usually within the first month after the start of therapy. The hyponatremia resolves once the SSRI is discontinued, but may recur if the patient starts taking the same or a different SSRI.

Epidemiological associations between SSRIs and gastrointestinal bleeding have been made in recent years. These agents may affect platelet function to a significant degree, but the clinical importance of this association is unknown. The antiplatelet effect may only occur during treatment with high doses or after long-term exposure to SSRIs. The SSRIs also have been associated with a decreased risk of myocardial infarction but are neutral in relationship to hemorrhagic and ischemic stroke, which again may be because of their antiplatelet properties. Selective serotonin reuptake inhibitors also appear to confer a fall and fracture risk similar to that seen with the TCAs.

Pharmacokinetically, the SSRIs have a flat dose-response curve, meaning that, for the majority of patients, increases beyond the minimum effective dose do not increase efficacy but can cause more side effects. Consistent with the flat dose-response curve, there is no relationship between plasma SSRI concentrations and clinical response. There have been few studies published that have determined the minimum effective dose of SSRIs in elderly people; therefore, dosing is guided by data obtained from studies involving younger people and the patient's clinical response to therapy.

All SSRIs should be avoided in combination with MAOIs, and all increase the risk of 5-HT syndrome when used concomitantly with other serotonergic drugs. The importance of drug interactions with the SSRIs has been debated for some time, as each is metabolized by various isoenzymes of the CYP system and inhibits them to different degrees. The most clinically significant CYP drug interactions include fluoxetine with carbamazepine, phenytoin, warfarin, or certain antipsychotic agents; sertraline with phenytoin or carbamazepine; and paroxetine with certain antipsychotic drugs. Even though the clinical significance of SSRI-induced drug interactions is unclear because of the high frequency of polypharmacy in elderly patients, the astute clinician will have a low threshold for considering this as a cause of an observed adverse drug reaction.

Citalopram and Escitalopram

Citalopram and its racemate, escitalopram, are neither particularly activating nor sedating, though some patients will experience anxiety initially and some will experience sedation. Both are useful for anxiety disorders and depression. Dosing of citalopram should start at 10 mg/day with a target dose of 20–40 mg/day, and the initial dose of escitalopram also is 10 mg with a target dose of 10–20 mg/day. Whether escitalopram offers any significant advantages over citalopram is unknown.

Fluoxetine

Fluoxetine was the first SSRI to be used in clinical practice. Its pharmacokinetics are unique among the class in that it has a relatively long half-life (4–6 days after chronic administration) and an even longer acting active metabolite, norfluoxetine (half-life of 4–16 days). Because of its long half-life, many clinicians do not feel that it is appropriate as first-line therapy in elderly patients and reserve it for those who fail other agents. However, it may be of use in patients who have difficulty adhering to their antidepressant drugs.

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Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. Circulation 2001;104:1894–8.

Fluoxetine is the most activating of the SSRIs, so nervousness, insomnia, and irritability are common when initiating therapy. It may be particularly useful in patients with significant psychomotor retardation. Despite its activating properties, fluoxetine is effective for treating anxiety once patients get through an initial adjustment period. The starting dose usually is 10 mg/day and the target dose is 20–40 mg/day.

Paroxetine

Paroxetine is the most sedating of the SSRIs and may be of particular use in patients with concomitant depression and anxiety. It also has the greatest anticholinergic properties among the class, with a binding affinity to muscarinic receptors similar to that of the TCA desipramine. Though adverse anticholinergic effects are rarely seen in the younger population, the drug may induce delirium in the geriatric patient with baseline cholinergic deficits. Paroxetine has a half-life of about 24 hours and has inactive metabolites. However, it exhibits nonlinear pharmacokinetics in the elderly so higher doses should be used with caution. For example, the steady-state plasma concentration of paroxetine is 6–14 times greater than what would be predicted on single-dose studies, indicating that paroxetine may inhibit its own clearance. The relatively short half-life, lack of active metabolites, and slight anticholinergic effects often are blamed for paroxetine's apparent greater likelihood to cause a discontinuation syndrome when it is stopped abruptly. The initial dose is 10 mg/day and the target dose is 20–40 mg/day. A controlled-release formulation also is available that is promoted as having fewer gastrointestinal adverse effects than the immediate-release version. The starting dose of paroxetine controlled-release is 12.5 mg/day and the target dose is 25–50 mg/day.

Sertraline

Sertraline is similar to citalopram and escitalopram in that it is neither particularly activating nor sedating, though patients may experience either. It has a half-life of 24–36 hours and an adverse effect profile similar to other SSRIs, though it is sometimes reported to have a slightly higher risk of gastrointestinal adverse events. Although not specifically performed in geriatric patients, recent results of the Sertraline Antidepressant Heart Attack Randomized Trial indicate that sertraline is safe and effective for treating comorbid depression in patients with recent myocardial infarction. The usual starting dose is 25 mg/day and the target dose is 50–100 mg/day; however, some patients may require larger doses.

Other Atypical Antidepressants

Bupropion

Despite its half-life of about 24 hours, bupropion usually is given 2 times/day as a sustained-release dosage form to minimize the high peak concentrations that have been associated with seizures. Bupropion is fairly activating, and nervousness and insomnia are common adverse effects. It is a reasonable choice for patients with significant psychomotor retardation, fatigue, or lack of motivation. Advantages include fewer sexual adverse effects than the SSRIs and apparent lack of cardiovascular effects, such as orthostatic hypotension, or cardiac conduction abnormalities. The usual starting dose is 100 mg/day in divided dosages, with a target dose of 200–300 mg/day in divided dosages. It is contraindicated in patients with a history of seizures or eating disorders. It also is a significant inhibitor of CYP2D6 and may result in clinically significant drug interactions when coprescribed with substrates of this isoenzyme.

Mirtazapine

Mirtazapine has emerged as an excellent choice in treating depression in certain geriatric patients. Data regarding its use in elderly patients were pooled from seven randomized, double-blind, placebo-controlled, multicenter trials. Mirtazapine was well tolerated, with tolerability and safety comparable to that seen in younger patients. Based on HAM-D scores, the response rate in geriatric patients receiving mirtazapine was comparable to those rates reported in younger patients with depression receiving the drug, as well as those seen in elderly patients receiving other antidepressants. It also is noteworthy that mirtazapine produced a 58% improvement from baseline in sleep disturbances and a 38% improvement from baseline in anxiety. Therefore, mirtazapine's sedating effects, particularly at lower doses, would be useful in patients with insomnia or with concomitant anxiety and depression. The drug also promotes weight gain and may be useful in patients with decreased nutritional intake and weight loss. The starting dose is 7.5 mg/day at bedtime and the target dose is 15–45 mg/day. Mirtazapine has some anticholinergic activity, but adverse effects from this are rarely encountered clinically. It has minimal gastrointestinal adverse effects and probably has fewer sexual side effects than SSRIs.

Nefazodone

Nefazodone, as with mirtazapine and paroxetine, is sedating and often is used when insomnia or anxiety is present in addition to depression. Recently, concerns about hepatotoxicity in one patient for every 250,000–300,000 patient-years of exposure has led to the pharmaceutical company withdrawing brand name Serzone from the market. However, the generic product will continue to be manufactured. The drug is not recommended for those with underlying liver abnormalities. Nefazodone also is a potent inhibitor of CYP3A4 and should be used cautiously in combination with drugs that are substrates of this enzyme. It should be initiated at 100 mg/day with a target dose of 300–600 mg/day in divided dosages.

Psychomotor Stimulants

In addition to or instead of stimulating antidepressants, such as fluoxetine, bupropion, or venlafaxine, psychomotor stimulants, such as methylphenidate or modafinil, can be useful in patients with significant lethargy, hypersomnia, or psychomotor retardation. Some evidence exists that methylphenidate is particularly useful in medically ill patients or those who are enrolled in rehabilitation

programs. A common dosage is 5 mg/day in the morning that is then increased every 3 days to a target dose of 15 mg in the morning and at noon. Amphetamine-like adverse effects, such as insomnia, anxiety, increased blood pressure, tachycardia, and palpitations, occasionally are seen, and for this reason some clinicians prefer modafinil. Modafinil agent has amphetamine-like properties, but the mechanism of action is not fully known and its adverse effect profile is similar to that of methylphenidate with the possible exception of no increase in mean heart rate or average blood pressure. The major advantage of using psychomotor stimulants is that they require less time to achieve a beneficial response, at least in terms of psychomotor function. Whether the stimulates have any antidepressant activity is still being debated.

Treatment Duration

Response to antidepressant drugs depends not only on dose but also on length of treatment. Response may occur later in elderly patients than in younger patients and requires at least 6–12 weeks of treatment. When treatment with antidepressant drugs is continued for at least 4 months after remission of depressive symptoms, the rate of relapse is about 20% compared with 50% among patients treated with placebo. Thus, any patient who responds to antidepressant drugs should continue taking a maintenance dose of the drug for at least 6–12 months for a first episode and 12–18 months for a recurrence. However, because the elderly are both more likely to experience relapse and to relapse more quickly, initial treatment durations of up to 24 months are not unreasonable. Maintenance therapy should be considered for any patient with a history of one or more episodes of major depression (especially if these occurred within the past 5 years) or who is otherwise at high risk of recurrence. One risk factor for recurrence is having the first episode of depression occur after 60 years of age. Therefore, some psychiatrists recommend that all elderly patients with major depression continue taking antidepressant drugs for at least 2 years after the remission of symptoms. Lifelong treatment should be considered for elderly patients who have had three or more episodes in their life. Reducing the dose of the antidepressant appears to increase the risk of relapse and recurrence, and there is now a consensus that patients should be maintained on the dose to which they responded. Up to 75% of elderly patients who remitted from an episode of depression and were maintained on full-dose antidepressant treatment remained free of relapse and recurrence when followed for 2 years. Patients who are stabilized on drugs should be followed on a regular basis (e.g., every 3 months) to monitor efficacy, side effects and adherence. The potential benefits of these extended treatment durations must be balanced against the risks of adverse drug reactions, drug-drug and drug-disease interactions, and the financial costs of long-term therapy.

Treatment of Dysthymia or Minor Depression

Few data exist regarding the optimal treatment of older patients with depressive symptoms who do not meet the criteria for a diagnosis of major depression. Most clinicians elect to treat these patients similarly to major depression, including appropriate pharmacotherapy and/or psychotherapy, if symptoms are sufficiently persistent and bothersome to warrant treatment.

Psychotic Depression

A minority of older patients with a diagnosis of major depression also will present with symptoms of psychosis, such as delusions or hallucinations. Treatment typically is similar to that of depression without psychosis; however, an atypical antipsychotic drug is used initially for about 6 months.

Augmentation Strategies

An initial trial of antidepressant drugs will be unsuccessful in thirty percent of elderly patients, so additional or alternative treatment may be required. Two major strategies exist: augmentation or substitution. Patients who respond partially to treatment or not at all can be managed in one of two ways: augmentation or substitution. The advantage of augmentation is that it does not require discontinuation of the original antidepressant; therefore, patients who partially responded to treatment are not put at risk of returning to their baseline severity of depression. Also, response may be faster with augmentation than with a trial of new antidepressant drugs. The disadvantage of augmentation, particularly in geriatric patients, is that the combination of drugs increases the risk of side effects and drug-drug interactions. Lithium occasionally is used as an augmentation strategy in older depressed patients who do not respond adequately to antidepressant therapy alone. Data also exist documenting a decreased rate of depression recurrence when lithium is used. Combination therapy with various antidepressants, such as an SSRI plus a TCA, bupropion, or mirtazapine, is more commonly used than lithium in patients for whom treatment has been unsuccessful, even though few data exist supporting this approach. An additional option is adding liothyronine in doses of 25–50 mcg/day to existing antidepressant therapy. Thyroid hormones are thought to modulate the activity of norepinephrine and 5-HT, as well as modulating their functioning of these receptors. The addition of thyroid hormone therapy has been reported to be effective in both euthyroid and hypothyroid patients.

Substitution

A second strategy for nonresponders is substitution, which involves changing from one antidepressant drug to another. There are virtually no data on antidepressant substitution in refractory depression that occurs in late life, so all data on antidepressant substitution has been extrapolated from research involving patients of mixed ages. As a general rule, switching to another antidepressant

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within the same class (e.g., from one TCA to another) is less effective than switching to an drug from another class. A possible exception to this rule is the patient for whom an SSRI as first-line treatment has been unsuccessful. Two open and uncontrolled studies in younger adult outpatients reported response rates of 50% and 63% after substitution with a second SSRI. These findings must be considered tentative but suggest that it may be reasonable to consider a second SSRI trial before switching to another class of antidepressant. Uncontrolled data suggest that venlafaxine may be particularly useful in patients who have not responded to other antidepressants. When switching antidepressants in elderly patients, it is advisable to withdraw the first agent gradually (e.g., over 1–2 weeks) before introducing the new drug. However, even with this gradual crossover the patient needs to be carefully monitored for the possible effects of drug-drug interactions.

Patient Education

Patients started on antidepressant therapy should know the name of the agent they will be taking, its purpose, and any instructions regarding ideal administration time, such as late in the day for sedating agents such as mirtazapine or earlier in the day for such activating agents as fluoxetine. Patients also should be informed of adverse effects that are common or serious, and what to do if they occur. Of particular importance is the typical delayed improvement in symptoms with antidepressant therapy; patients must be informed that it can take 8–12 weeks before the dose is titrated to its target and reaches its full therapeutic effect.

Anxiety

As with depression, anxiety symptoms are common in older patients and may be brought on or worsened by medical illness or stress from life events. Unfortunately, anxiety in the elderly is an area that has been poorly studied, and little evidence is available from randomized, controlled trials to help guide therapy. Most treatment recommendations come from clinical experience or extrapolation of results of clinical trials involving younger patients. Older patients with anxiety disorders are known to have an increased use of health services with a corresponding increase in the cost of care, and they experience decreased quality of life compared to those without anxiety states. Concomitant anxiety and depression also appear to increase the likelihood of suicide compared to depression without anxiety symptoms. Unlike depression, no specific rating scales exist for anxiety in older patients, and the Hamilton Rating Scale for Anxiety (HAM-A) is the most commonly used tool for assessing response to therapy in clinical trials.

Prevalence

Similar to depression, rates of anxiety disorders appear to be lower in older patients than in younger patients. They are more common in women than men and appear to be more frequent in institutionalized versus community-dwelling individuals. Overall, about 20% of older patients have clinically significant symptoms of one or more anxiety disorders.

The prevalence of GAD is estimated to be 4–7%. About 60–90% of those with GAD also have depressive symptoms, so antidepressant therapy is the mainstay of treatment for this disorder. Phobias affect 3–10% of older patients, with agoraphobia being the most common manifestation, which complicates treatment because of a tendency for sufferers to avoid appointments. Panic disorder is much less common than in younger patients and tends to be less severe as well. About 1% of geriatric patients have panic disorder. Similarly, onset of obsessive-compulsive disorder (OCD) after 35 years of age is rare and is estimated to affect less than 1% of elderly patients. Hoarding is the most common manifestation of OCD in the older age group. Finally, post-traumatic stress disorder is not well studied in this age group, and new diagnoses are uncommon. However, when post-traumatic stress disorder occurs earlier in life, the symptoms can persist for decades and affect patients in their older years.

Differential Diagnosis

Older patients presenting with anxiety symptoms should be evaluated for underlying illnesses that can provoke these symptoms. For example, paroxysmal atrial fibrillation can induce a high-anxiety state with physiological manifestations of a panic-like condition, including tachycardia. Hyperthyroidism is another common cause of anxiety symptoms. Toxicity from prescription and nonprescription substances, including sympathomimetic agents, theophylline, caffeine, stimulating antidepressants, thyroid hormones, amphetamines, or withdrawal of benzodiazepines, also should be excluded.

Treatment of Anxiety States

General Points

The fundamentals of treating anxiety states are not different in older versus younger patients, but as with depression, a greater emphasis may need to be placed on drug-drug and drug-disease interactions, potential for adverse effects, pharmacokinetic or pharmacodynamic changes, cost of therapy, and adherence issues. Most treatment of geriatric anxiety occurs in the primary care setting by generalists.

Benzodiazepines

Benzodiazepines are effective and rapid-acting agents for treating a variety of anxiety disorders. However, they are best avoided whenever possible, particularly for chronic use because of their propensity to cause depression, sedation, decreased cognition, falls and associated fractures, and physiological and psychological dependency. In selected patients for whom treatment with other agents does not result in the desired response, the benefits of long-term benzodiazepine use may outweigh the risks. When benzodiazepines are used, drugs that are metabolized through phase II (conjugative) reactions are preferred over drugs that are metabolized through both phase I (biotransformation) and phase II reactions. As previously

discussed, common benzodiazepine agents that are metabolized only through phase II reactions are lorazepam and oxazepam.

Two common uses for benzodiazepines in anxiety disorders are for treating panic attacks and GAD. A short-acting agent, such as alprazolam, provides quick relief during a panic attack and can be useful in patients who have infrequent symptoms; however, better tolerated agents, such as SSRIs, are preferred for chronic use and prevention of symptoms. Because SSRIs can initially worsen anxiety symptoms, an intermediate-acting drug, such as lorazepam or oxazepam, can be used initially in severely anxious patients when initiating SSRI therapy. Many clinicians use concomitant therapy for 6–8 weeks and then taper the benzodiazepine over an additional 4 weeks.

For patients who want to discontinue benzodiazepines after taking them for longer than 4–8 weeks, tapering the dose is the standard of care. Tapering the dose prevents flares of the underlying disease state and minimizes physiological withdrawal symptoms. Typically, these agents can be tapered over 1 month, although patients who have been taking them for years often require longer periods. In most cases, giving the patient another antianxiety agent, such as an SSRI, helps to minimize anxiety symptoms when a benzodiazepine is being discontinued.

Central Nervous System Depressants

Barbiturates, such as phenobarbital, are not recommended as antianxiety agents because of their poor tolerability, lethality in overdose, and drug interactions. Other anticonvulsant agents, such as gabapentin, divalproex sodium, and carbamazepine, have been successful anecdotally in treating anxiety symptoms in older patients, but better studied and better tolerated agents, such as the SSRIs, are preferred. Meprobamate and carisoprodol (which is metabolized to meprobamate) are sedating and carry a significant abuse potential. They have no advantages over the benzodiazepines and should not be routinely used.

Buspirone

Buspirone acts as a partial agonist at 5-HT-receptors and is useful for long-term treatment of mild to moderate GAD. It has a slow onset of action and is somewhat activating, which may initially worsen symptoms. However, it has little abuse potential and usually is well tolerated in the long term. The most common adverse effects reported include nausea, dizziness, and somnolence. In addition to its slow onset, it has little cost advantage over the SSRIs and requires multiple daily dosing that could potentially affect adherence.

β-Adrenergic Antagonists

β-Adrenergic antagonists may be useful for relief of the autonomic symptoms of anxiety but do not relieve the mental symptoms. They are most useful for situational anxiety, such as public speaking, where the appearance of calmness is important. Little role exists for them in long-term therapy of anxiety states.

Antidepressants

As discussed in the Depression section, a variety of antidepressants are useful for managing anxiety disorders concomitantly with depressive symptoms. Because the majority of patients with anxiety symptoms also have depressive symptoms, this dual role is useful. However, recently it has become clear that antidepressant therapy, particularly with the SSRIs, also is useful for anxiety in patients who do not have depressive symptoms. Data also exist supporting the effectiveness of TCAs for anxiety symptoms, but as in depression, their use is limited by a significant adverse effect profile in older patients.

Virtually all available antidepressants positively affect anxiety symptoms over the long term. Of the SSRIs, paroxetine is the most sedating and is a good choice for initial therapy. Sertraline, citalopram, or escitalopram also are appropriate. Fluoxetine, although it tends to worsen anxiety symptoms initially to a greater degree than the other SSRIs, also may be useful. The FDA-approved labeling for fluvoxamine includes OCD, but the agent appears to have no advantage over other agents for this indication. As in depression, therapy should be started with low doses and increased gradually to the target dose. In general, higher antidepressant doses are required for OCD and panic disorder than for depression or GAD.

Of the non-SSRIs, mirtazapine is more commonly used as it relieves anxiety symptoms and helps sleep. Mirtazapine also causes weight gain, which can be a positive or negative effect, depending on the clinical situation. Nefazodone is another option and tends to be sedating. Bupropion is fairly activating but also has been used successfully to treat anxiety states. Venlafaxine is less activating than bupropion and also may be useful.

Agents differ in their FDA-approved package labeling for the various anxiety conditions. Currently, labeled uses for the newer antidepressants are shown in Table 1-3. However, the lack of FDA-approved labeling for a specific indication should not be interpreted to mean the drug would be ineffective, as each of the drugs are effective for a variety of disease states.

Sedating Antihistamines

Sedating antihistamines, such as hydroxyzine, were previously used extensively to treat anxiety disorders. The doses required to relieve anxiety symptoms typically cause severe sedation, decreased cognition, and anticholinergic effects. Therefore, routine use of antihistamines is no longer recommended.

Antipsychotic Drugs

Antipsychotic drugs with considerable sedative activity, including the typical drug chlorpromazine, or atypical drugs, such as olanzapine or quetiapine occasionally are

Lenze EJ, Mulsant BH, Shear MK, et al. Anxiety symptoms in elderly patients with depression: what is the best approach to treatment? Drugs Aging 2002;19:753–60.

Table 1-3. Food and Drug Administration-labeled Indications for SSRIs (Other than Major Depression)

	OCD	Panic	Social Anxiety	GAD	PTSD
Fluoxetine	X	X			
Fluvoxamine	X				
Sertraline	X	X			X
Paroxetine	X	X	X	X	X
Venlafaxine			X	X	

GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; SSRI = selective serotonin reuptake inhibitor.

used to treat anxiety symptoms. However, because of the risk of long-term complications such as TD, the use of antipsychotic drugs is only recommended after treatment with multiple other drug classes is unsuccessful.

Non-pharmacological Therapies

Various non-pharmacological therapies have been used successfully to treat anxiety disorders. Cognitive/behavioral therapy or interpersonal therapy, used alone or in combination with drugs, can help relieve symptoms. For some disorders, such as certain phobias, graded exposure therapy is the preferred treatment and appears to be more effective than drug therapy.

Patient Follow-up

Patients should be assessed frequently during drug titration to monitor for relief of symptoms and adverse effects. Ready access to a pharmacist may help allay the anxious patient's concerns about beginning a new drug. In general, the onset of action of antidepressants or buspirone is slower than that of benzodiazepines, and patients should be educated in that regard. Reevaluation of therapy should occur every 3–4 months. No consensus exists regarding the optimum therapy duration for anxiety disorders, but most patients will have symptoms that persist for long time periods; thus, many patients are candidates for long-term pharmacotherapy.

Realistic goals of therapy are to reduce symptoms to a point where they minimally interfere with functioning or quality of life with minimal adverse effects. In most cases, symptoms are not completely relieved, but they can be significantly improved. Up to 50% of patients will not experience a satisfactory response to the first agent chosen, so a pragmatic and cautious trial-and-error approach is necessary to find an agent that will be both effective and well tolerated.

Sleep Disorders

Characteristics, Epidemiology, and Effect on Outcomes

Sleep disorders, defined as subjective patient reports of an insufficient quality or quantity of sleep, are common in the elderly. About 50% of people 65 years of age or older who live at home report a sleep disturbance compared to 67% of those living in LTCFs. Despite being better sleepers using objective criteria, such as time to sleep onset and total hours of sleep achieved, elderly women are more likely than men to complain of a sleep problem.

Compared to younger patients, the elderly spend more time in bed but less time sleeping, are more easily awakened, and have more fragmented sleep patterns. Changes in sleep architecture also occur with age; older patients experience less rapid eye movement (REM) sleep and deep (stages 3 and 4) restorative sleep. This is particularly true among the very old.

The causes of sleep disorders in the elderly are varied. Poor sleep has a definite genetic component that is not modifiable. The large burden of medical disease in the elderly also contributes to sleep problems. Pain syndromes in particular commonly are reported to interfere with sleep. Breathlessness because of asthma, chronic obstructive pulmonary disease, sleep apnea, or heart failure can negatively affect sleep. Nocturnal polyuria because of benign prostatic hypertrophy or detrusor instability can force patients to get up to urinate during the night. The onset of sleep typically is delayed, and frequent awakenings can significantly decrease sleep efficiency and total sleep time. Other conditions, such as PD or restless leg syndrome, also may have negative effects on sleep in the geriatric population. In addition, CNS stimulants, such as sympathomimetics, caffeine, theophylline, corticosteroids, amphetamines, or activating antidepressants, may cause or worsen insomnia.

Environmental factors also may play a role in sleep disturbance, particularly in the institutionalized elderly. Uncomfortable bedding, nonideal room temperature, bright lights or noise in the surroundings, or nursing care occurring at night can all create a poor environment for sleep. Psychiatric disorders, including depression, anxiety, alcoholism, or dementing illnesses, may cause or worsen sleep disorders, and they should be included in the differential diagnosis. Behavioral causes of poor nighttime sleep, such as frequent naps during the day, early retirement to bed, or use of the bed for reading or watching television also should be investigated.

Alterations in the normal circadian rhythm also may occur with aging and result in sleep disorders. These may be because of external or internal factors. For example, after retirement, individuals who previously led a structured life may find that they no longer wish to go to sleep at what was previously a normal bedtime. As a result, they may sleep later into the day. Frequent daytime naps can contribute to this phenomenon. Physiologically, a reduction in melatonin secretion by the pineal gland may cause internal desynchronization, where different circadian rhythms become out of step with each other.

Elderly patients with sleep disorders have up to twice the mortality rate of those without sleep disorders. Whether this is because of an adverse effect of insomnia on prognosis or whether those with the worst prognosis are predisposed to sleep disorders is not known. In either case, sleep disorders represent a frequent cause of decreased quality of life in older patients.

Non-pharmacological Therapy

Treatment of sleep disorders should begin with identifying reversible causes. Issues with underlying

medical or psychiatric conditions, including the possibility of drug-induced sleep disorders, and the environment should be addressed first. The next step is to educate patients about good sleep hygiene and appropriate expectations regarding sleep. Sleep hygiene tips are listed in Table 1-4. It also is vitally important to address patient expectations. For example, if a patient retires to bed at 8 PM, rising at 3 AM or 4 AM the next morning is reflective of a full night's sleep rather than a sign of a sleep disorder. Patients also should be encouraged to focus on the quality rather than expected quantity of sleep. A patient who sleeps for only 5 hours/night but who awakens fully rested and does not experience daytime sleepiness should not be concerned that he or she is sleeping less than 8 hours/night.

Table 1-4. Tips for Improving Sleep Hygiene

Retire and rise at about the same time each day.
Avoid using the bed for activities, such as reading or watching television.
Avoid daytime naps or limit them to one nap of 30 minutes duration.
Increase physical activity during the day, but avoid strenuous activity close to bedtime.
Minimize the use of stimulants, (e.g., caffeine), especially in the evening.

Pharmacotherapy

In general, pharmacotherapy should play only a minor role in treating sleep disorders. This was underscored by a recent study in which elderly patients who were treated with a cognitive and behavioral approach had a more sustained response and were more satisfied with their care than patients who received pharmacotherapy with a benzodiazepine.

Antihistamines

The sedating antihistamines, such as diphenhydramine, are probably the most commonly used sleep-inducing agents in the elderly because of their availability over the counter. Patients who seek medical care for insomnia often have used a nonprescription antihistamine with varying degrees of success. However, this class cannot be recommended for routine use because of the frequent anticholinergic adverse effects, including cognitive changes, constipation, delirium, and urinary retention that they cause. They also have been associated with daytime sedation and an increased risk of falls.

Barbiturates and Chloral Hydrate

Although once commonly used for insomnia, barbiturates, such as phenobarbital and secobarbital, and chloral hydrate are no longer considered rational treatment options. They are less effective and more lethal in overdose than the benzodiazepines, and long-acting barbiturates, such as phenobarbital, may cause prolonged sedation, an increased risk of falls and fractures, and cognitive decline.

Benzodiazepines

The benzodiazepines are among the most frequently prescribed classes of drugs for sleep disorders. Although they can be highly effective, their use is fraught with problems. Because tolerance to the hypnotic effect develops over time, patients eventually need to increase the dose to maintain the sleep-inducing effects. Therefore, prescribers and patients should agree on the planned therapy duration when a benzodiazepine is prescribed. Initial use for only a few days is a reasonable starting point, although this can be increased to 2–3 weeks without major problems. When combined with non-pharmacological therapy, this approach can provide immediate relief while patients initiate nondrug strategies that are more likely to be a long-term solution to sleep difficulties. After about 3 weeks of continuous therapy, much of the effectiveness of these agents is lost.

Benzodiazepines also may alter sleep architecture and decrease the amount of deep, restorative sleep even while increasing the total amount of sleep. Fortunately, infrequent use of a benzodiazepine does not significantly affect sleep architecture, making them best for short-term, episodic use.

Long-acting agents, such as flurazepam, should be avoided in the elderly. With repeated dosing, diazepam also is a long-acting agent, though its high lipophilicity results in a short duration after a single dose. In addition to long elimination half-lives of up to several days, these agents undergo phase I metabolism to pharmacologically active metabolites. They have been associated with increased confusion, daytime sedation, falls, and fractures in older patients.

Intermediate-acting agents, including lorazepam, oxazepam, and temazepam, are associated with less daytime sedation than the long-acting members of the class; however, next-day somnolence can still be an issue. These agents also have been associated with an increased risk of falls and fractures. They have a slower onset of action than the short-acting benzodiazepines and should be dosed about 30 minutes before bedtime. They are useful both in patients who have difficulty falling asleep and in patients who have difficulty staying asleep. The usual hypnotic doses of lorazepam, oxazepam, and temazepam in the elderly are 0.5–1 mg, 10–30 mg, and 7.5–15 mg, respectively.

The short-acting benzodiazepines, alprazolam and triazolam, carry the lowest risk of daytime sedation. However, they are the most likely to cause anterograde amnesia. They may be most useful in patients who have difficulty falling asleep but who remain asleep once this occurs.

As previously discussed, pharmacokinetic and pharmacodynamic changes associated with aging may increase older patients' risk of adverse reactions to benzodiazepines. Drugs that undergo both phase I and phase II metabolism, such as diazepam, flurazepam, alprazolam, and triazolam, may be eliminated more slowly in older versus younger patients. Drugs metabolized only by the phase II route, including lorazepam, oxazepam, and temazepam, are probably safer. Regardless of what agent is chosen, it should be started at a low dose and increased gradually until the desired effect is seen.

Rebound insomnia can be problematic with chronic dosing, which may occur with all agents but is probably

worst with the agents with the shortest half-lives. If patients are taking an agent every night or almost every night for more than 2–3 weeks, it may be necessary to taper the drug over a short period. Patient education is vital to ensure that drugs are used at the lowest doses and the shortest duration that is effective. Long-term pharmacotherapy is rarely the solution to sleep issues.

Nonbenzodiazepine Hypnotics

In recent years, two nonbenzodiazepine sedative/hypnotics, zolpidem and zaleplon, contain FDA-approved labeling for the indication of short-term treatment of insomnia. Both are structurally different from benzodiazepines but selectively bind to benzodiazepine receptors. Unlike the benzodiazepines, these agents do not significantly decrease stage 3, stage 4, or rapid eye movment sleep.

Zaleplon has a quick onset and short duration of action, whereas zolpidem's onset and duration are comparable to that of the short-acting benzodiazepines. Zaleplon is most useful in patients with difficulty falling but not staying asleep because it does not decrease nocturnal awakenings. Daytime sedation is minimal with this agent, but it does have a small, dose-dependent risk of amnesia similar to the short-acting benzodiazepines. The usual starting dose in the elderly is 5 mg/day, and the maximum recommended dose is 20 mg/day.

Zolpidem, in contrast, may be more useful for patients who have difficulty remaining asleep, similar to the intermediate-acting benzodiazepines. Daytime sedation is higher than with zaleplon, but anterograde amnesia is less. The usual starting dose in the elderly is 2.5 mg or 5 mg/day, with a maximum recommended dose of 10 mg/day. Both zolpidem and zaleplon are FDA-labeled for use 2–3 times/week for up to 3–4 weeks.

Antidepressants

Antidepressant therapy typically is not recommended for treatment of insomnia in the absence of anxiety or depressive symptoms. However, if either is present, antidepressants often are the drugs of choice. A more sedating antidepressant, such as mirtazapine, nefazodone, or paroxetine, usually is selected in this case, but almost all agents eventually will improve sleep. Worsening insomnia may initially be a problem, particularly with the SSRIs or bupropion.

Occasionally, the antidepressant trazodone is used for its sedative rather than antidepressant properties in patients who have difficulty sleeping. It has no abuse potential and tolerance does not develop, which are advantages over the benzodiazepines and nonbenzodiazepine hypnotics. Orthostasis occasionally is seen, although it is less frequent and severe with this agent than with TCAs. More rare but serious adverse effects include priapism in men and 5-HT syndrome in those who receive other serotonergic agents. The usual starting dose is 25–50 mg at bedtime, which may be increased to 100 mg or more at bedtime.

Melatonin

The reduction in melatonin secretion associated with aging has led to interest in using supplemental melatonin to help regulate the sleep-wake cycle in older patients. Little evidence exists documenting the effectiveness of melatonin for this purpose, although some promising data suggest usefulness in other situations, such as jet lag. Questions regarding appropriate dose and timing also remain, and because it is considered a dietary supplement, purity and potency issues also must be considered. In the future, melatonin may be considered a reasonable treatment option, but the lack of data precludes its routine use currently.

Antipsychotic Drugs

Many antipsychotic drugs have sedating effects and theoretically could be used for insomnia. However, in the absence of psychotic symptoms requiring treatment, they are not recommended for this purpose because of their high rate of neurological adverse effects, not all of which may be reversible.

Summary: Role of the Pharmacist

Today, more than ever, pharmacists are looked on as vital members of the health care team. As such, they need to be knowledgeable and well versed in various psychiatric disease states afflicting the geriatric patient, as well as the corresponding treatment regimens available. Pharmacists are the drug experts and are looked on by other health care providers for assistance with drug selection, dosage decisions, and monitoring. The geriatric population is growing in number and complexity. Many of these patients will be faced with cognitive, mood, anxiety, and sleep disorders which may accompany significant physical disease as their bodies, life circumstances, and social status evolve with increased age. Patients as well as caretakers look to the pharmacist for information and guidance, counseling, and encouragement regarding these complicated, embarrassing, and difficult to understand psychiatric disease states.

Annotated Bibliography

1. Burns A, Dening T, Lawlor B. Clinical Guidelines in Old Age Psychiatry. London: Martin Dunitz, 2002.

   This book contains discussions of available clinical guidelines for the detection and treatment of mental illness in the elderly. It covers a variety of topics, including depression, anxiety, dementias, and psychotic disorders. The discussions include the guideline's purpose, a brief summary of its contents, the source or sponsoring organization, and where the guideline may be obtained in its entirety. This book is a good overview of the guidelines available to direct therapy and is limited primarily by the relatively few relevant guidelines in existence. It provides a reasonable starting point for clinicians who want to familiarize themselves with the most current recommendations for geriatric psychopharmacotherapy.

2. Wilson K, Mottram P, Sivanranthan A, Nightingale A. Antidepressants versus placebo for the depressed elderly. Cochrane Database Syst Rev 2004;(4):CD000561.

This systematic review of placebo-controlled trials of antidepressant therapy in community-dwelling older patients was last amended in November 2002. The authors identified 17 relevant trials, including a total of 245 patients who received a tricyclic antidepressant (TCA), 365 patients who received a selective serotonin reuptake inhibitor (SSRI), and 58 patients who received a monoamine oxidase inhibitor (MAOI). The included studies lasted 4–8 weeks. All three drug classes had statistically significant benefits on outcomes and withdrawal rates that were comparable to placebo. The effect size was comparable for each class of drugs. This review emphasizes that pharmacotherapy of geriatric depression is effective and well tolerated in the short term, and that more trials, particularly with newer agents, are necessary.

3. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized, controlled trial. JAMA 1999;281:991–9.

This study randomized 78 community-dwelling elderly patients with chronic insomnia to one of four groups: cognitive behavior therapy, including stimulus control, sleep restriction, improved sleep hygiene, and cognitive therapy; pharmacotherapy with temazepam; both; or placebo only. Outcome measures included time spent awake after the initial onset of sleep, sleep efficiency (time spent asleep divided by time spent in bed), and clinical ratings by patients, significant others, and clinicians. Over an initial 8-week evaluation period, cognitive behavior therapy, pharmacotherapy, and the combined approach were more effective than placebo. Patients continued as assigned for up to 24 months. During this follow-up period, cognitive behavior therapy with or without pharmacotherapy was rated more effective than pharmacotherapy alone by patients, significant others, and clinicians. Although a small sample size was used in this trial, the authors concluded that either cognitive behavior therapy or pharmacotherapy is equally effective for short-term insomnia treatment in the "healthy" elderly (i.e., those without comorbid medical or psychiatric conditions). The combined approach (cognitive behavior therapy and pharmacotherapy) also produced benefits early, but gains were not necessarily maintained. Although several patients dropped out, initiated, or resumed drugs, the authors also concluded that long-term (12–24 months) pharmacotherapy alone was not an effective intervention. Clearly, the results of this trial cannot be extrapolated to a more representative sample of elderly patients who were excluded from this trial. In addition, data on the use of pharmacotherapy for chronic insomnia remain limited at best.

4. Alexopoulos GS, Katz IR, Reynolds CF, Carpenter D, Docherty JP, eds. Pharmacotherapy of Depressive Disorders in Older Patients. Postgrad Med Special Report. New York, NY: McGraw-Hill Companies, Inc., October 2001:1–86.

This expert consensus guideline, sponsored by Forest Laboratories and Pfizer, is the result of a 64-question survey sent to 50 physician experts. The experts were chosen based on "their national clinical-academic reputation (e.g., receipt of federal research grants in the past 5 years and authorship of important publications)". Each also was given a $500 honorarium; the response rate was 100%. The guideline is fairly comprehensive and contains recommendations for assessment of depression, drug selection, dosing and treatment duration, treatment resistance, strategies for continuation and maintenance treatment, and such special treatment issues as medical comorbidities or concomitant drugs. It also contains a guide for patients and families.

5. Kindermann SS, Dolder CR, Bailey A, Katz IR, Jeste DV. Pharmacological treatment of psychosis and agitation in elderly patients with dementia. Drugs Aging 2002;19:257–76.

This review of reports, published from 1960 through 2000, was intended to address drug efficacy in treating behavioral and psychological symptoms of dementia (BPSD) in elderly patients. It included 48 studies, encompassing both trials with antipsychotic agents as well as a small section on the use of nonantipsychotic drugs. Excluded from the review were studies where psychosis or behavioral disturbances were not the focus of treatment. Also excluded were studies that involved patients with Parkinson's disease (PD), and studies that included fewer than 10 patients. Only studies reporting number of patients improved or percentage of patients improved were used when calculating overall percentage of improvement. Clinical considerations, including symptom review, choice of agent, and adverse effects, were summarized in the conclusion. The authors suggested that the atypical antipsychotic drugs be the preferred agents for treating BPSD in this population. Other agents, such as benzodiazepines, should be reserved for target symptoms that do not respond to the atypical agents. Pharmacological therapy should always be accompanied by non-pharmacological, behavior modification methods.

SELF-ASSESSMENT QUESTIONS

1. A 66-year-old man is visiting his primary care physician because of memory problems. The patient is misplacing items, such as his keys and checkbook. His wife asks the physician about "normal forgetfulness" with age. The physician administers an Mini-Mental State Examination (MMSE) that reveals a score of 24. Which one of the following is an appropriate next step in the care for this patient?
   A. The physician should suggest that the patient's wife seek long-term care facility (LTCF) placement for her husband.
   B. The patient should undergo additional evaluation for reversible causes of memory loss.
   C. The patient should be started on divalproex sodium.
   D. The physician should inform the patient and his wife that this is normal forgetfulness.

2. A 90-year-old woman who resides in a LTCF is admitted to the hospital with symptoms of agitation and confusion. Vital signs include a heart rate of 77 beats/minute, blood pressure of 160/75 mm Hg, and respiration rate of 30 breaths/minute. She has a slight fever and is incontinent of urine. Her past medical history includes hypertension, Alzheimer's disease (AD) and depression. She currently is receiving transdermal clonidine 0.1 mg (one patch/week), extended-release venlafaxine 150 mg/day, and donepezil 10 mg at bedtime. Vitamin E 1000 units/day was recently added to her regimen by her family physician. Her psychiatric symptoms are most likely caused by which one of the following?
   A. An adverse drug reaction secondary to clonidine.
   B. Delirium because of infection.
   C. A drug-drug interaction between venlafaxine and clonidone.
   D. The recent addition of vitamin E to her drug regimen.

3. A 75-year-old retired school teacher has a family history of AD, hypertension, heart failure, and osteoporosis. She takes drugs for each disease state. Recently, her husband has noticed that she has increased symptoms of paranoia, with verbal abuse directed toward him. Her family practitioner decides to start therapy. Which one of the following treatments is the best?
   A. Risperidone 6 mg/day at bedtime.
   B. Risperidone 2 mg/day at bedtime.
   C. Risperidone 0.5 mg/day at bedtime.
   D. Haloperidol 0.5 mg/day at bedtime.

4. A 66-year-old woman recently has recovered from a left-sided cerebrovascular accident. She currently is displaying symptoms of mania that are distressing to her daughter, the primary caregiver. The patient is diagnosed with bipolar disorder. Which one of the following do you suggest to the geriatrician as first-line treatment of the manic phase of bipolar disorder in this woman?
   A. Divalproex sodium.
   B. Lithium carbonate.
   C. Carbamazepine.
   D. Gabapentin.

Questions 5 and 6 pertain to the following case.
An 80-year-old man who resides in a LTCF is transferred to the geriatric psychiatry unit at your hospital after biting and kicking staff members. His current psychiatric drugs include risperidone 0.5 mg at bedtime and zolpidem 5 mg at bedtime as needed for sleep.

5. Which one of the following is an appropriate next step in the treatment regimen for this patient?

A. Add divalproex sodium, started at 125 mg/day and titrated to achieve a plasma concentration of about 50 mcg/ml.
B. Add gabapentin, started at 300 mg at bedtime and titrate the dose to 3600 mg/day.
C. Add a benzodiazepine, preferably alprazolam 0.5 mg/day, and titrate to sedation.
D. Increase risperidone to 1 mg/day, 0.5 mg in the morning and 0.5 mg at bedtime.

6. Which one of the following rating scales is used extensively in behavioral and psychological symptoms of dementia (BPSD) trials, and could best be used for this patient to measure agitated behaviors in response to pharmacological therapy?

A. Neuropsychiatric Inventory (NPI).
B. Cohen-Mansfield Agitation Inventory (CMAI).
C. Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD).
D. Mini-Mental State Examination.

Questions 7 and 8 pertain to the following case.
A 77-year-old man with dementia was admitted to the hospital after a fall. He has a past medical history of hypertension, hyperlipidemia, benign prostatic hypertrophy, and vascular dementia. His drugs at admission included hydrochlorothiazide 25 mg/day, atenolol 50 mg/day, atorvastatin 10 mg/day, terazosin 5 mg/day, aspirin 81 mg/day, and chlorpromazine 25 mg/day as needed for agitation. He currently is agitated and is attempting to strike the nursing staff. His physician wants to change the chlorpromazine to a routine schedule and increases the dose to 25 mg by mouth 2 times/day.

7. Chlorpromazine is not the drug of choice in this situation for which one of the following reasons?

A. The expense of the drug is prohibitory.
B. The drug is likely to have a negative effect on cholesterol metabolism.
C. The drug is likely to induce angina.
D. The drug is likely to contribute to another fall.

8. The best alternative to chlorpromazine for this patient is which one of the following drugs?

A. Risperidone 0.5 mg at bedtime.
B. Lorazepam 0.5 mg every 4 hours as needed.
C. Thioridazine 25 mg every 4 hours as needed.
D. Olanzapine 15 mg at bedtime.

9. A 77-year-old woman is admitted to a geriatric psychiatry unit because of aggressive behavior directed toward her family members. The psychiatrist starts therapy with risperidone 0.5 mg at bedtime along with benztropine 0.5 mg at bedtime. Her family inquires about the use of benztropine. Which one of the following is the best response to the patient's family?

A. Benztropine is necessary to prevent the adverse effects of risperidone.
B. Benztropine is used to help their mother sleep.
C. Benztropine is used as an adjunct to the risperidone therapy.
D. Benztropine may not be necessary and you will speak with her psychiatrist about discontinuing it.

10. A 75-year-old woman with a history of mild AD is having difficulty sleeping because of bothersome hallucinations. The hallucination is visual in nature and not unpleasant, in that the patient sees her deceased husband at the foot of her bed. Her family asks you about the possibility that their mother has schizophrenia as her younger sister had similar symptoms several years ago and had to be institutionalized. Her drugs include a multivitamin, one tablet daily, calcium carbonate 500 mg one tablet 3 times/day, alendronate 10 mg one tablet every morning, and hydrochlorothiazide 25 mg one tablet once daily. Which one of the following is the best response to the family?

A. It is possible that the patient may be displaying a symptom of schizophrenia. Further workup is indicated.
B. Her hallucinations may be characteristic of those experienced by a patient with cognitive impairment, such as AD.
C. Her hallucinations may be due to one of her drugs, namely hydrochlorothiazide. You recommend that the drug be discontinued.
D. She is probably not hallucinating but seeing her caregiver come into the room at night. You recommend a sedative hypnotic.

Questions 11 and 12 pertain to the following case.
A 77-year-old woman who resides in a LTCF is given olanzapine 10 mg every evening for symptoms of agitation associated with her AD. In the 2 weeks after drug initiation, she is seen walking down the halls with a shuffling unsteady gait.

11. Which one of the following pharmacodynamic principles explains the adverse effects the patient is experiencing?

A. The number of dopamine neurons and dopamine type 2 (D_2)-receptors increases in the elderly, leading to extrapyramidal symptoms (EPS) when a certain threshold of neuronal loss is reached.
B. The increased number of cholinergic neurons and receptors results in older patients being more susceptible to the anticholinergic effects of antipsychotic drugs, tricyclic antidepressants (TCAs), and antihistamines.
C. The γ-aminobutyric acid (GABA) type A benzodiazepine receptor complex is known to have age-dependent increases in number and in composition.
D. More time is required to return to the original steady-state level of functioning after another drug is added. Her symptoms should resolve after another week.

12. Which one of the following approaches is the best choice for treating the patient's recent symptoms?
    A. Add benztropine 1 mg/day at bedtime.
    B. Substitute clozapine 6.5 mg/day for olanzapine.
    C. Substitute quetiapine 50 mg twice daily for olanzapine.
    D. Decrease olanzapine to 5 mg/day.

13. An obese 70-year-old woman with hypertension, hyperlipidemia, and diastolic heart failure recently has been diagnosed with her first episode of major depressive disorder. She complains of significant lethargy and depressed mood. Her current drugs include hydrochlorothiazide 25 mg/day, ramipril 10 mg/day, atorvastatin 10 mg/day, diltiazem CD 240 mg/day, and calcium carbonate 500 mg 3 times/day. Which one of the following regimens is an appropriate first-line agent for her depression?
    A. Citalopram 10 mg/day.
    B. Nortriptyline 25 mg at bedtime.
    C. Mirtazapine 7.5 mg at bedtime.
    D. Nefazodone 140 mg 2 times/day.

14. Which one of the following depression rating scales is best for a pharmacist to administer to a 75-year-old man with diagnoses of moderate AD, osteoarthritis, and high blood pressure?
    A. Mini-Mental State Examination.
    B. Hamilton Rating Scale for Depression (HAM-D).
    C. Center for Epidemiological Studies-Depression (CES-D) scale.
    D. Beck Depression Inventory (BDI).

15. You have been asked to make a recommendation about the appropriate initiation, titration, and length of antidepressant therapy for a 77-year-old man with a history of osteoporosis, osteoarthritis, cardiovascular disease, and a seizure disorder. This is his first episode of major depression. His current drugs include alendronate 35 mg/week, celecoxib 200 mg/day, calcium citrate 400 mg 3 times/day, atenolol 50 mg/day, aspirin 81 mg/day, lisinopril 10 mg/day, and carbamazepine 200 mg 2 times/day. Which one of the following is the best therapy at this time for this patient?
    A. Sertraline 50 mg/day for 1 week, then 100 mg/day for 6–9 months.
    B. Paroxetine 10 mg/day for 2 weeks, then 20 mg/day until symptoms resolve.
    C. Nefazodone 50 mg 2 times/day for 5 days, then 100 mg 2 times/day for 6–9 months.
    D. Citalopram 10 mg/day for 1 week, then 20 mg/day for 9–12 months.

16. You are designing a clinical trial to assess the effect of a new antidepressant on mood in medically ill elderly patients who do not have dementing illnesses. Which one of the following rating scales is best to use for this study?
    A. Neuropsychiatric Inventory.
    B. Beck Depression Inventory.
    C. Center for Epidemiological Studies-Depression scale.
    D. Geriatric Depression Scale (GDS).

17. An elderly man complains of waking up early in the morning and being unable to fall back asleep. He typically retires to bed at 9 PM and falls asleep without difficulty but then wakes up in the early morning. Once awake, he cannot fall back to sleep. He lives alone, is showing no signs of depression, and does not complain of excessive daytime tiredness. Which one of the following treatment options is best for him?
    A. Education and sleep hygiene interventions only.
    B. Zolpidem 5 mg at bedtime as needed for up to 14 days.
    C. Zaleplon 5 mg at early morning awakening as needed for up to 14 days.
    D. Paroxetine 10 mg/day.

18. A 67-year-old woman is in the clinic complaining of anxiety symptoms that began about 4 weeks ago. Her medical history is significant for ovarian cancer, hypertension, rheumatoid arthritis, and dysthymia. Her current drugs include hydrochlorothiazide 25 mg/day, amlodipine 10 mg/day, celecoxib 200 mg 2 times/day, methotrexate 7.5 mg/week, and sertraline 150 mg/day. All of the drug dosages have been stable for some time except for sertraline, which was started at her last visit the previous month and titrated to the current dose. Her dysthymic symptoms have resolved in the interim. Which one of the following is the best intervention for her at this time?
    A. Begin lorazepam 0.5 mg 2 times/day as needed for anxiety symptoms.
    B. Decrease the sertraline to 50 mg/day.
    C. Add mirtazapine 7.5 mg/day at bedtime.
    D. Add buspirone 5 mg 2 times/day.

19. An 88-year-old woman currently is in the middle to late stages of AD. In addition, she has a past medical history of cerebrovascular accident (CVA), hypertension, depression, and heart failure. Her drug regimen includes donepezil 10 mg every night, sertraline 50 mg every night, olanzapine 10 mg every night, clopidogrel 75 mg/day, lisinopril 10 mg/day, buspirone 5 mg/day, furosemide 20 mg/day, and potassium chloride 10 mEq/day. The patient's family is having difficulty paying her prescription bill every month and wants your opinion as to which drugs could be removed from her regimen. Which one of the following drugs should you recommend be discontinued?
    A. Donepezil.
    B. Buspirone.
    C. Sertraline.

D. Clopidogrel.

20. The caregiver of an elderly man with multiple medical problems is concerned because the patient has been expressing an increase in somatic complaints over the past few months. The caregiver is concerned that the patient is experiencing a bout of depression; however, the patient denies a depressed mood. Which one of the following is the best way to counsel the caregiver in this situation?

    A. Depression could be responsible for the increase in somatic symptoms even though a depressed mood is not present.
    B. Because no evidence exists that treating depression improves outcomes in the elderly, no treatment is necessary if the patient does not feel depressed.
    C. Improvement in the therapy of the patient's underlying medical problems would likely unmask a depressed mood.
    D. Adverse effects from antidepressant therapy would likely outweigh any potential benefits for this patient.

21. A 77-year-old woman recently was diagnosed with generalized anxiety disorder (GAD). Her other conditions include coronary artery disease, hypertension, osteoarthritis, and gout. She denies having a depressed mood or a loss of interest in activities. Which one of the following drugs is best as first-line treatment for this patient?

    A. Diazepam 10 mg/day.
    B. Amitriptyline 50 mg/day at bedtime.
    C. Sertraline 25 mg/day.
    D. Carbamazepine 200 mg 2 times/day.

22. A 74-year-old woman with multiple medical problems is complaining of an increase in anxiety symptoms, including nervousness, loss of appetite, and difficulty sleeping. The patient's caregiver wants to know how likely it is that this is a new psychiatric problem rather than somatic symptoms of the patient's underlying disease(s) and current drugs. Which one of the following is the best response?

    A. Because of the patient's age, the most likely explanation is a new-onset anxiety disorder.
    B. Because elderly patients rarely experience new psychiatric disorders, it is highly unlikely that this is not connected with a preexisting disease or drugs.
    C. In either case, little can be done to improve the situation so the patient should not worry about it.
    D. The symptoms could be because of a new condition, underlying diseases, or medical therapy and a thorough assessment is appropriate.

23. A 70-year-old man with a 40-year history of post-traumatic stress disorder (PTSD) complains of a recent increase in anxiety symptoms and nightmares related to his traumatic event. His medical history is significant for prostate cancer, chronic obstructive pulmonary disease, and alcohol abuse; however, he has been abstinent for 8 years. Which one of the following therapies is best for him?

    A. Diphenhydramine 25 mg as needed for anxiety symptoms.
    B. Nortriptyline 50 mg/day at bedtime.
    C. Sertraline 50 mg/day.
    D. Propranolol 10 mg as needed for anxiety symptoms.

24. A 65-year-old woman is receiving rivastigmine 6 mg/day, along with olanzapine 10 mg/day for agitation associated with AD. Her caregiver is concerned because the patient is experiencing flu-like symptoms, including nausea, vomiting, and diarrhea. The caregiver asks if this could be related to the medicine the patient is taking. Which one of the following is the best response?

    A. Yes, these symptoms are the result of an increase in liver function tests seen with rivastigmine.
    B. Yes, these symptoms are a result of the drug interaction between olanzapine and rivastigmine.
    C. No, these symptoms are probably the flu; please be sure to keep the patient hydrated and the symptoms will pass.
    D. Yes, these symptoms are common adverse effects associated with cholinesterase inhibitors.

25. A 69-year-old woman goes to her physician's office for her monthly visit, and she is subsequently diagnosed with major depression. Citalopram 10 mg/day is initiated, and she is given a 1-month supply. A follow-up appointment is made for 1 month from today. On her follow-up visit, the patient is still experiencing symptoms of depression. Which one of the following drug changes would you make at this point?

    A. Stop citalopram and begin paroxetine 10 mg/day.
    B. Increase citalopram to 20 mg/day.
    C. Stop citalopram and start extended-release venlafaxine 75 mg/day.
    D. Use combination therapy with citalopram 10 mg/day and extended-release venlafaxine 37.5 mg/day.