6

Psychopharmacology

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Psychiatric illness among older adults is commonplace and is a considerable factor in determining the quality of life in those older than 65 years of age. A number of factors contribute to the lowered vulnerability to episodes of mental illness including psychosocial stressors, medical comorbidities, and the life changes that accompany aging. Some older adults are able to reduce the risk of an episode of illness with such techniques as easy access to health care resources, use of social support systems, and healthy coping skills. Others are less fortunate in the absence of these resources and are at greatest risk for either an initial episode of illness or a relapse of an existing illness. Depression, anxiety, substance abuse, sleep dysregulation, and cognitive disorders are among some of the common culprits negatively impacting the mental health of older adults. Although the awareness of mental health issues among older adults is improving, the need for accurate identification of target symptoms and correct diagnosis is critical to positive clinical outcomes. Included in this treatment plan are pharmacologic options that aim to alleviate symptoms, reduce risk, and facilitate healing and well-being.

In 2000, an estimated 9 million older adults suffered from some form of mental illness. This number is expected to increase to 20 million by the middle of this century given the aging demographics (US Bureau of the Census, 2000). In 2010, the US Census Bureau will conduct another major census of the American populace allowing for a snapshot of the accuracy of these predictions in the first decade of the 21st century. It is reported that nearly 20% of those 55 years and older experience mental health disorders that are not part of normal aging. The common disorders in order of prevalence are anxiety, severe cognitive impairment, and mood disorders. There is concern that mental disorders in older adults are underreported. The rate of suicide is highest among older adults compared to any other age group, and the suicide rate for persons 85 years and older is the highest of all at twice the overall national rate (Metlay, 2008).

The composition of the population 65 years and older continues to shift to a more ethnically, racially, and culturally diverse group of older adults because of significant growth in minority populations. These factors combined will become the foundation for shifts in clinical practice aimed at both mental health maintenance and psychiatric disease prevention in the aging sector of the American population. Nurses continue to be a critical dimension

in the health care of older adults, and the practice of nursing will be contoured by the factors influencing the care of this group.

Older adults often deal with a multiplicity of medical and psychiatric problems and commonly part of the treatment regimen includes prescription and nonprescription medications. Older adults constitute just 13% of the United States population, but consume 35% of all prescription drugs (Metlay, 2008). Psychotropics are the second most commonly prescribed class of drugs in geriatric patients and the most frequently associated with adverse drug reactions (Ives, 2001). Symptoms that become the focus of treatment include insomnia, agitation, aggression, and other disruptive behaviors. Commonly treated syndromes or disorders include anxiety, depression, mood cycling, psychosis, and cognitive disorders with associated dysregulations in sleep across all of these disorders (Thomas, 2009; Blanchette et al., 2009; Pariente et al., 2008).

Older adults commonly combine prescription and nonprescription medications, often unaware of the potentially negative impact that these combinations can produce. Recent research-based information on the combination of prescription and over-the-counter medications by Qato et al. (2008) revealed that among community-dwelling older adults, prescription and nonprescription medications were often used together, with nearly 1 in 25 individuals potentially at risk for a major drug-drug interaction. Given the commonplace use of herbal preparations among the general population and older adults in particular, clinicians often need a reliable source of reference in understanding the implications of these compounds. A resource such as the *Physician's Desk Reference for Herbal Medicines* (Kush et al., 2007) is a helpful compendium of information that can serve as a guide to clinicians who have questions related to the use of these medications separately or in combination with other drugs.

Undiagnosed and untreated mental illness can lead to unnecessary and costly procedures and hospitalizations, increased disability, premature death, increased morbidity, increased risk of institutionalization, and a significant decrease in quality of life for older adults. Changing demographics, combined with the disproportionate rate at which older adults use medical resources and the pressures to contain costs, will require that healthcare providers become increasingly knowledgeable in the care of a diverse older population (Edlund, 2004) and vigilant in diagnosing and treating mental illness in this population. It is essential that clinicians working with older adults aggressively address the mental health issues of this population to meet the goals for *Healthy People 2010*, which seek to increase quality years of life and eliminate health disparities (US Department of Health and Human Services, 2000).

CHALLENGES IN PRESCRIBING FOR OLDER ADULTS

Mental health problems in older adults often differ in clinical manifestations, pathogenesis, and pathophysiology from mental health problems of younger adults (Sadock & Sadock, 2009). Thus, the diagnosis and treatment of older adults can present more difficulties. Factors contributing to such difficulties include normal age-related changes, the coexistence of chronic medical problems and disabilities, the use of multiple medications, and the presence of cognitive impairment (Nixdorff et al., 2008). In addition, the signs and symptoms of health problems in the older adult may not be as obvious as in the younger adult, given the complexities presented by medical comorbidities and natural changes incurred in the course of aging. There may also be differences in the quantity and quality of symptoms with older persons. Older adults may present with vague versus specific complaints. For example, lightheadedness may be the only symptom reported by an older adult experiencing anxiety, or multiple general somatic complaints may be the predominant presentation if experiencing depression. Older adults may also hesitate to mention changes in their bodies associated with health problems, because they perceive these changes as normal aging (Leff & Sonstegard-Gamm, 2006).

Clearly, changes need to be explored to determine whether there is underlying disease or whether the changes are age-related and normal. Additionally, older adults often perceive their health based on their ability to function rather than on the number of health problems. This population is unique in that they may be diagnosed with two or more chronic diseases, take a number of medications, and still function at a high level of health (Kane, Ouslander, & Abrass, 2004). These cohort-related trends may reflect both cultural and generational patterns of response.

Prescribing a psychotropic drug for an older adult should be based on a thorough assessment, target symptoms, stages and progression of illness, provider's knowledge of drug choices, and the pharmacokinetic and pharmacodynamic changes that accompany aging. In addition, a review of current medications that may interact with or contribute to adverse drug reactions should be conducted. A dose appropriate for the older adult should be prescribed in a dosing schedule that enhances compliance. Individualizing treatment plans that include psychoeducation and evaluating responses to drug interventions are essential because of the great deal of variability among the older adult population (American Nurses Association, 2001). Box 1 references several Web-based resources that may be helpful sources of information for clinicians working with elders who have diagnosed psychiatric conditions.

FACTORS INFLUENCING PHARMACOTHERAPY IN OLDER ADULTS

Pharmacotherapy in older adults may be complicated by multiple factors, among them the pharmacokinetic (drug absorption, distribution, metabolism, and excretion) and pharmacodynamic changes associated with aging (Box 6-2). These changes involve altered receptor response.

Pharmacokinetics is a source of concern from a variety of perspectives for clinicians who work with older adults. The sections that follow assist clinicians

BOX 6–1 WEB-BASED RESOURCES: GERIATRIC PSYCHIATRY AND GERONTOLOGY

The Gerontological Society of America (www.geron.org). This is an excellent resource that disseminates research-based information on many topics related to gerontology. Full text journals are accessible from the Web page.

National Institute on Aging (www.nih.gov/nia). This site contains an impressive compilation of information for the public on broad issues related to aging, and biomedical, behavioral, and social research related to aging. A variety of publications for professionals are available through this site.

Drug Interactions (http://www.drugs.com/drug_interactions.html). This is a particularly helpful Web site that offers the clinician some pragmatic information related to potential drug interactions. Drug–drug interactions can be checked on an interactive program.

American Psychiatric Association (www.psych.org). This Web site is an excellent resource for the clinician who is seeking information related to practice guidelines and evidence-based approaches to the treatment of psychiatric illnesses.

BOX 6–2 AGE-RELATED PHARMACOKINETIC CHANGES

Absorption	**Metabolism**
Delayed gastric emptying	Decreased liver size
Increased gastric pH	Decreased hepatic blood flow
Decreased intestinal motility	Decreased level of drug metabolizing enzymes
Decreased mucosal surface area	
Distribution	**Excretion**
Decreased lean body (muscle) mass	Decrease blood flow
Increased body fat	Decreased glomeruli
Decreased total body water	Decreased glomerular filtration
Decreased albumin	Decreased tubular secretion
Decreased (1-acid glycoprotein	Decreased creatinine production
Decreased creatinine clearance	

Source: Adapted from Kane, Ouslander, & Abrass, 2004; Keltner & Folks, 2005.

in the understanding of such pharmacokinetic-based concerns, and address these issues according to the categories of absorption, distribution, metabolism, and excretion.

Absorption

Although there is an age-related decrease in small bowel surface and an increase in gastric pH, changes in drug absorption seem to be the pharmacologic parameter least affected by increasing age (Kane et al., 2004). In contrast, the distribution of a drug is influenced by age-related changes in body composition of water (total and intracellular) and lean body mass relative to body fat. Specifically, the percent of total body water decreases by 10% to 15% between the ages of 20 and 80 years. This relative decrease in total body water leads to a higher blood and tissue concentration of some water-soluble drugs. In addition, the ratio of lean mass to body fat decreases with age. Thus, a drug distributed only in lean tissue, such as lithium, should be given in a lower dose because of the decrease in lean body mass with aging (Lueckenotte, 1996).

Distribution

Although the percentage of lean body mass to body fat decreases with age, the percentage of body fat increases from 18% to 36% in men and from 33% to 45% in women. An increase in total body fat increases the volume of distribution for lipophilic drugs, such as the long-acting benzodiazepines, diazepam (Valium), and chlordiazepoxide hydrochloride (Librium). Thus, many lipid-soluble

psychotropic drugs are distributed more widely, prolonging the action of the drug and increasing the likelihood of serious adverse consequences (Keltner & Folks, 2005; Stahl, 2008).

In addition to changes in total body water and body fat, the distribution of drugs into the peripheral circulation and tissues is influenced by serum albumin (protein binding) and (1-acid glycoprotein levels. With age, there may be a decrease in serum albumin levels. This results in increased fractions of free drug (not bound to protein) circulating in the body. This is of great importance because the unbound, free drug is what is pharmacodynamically active. In contrast to decreasing levels of serum albumin, (1-acid glycoprotein levels increase with age resulting in the increased binding of drugs that normally bind to this protein. An increase in (1-acid glycoprotein levels may affect the distribution of a number of psychotropic drugs, such as the tricyclic antidepressants, resulting in a prolonged half-life of these drugs. However, the clinical consequences of an increase in (1-acid glycoprotein have not been well studied in older adults (Keltner & Folks, 2005; Stahl, 2008).

Metabolism

Drug metabolism in the older adult is complex, difficult to predict, and affected by age-related hepatic changes. These include a decrease in liver size, blood flow, and hepatic microsomal enzyme (cytochrome [CPY] P-450) activity. In addition, a variety of other factors can influence hepatic drug metabolism, such as caffeine; tobacco; foods that act as CPY P-450 inducers or inhibitors, such as grapefruit juice, cruciferous vegetables, or charbroiled meats; alcohol; current disease state; nutritional status; gender; genetic determinants; and life-long exposure to various chemicals (Stahl, 2008). There is evidence that the first phase of drug metabolism declines with age, whereas the second phase seems to be less affected. An older adult with normal liver function tests may not be able to metabolize drugs as efficiently as a younger individual, given normal changes in the hepatic system that occur with aging.

Excretion

Excretion of drugs by the kidneys is better understood than hepatic drug metabolism in the older adult. Age-related changes in renal function include decreases in renal blood flow, glomerular filtration rate, production of creatinine, and creatinine clearance. Because of an age-related decline in muscle mass resulting in the decreased production of creatinine, a serum creatinine level is not a reliable marker of renal function in the older adult. The serum creatinine, however, is used to calculate the creatinine clearance, a more accurate reflection of renal function in this patient population. A drug that depends on renal excretion for its elimination, such as lithium, is likely to accumulate to potentially toxic levels unless the dosage is adjusted to a lower dose in light of clinical monitoring of both therapeutic and potentially adverse effects (Keltner & Folks, 2005). Other factors, such as intrinsic renal disease, state of hydration, and cardiac output, also can affect the renal clearance of a drug. Thus, it is important to calculate a baseline estimate of creatinine clearance before initiating drug therapy in older adults.

In addition to the pharmacokinetic changes that occur with aging, pharmacodynamic changes also occur. These changes impact an individual's responsiveness to the concentration of a given drug (altered receptor response). It is known that an age-related sensitivity to both the therapeutic and toxic effects of many medications, especially centrally acting medications, increases. This sensitivity is heightened in the very frail and the very old individual. Kane et al. (2004) noted that this sensitivity was true for certain drugs, such as sedating medications, but not true for other drugs, such as blood pressure medications mediated by β-adrenergic receptors, which seem to decline with age. Although considerably less is known about the pharmacodynamic changes that occur with aging,

increased sensitivity to the concentration of a particular drug must be considered, particularly when the medication has serious adverse side effects.

It is also important to understand the types of drug interactions to prevent the potential detrimental effect from two or more drugs that can interact with each other. One type of interaction occurs when a drug interferes with another drug's ability to interact with the receptor responsible for effect. Another example of a potential drug–drug interaction occurs when one drug enhances another's therapeutic or adverse effect by stimulation of the receptor by both drugs. For example, two agents that have properties of lowering blood pressure, when combined, may lead to greater chances of hypotension. The other general type of drug interaction occurs when one medication affects the plasma concentration of another medication by affecting absorption, distribution, metabolism, or elimination. This is termed a "pharmacokinetic interaction."

The CYP P-450 isoenzymes are located mostly in the liver and the small intestine. They are responsible for the first phase of biotransformation, the rate-limiting step in drug clearance. A CYP P-450 drug interaction occurs when a drug either speeds up (induction) or slows down (inhibition) enzymatic activity. The most clinically relevant isoenzymes include CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Stahl, 2008). Competitive inhibition of the CYP P-450 hepatic isoenzymes is an example of this type of interaction and is common in psychotropic drug use. Visit www.druginteractions.com for a review of the rudiments of the P-450 system and pragmatic information related to assessment for potential drug interactions. An additional resource can be found at http://www.preskorn.com/. This is the Web site of Sheldon Preskorn, MD, a renowned scientist in the area of drug metabolism and P-450-driven drug interactions. His site is informative, user friendly, and contains an extensive collection of clinical resources related to the implications of P-450 in practice.

The choice, dose, and dosing frequency of a medication for an older adult must be carefully planned in light of the pharmacokinetic and pharmacodynamic changes that occur with aging. This is true for all medications prescribed for this population but is even more critical for the prescription of psychotropic medications, the second most common category of drugs prescribed for older adults after cardiac medications. Psychoactive drugs are prescribed for 65% of nursing home residents, with some residents using three or more psychoactive drugs concurrently (Beers & Berkow, 2004).

Forty-eight medications or classes of medications to avoid in older adults have been identified by a national expert panel charged with updating widely used criteria for potentially harmful medications in older adults (Fick et al., 2003). A study of adverse drug effects found that 35% of ambulatory older adults experienced an adverse drug effect and 29% required healthcare services (physician, emergency department, or hospitalization) for the adverse drug effect. Some two thirds of nursing facility residents have adverse drug effects over a 4-year period. Of these adverse drug effects, one in seven results in hospitalization (Fick et al.). Geriatrician Mark Beers (1997) is the developer of a well-documented list of medications to avoid in older adults, known as the "Beers Criteria," which continues to be a reliable guide to clinicians who provide treatment to this population. A complete list of the medications included in the Beers Criteria can be found at http://www.dcri.duke.edu/ccge/curtis/beers.html.

Voyer, Cohen, Lauzon, and Collin (2004) point out that the prevalence of psychotropic drug use among community-dwelling older persons (usually defined as those 65 years and older) varies from about 20% to 48%, and that many of these older adults use the psychotropic medications for more than 6 months. This time period may often exceed the time period for which the drug is needed (e.g., benzodiazepines). Along with the protracted use of these drugs may be the associated liabilities that are common to drug accumulation in older adults, caused by changes in pharmacokinetics. Such trends are noteworthy from the perspective that the use of these drugs may fall outside of

evidence-based recommendations, and as such create liabilities for both the patient and the clinician who prescribes the drugs.

Bartels et al. (2003) noted that until recently there has been little information available to guide the practitioner in choosing appropriate psychotropic interventions for older adults. Recent advances in mental health treatment have led to the development of an evidence base specific to older adults (Bartels et al.). Thus, prescribing a psychoactive medication for an older adult with multiple comorbidities, who is taking an average of four to five medications, requires a thorough knowledge of the psychotropic drug and the latest consensus data specific for prescribing for this population, particularly in light of the pharmacokinetic and pharmacodynamic issues addressed previously.

To accomplish successfully the goal of maximizing outcomes while minimizing adverse events requires a multifactorial approach to prescribing psychotropic agents in older adults. The practitioner must consider medical comorbidity and polypharmacy, age-related physiologic changes, cognitive ability, caregiver status, and psychosocial factors. Medical comorbidity and polypharmacy (nine or more medications or 12 or more doses per day) are common in the geriatric population. Polypharmacy has been shown to be a risk factor for developing adverse drug events in the older adult (Peterson et al., 2005). Proper education of patients and caregivers and monitoring medication regimens are important for early identification of adverse events and adherence problems. Equally important is the communication between different prescribers to avoid drug interactions and maximize outcomes.

Among older adults, as is the case with large numbers of the adult population in the United States, both over-the-counter medications and herbal supplements are commonly used to relieve symptoms (McEnany, 2001). Unfortunately, what many consumers do not realize is that "herbal" or "naturopathic" remedies are not benign substances, and are often cleared through hepatic metabolism, specifically by P-450 mechanisms. As such, the potential for drug interactions with prescribed medications is significant, and merits the attention of the prescriber. The clinician needs to assess usage patterns of both over-the-counter and herbal remedies closely to reduce the chances of a drug interaction and associated adverse events for the patient.

To ensure adherence feasibility the assessment of medication cost and insurance coverage is an important factor to consider. Sometimes the prescriber is forced to make medication choices based on external factors, such as insurance formularies or restrictions, and on the patient's ability to pay for medications. It is essential for clinicians to recognize that good prescribing practice is a multifaceted process as depicted in Figure 6-1.

Clinicians may find the Web site https://www.pparx.org/Intro.php helpful when dealing with patients who are uninsured or who have limited resources available for medications. This is an online resource that contains all of the details for how to access patient assistance programs for medications free of cost to the medically disadvantaged or indigent. The site has direct links to many of the pharmaceutical companies offering patient assistance programs, along with detailed descriptions of the procedures related to ordering medications.

Although psychiatric conditions are often underdiagnosed in the older adult, healthcare providers should carefully examine the necessity of pharmacotherapy before prescribing new medications. In addition, the necessity and compatibility of all long-term medications should be periodically reexamined. If deemed necessary, prescriptions, dosages, and intervals should be based on the patient's age, renal and hepatic function, and concomitant diseases and medications. To increase the quality of care and limit the inappropriate use of psychotropic medications in residents of long-term care facilities, the Omnibus Budget Reconciliation Act (OBRA) was passed in 1987. The interpretive guidelines enforcing OBRA were implemented in 1990 and updated in 1999. Because proper documentation of necessity and attempted withdrawal trials of medications

FIGURE 6–1

Multifaceted Process for Prescribing Psychiatric Medication in the Elderly.

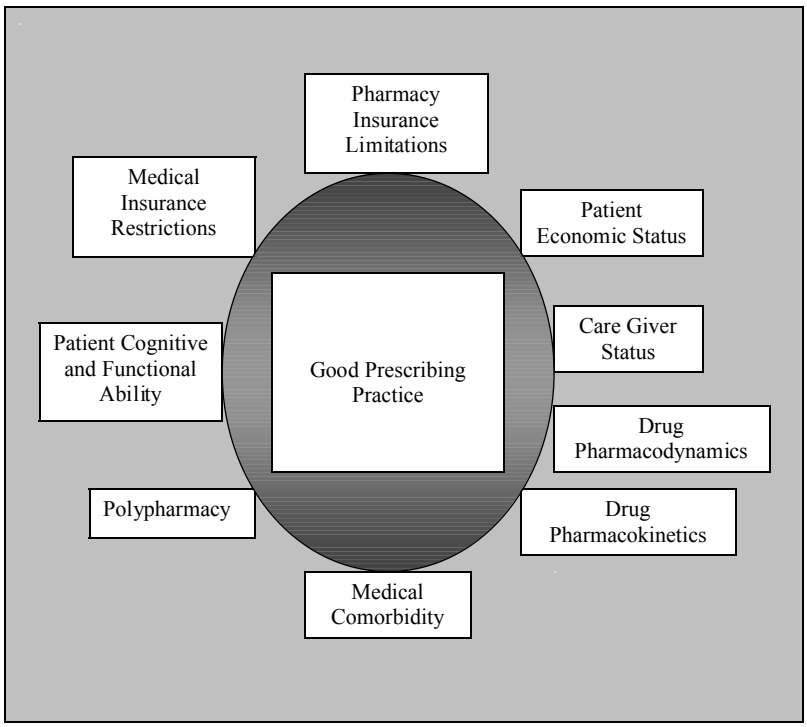

Figure 6-1 FPO

became requirements, the outcome of OBRA has been increased attention to appropriate prescribing of psychotropic medication in such a fashion as to minimize adverse events and detrimental effects on physical and cognitive function.

PSYCHOTROPIC DRUGS

Psychotropic drugs can be broadly categorized as antidepressants, anxiolytics, sedative-hypnotics, antipsychotics, and mood stabilizers. These categories of drugs, their characteristics, and the drugs included in each class are listed in Table 6-1. Each category of psychotropic drug is discussed in detail with recommendations for their use in older adults.

Antidepressants

The goal of antidepressant therapy includes improving and maintaining mood, physical and social daily functioning, and quality of life while minimizing side effects. Doses should be started low and titrated slowly to the desired effect. Antidepressants typically take 2 to 4 weeks before benefits can be discerned in the younger population, but 6 to 12 weeks in the older adult population. Titration should be adjusted based on tolerability of side effects and effectiveness.

Antidepressants can be subdivided into four categories: (1) tricyclic antidepressants (TCAs), (2) monoamine oxidase inhibitors (MAOIs), (3) selective serotonin reuptake inhibitors (SSRIs),

TABLE 6–1

Categories of Psychotropic Drugs

Category	*Characteristics*	*Drug Classes*
Antidepressants	Equally effective but differ based on side-effect profile and potential for drug interactions	Tricyclic antidepressants Monoaminine oxidase inhibitors Selective-serotonin reuptake inhibitors Nonselective-serotonin reuptake inhibitor second-generation antidepressants (dopamine reuptake inhibitors, 5HT2 antagonists) Serotonin-norepinephrine reuptake inhibitors
Anxiolytics	Short-acting agents without active metabolites preferred in older adults to minimize lasting adverse events	Short-acting benzodiazepines Long-acting benzodiazepines Buspirone
Sedative-hypnotics	Should be avoided because of side-effect profiles	Barbiturates Miscellaneous hypnotic/sedatives Melatonin agonists (may provide a safer alternative)
Antipsychotics	Second-generation agents in low doses preferred because of less anticholinergic and extrapyramidal system side effects BLACK BOX WARNING in relation to the use of these medications in persons with dementia	First-generation antipsychotics Second-generation antipsychotics
Mood stabilizers	Both on-label and off-label uses of medications aimed to stabilize mood	Lithium carbonate Divalproate Lamotrigine Others

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007).

and (4) non-SSRI second-generation antidepressants (Table 6-2). The latter category includes serotonin-norepinephrine reuptake inhibitors (SNRIs) and a dopamine-norepinephrine reuptake inhibitor.

Although the older TCAs are effective for treating depression, most should be avoided in the older adult because of their substantial side-effect profile, which includes excessive sedation; anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, and confusion); and cardiovascular effects (orthostasis, tachycardia, and electrocardiogram changes). Because of their cardiovascular effects, TCAs are lethal in overdose, which is always a serious concern in depressed patients. If the decision is to use a TCA, then the best choices are desipramine and nortriptyline, because these agents have the least anticholinergic side-effect profile. Interestingly, the TCAs have fallen out of fashion as first-line agents for the treatment of depression. However, their use is on the rise in off-label applications in the treatment of migraines, chronic pain, sleep disturbances, and various neuropathic pain syndromes. The concern related to use in depression also applies to use off-label.

TABLE 6–2

Categories of Antidepressants and Mode of Action

Drug Class	*Mode of Action*
Tricyclic antidepressants	Increases the synaptic concentration of serotonin or norepinephrine in the central nervous system by inhibition of their uptake by the presynaptic neuronal membrane
Monoamine oxidase inhibitors	Inhibits the monamine oxidase A and B enzymes responsible for the intraneuronal metabolism of norepinephrine and serotonin
Reversible inhibitors of monoamine oxidase, type A (not available in the United States)	Selectively inhibits monoamine oxidase type A
Selective serotonin reuptake inhibitors	Inhibits central nervous system neuronal reuptake of serotonin
Nonselective serotonin reuptake inhibitor second-generation antidepressants	Variety of modes of action, including effects on serotonin, norepinephrine, and dopamine

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007).

Although MAOIs, such as phenelzine (Nardil) and tranylcypromine (Parnate), have been found to be useful for some patients with atypical depression and in those resistant to the other antidepressants, they do have significant drug and food interactions and potentially can cause serious side effects. They can lead to a life-threatening rise in blood pressure, especially if combined with certain foods containing tyramine, such as wines, cheeses, smoked fish, beef or chicken liver, sausage, yeast, or certain bean pods. MAOIs also can potentiate many categories of drugs, such as central nervous system stimulants and sympathomimetics, and lead to hypertensive crisis. They are additive to the effect of sulfonyureas and can lower blood sugar to dangerous levels. Combining with other antidepressants has the potential to cause either seizures or serotonin syndrome, which may result in nausea, anxiety, tremor, or difficulty sleeping. MAOIs, therefore, are generally avoided in elderly patients because of their significant side-effect profile and food-drug and drug-drug interactions.

There are two types of monoamine oxidase (types A and B) and each of these enzymes is involved with the breakdown of neurochemicals in the synaptic cleft. The conventional MAOIs in use in the United States target type B. A more recently developed MAOI includes a selective and reversible MAOI that specifically targets monoamine oxidase type A. Examples of these drugs include moclobemide and brofaromine, but this class of antidepressants has not been approved for use in the United States. Lotufo-Neto, Trivedi, and Thase (1999) completed a meta-analysis on the effectiveness of these drugs and found them to have equal efficacy with tricyclics and to be well tolerated.

The SSRIs, noted in Table 6-3, create a more attractive alternative, although not without flaws. On a positive note, they have good efficacy data and because of an extended half-life, an advantage to adherence is once-daily dosing. However, they can cause a serious adverse event, such as serotonin syndrome, syndrome of inappropriate antidiuretic hormone (hyponatremia), and withdrawal

TABLE 6–3

Common SSRIs: Dosing and Hepatic Enzyme Affected

Medication	*Starting Dose in Older Adults Per Day (mg)*	*Maintenance Dose in Older Adults Per Day (mg)*	*Oral Solution Available*	*Hepatic Enzyme Affected*
Citalopram (Celexa)	10	20 to 40	Yes	Minimal
Escitalopram (Lexapro)	5	5 to 20	No	Minimal
Fluoxetine (Prozac)	10	20 to 40	Yes	CYP2C9, CYP2C19
Fluvoxamine (Luvox, Solvay)	50	50 to 200	No	CYP1A4, CYP2C9, CYP2C19
Paroxetine (Paxil, Paxil CR)	10	20 to 30	Yes	CYP2D6
Sertraline (Zoloft)	25	50 to 150	Yes	Minor CYP2D6, CYP3A4, CYP2C19

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007).

syndrome, if cessation is not titrated at an appropriate rate during the discontinuation of the drug. Discontinuation effects are more likely to occur with drugs in the SSRI class that have shorter half-lives (e.g., citalopram) versus those with longer half-lives (e.g., fluoxetine). Tolerability can be adversely affected by gastrointestinal effects, sexual dysfunction, and sleep disturbances. Although side effects tend to be an effect of the class of medication, drug-drug interactions are more individualized. Sleep disturbance, weight gain, and sexual dysfunction are very common to these agents.

The non-SSRI second-generation agents listed in Table 6-4 include venlafaxine (Effexor, Effexor XR); desvenlafaxine (Pristiq); duloxetine (Cymbalta); bupropion (Wellbutrin, Wellbutrin XR, Wellbutrin XL, Zyban); mirtazapine (Remeron); trazodone (Desyrel); and nafazodone (Serzone). In 2004, Bristol Meyers Squibb, the manufacturer of nefazadone, made the decision to remove this drug from the market because of issues of hepatotoxicity (Choi, 2003). Two newer SNRI antidepressants have been introduced to the market: duloxetine and desvenlafaxine. Each agent has unique characteristics relevant to prescribing in the older adult. Venlafaxine inhibits the reuptake of serotonin and with higher doses, norepinephrine. Venlafaxine is available in both immediate and extended-release preparations, and documentation states that the extended-release form of the medication has an improved side-effect profile, which may enhance adherence (Nemeroff, 2003). Both venlafaxine and desvenlafaxine are similar in action to the older TCAs but without the anticholineric side effects of the TCAs. Venlafaxine has been approved for use in both depression and generalized anxiety disorder, whereas desvenlafaxine is only indicated for the treatment of depression. Like other antidepressants that interfere with serotonin reuptake, venlafaxine may interact pharmacodynamically with other serotonergic agents (e.g., tryptophan or dextromethorphan) and should be avoided because

TABLE 6–4

Non-SSRIs: Dosing and Hepatic Enzyme Affected

Medication	*Starting Dose in Older Adults (mg)*	*Maintenance Dose in Older Adults Per Day (mg)*	*Hepatic Enzyme Affected*
Venlafaxine (Effexor, Effexor XR)	25 BID; XR, 37.5 QD	75 to 150	CYP2D6, CYP2E1
Duloxetine (Cymbalta)	20 BID	Up to 30 BID	CYP1A2, CYP2D6
Desvenlafaxine (Pristiq)	50 QD	50 QD	Minimal, if any
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	37.5 BID; SR, 100 QAM; XL, 150 QAM	100 to 150	CYP2B6, CYP2D6
Mirtazapine (Remeron, Remeron SolTab)	7.5 QHS	15 to 30	CYP1A2, CYP2D6, CYP3A4
Trazodone (Desyrel)	25 QHS	25 to 50	CYP3A4
Nefazodone (Serzone [no longer available in the United States])	50 BID	200 to 400	CYP3A4, CYP2D6

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007); Package insert, Pristiq, Wyeth (2008).

of potential serotonin syndrome. Side effects with venlafaxine are similar to the SSRIs with the addition of dose-related elevated blood pressure. Proper monitoring of blood pressure should be performed initially and at follow-up visits because of the prevalence of hypertension and cardiovascular diseases in the older adult. Elevated serum levels and toxicity can occur if combined with either CYP2D6 (paroxetine, amiodarone, cimetidine, and quinidine), or CYP3A4 (clarithromycin, erythromycin, diltiazem, grapefruit juice, and ketoconazole) inhibitors (Semla, Beizer, & Higbee, 2003). Although dosage adjustment for age alone is unnecessary, dosing should be started low and increased gradually (Wyeth-Ayerst, 2003). A 25% decreased dosage adjustment is required with renal impairment and 50% with moderate hepatic impairment (Semla, Beizer, & Higbee).

Desvenlafaxine is the newcomer to the market as of 2008 (Wyeth, 2008) and it has some differences from venlafaxine on some salient points. The most important difference is in the lack of interference with other drugs metabolized through the P-450 enzyme system. This is an important feature for older adults who are likely to be on a number of prescription and over-the-counter medications. It has a once-daily dosing recommendation, which may enhance adherence.

Desvenlafaxine has been indicated by the Food and Drug Administration (FDA) for the

treatment of major depressive disorder (Wyeth, 2008). However, it has been used in a number of off-label applications in the treatment of fibromyalgia and neuropathic pain (Stahl, 2008). This medication requires adjustment in dosing in older adults who have hypertension, hypercholesterolemia, history of clotting factor disorder, seizures, stroke, glaucoma, and renal or hepatic disease. It is contraindicated with concomitant use of MAOIs.

Duloxetine is an SNRI that has been indicated by the FDA for the treatment of major depression, generalized anxiety disorder, fibromyalgia, and diabetic neuropathic pain. This medication may be administered in either a once-daily or twice-daily schedule, depending on the tolerability of the medication. It is contraindicated with concomitant use of MAOIs. Potential adverse effects with this medication are not dissimilar to other SNRIs and include potential for hepatotoxicity, orthostasis, abnormal bleeding, seizures, hyponatremia, and urinary hesitation and retention (Eli Lilly, 2004). Coadministration of duloxetine with potent CYP1A2 inhibitors should be avoided. Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 results in higher concentrations (on average of 60%) of duloxetine. Use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine should ordinarily not be prescribed for patients with substantial alcohol use (Eli Lilly).

Bupropion is a weak SNRI and it has some dopamine reuptake inhibition (Glaxo SmithKline, 2003). It offers the advantages of no sedative side effects, no cardiotoxicity, and no sexual side effects. Buproprion, however, can increase agitation, headache, tremor, insomnia, and anorexia. The primary safety issue with bupropion is its ability to cause seizures. Coadministration of bupropion with drugs that lower the seizure threshold, such as typical antipsychotics, TCAs, fluoroquinolones, theophylline, and any drug that can increase buproprion levels or toxicity (2D6 substrates, levodopa, MAOIs), should be avoided because of the seizure risk. Dosage adjustment must be made because of hepatic or renal disease. Bupropion is available in immediate-release, sustained-release, and once-a-day formulations. There is some evidence in the literature that the extended-release formulation may have a more tolerable side-effect profile, possibly contributing to greater adherence (Nemeroff, 2003). Both the immediate-release and sustained-release formulations of these drugs require twice-daily dosing, whereas the once-a-day version is given in a single dose.

Mirtazapine is different than the SNRIs in that it antagonizes ($_2$-adrenergic receptors, blocks two serotonin receptor subtypes, and has a strong affinity for histaminic receptors. It causes somnolence, particularly at lower doses, which relates to its affect on antihistamine receptors and should therefore be dosed at bedtime. Mirtazapine has low risks of drug interactions and no cardiotoxicity. It also has been associated with weight gain and can therefore be useful in depressed anorexic older patients. In rare instances, it can cause agranulocytosis. It is important to monitor WBC and neutrophil counts if the patient presents with associated signs or symptoms, such as infection or fever. Mirtazipine clearance is decreased up to 40% in older adults, particularly with males, compared to younger males, so dosing should be started low (Organon, 2002). Nicholas and colleagues (2003) have documented the possibility of elevated total cholesterol with the use of this agent.

Trazodone and nefazodone hydrochloride are serotonin reuptake inhibitors and serotonin 5-HT2 receptor antagonists. Trazodone causes significant sedation without significant anticholinergic activity and should therefore be reserved for use at bedtime for patients with insomnia. Nefazodone has less sedative effect, but has significant drug interactions, and has also been known to cause hepatic failure. Nefazodone inhibits the CYP3A4 isoenzyme and also increases blood levels of digoxin, a drug with a narrow therapeutic index (Bristol-Myers Squibb, 2001). Because of concerns of hepatotoxicity, the sale of the brand name antidepressant Serzone was discontinued by the

manufacturer in 2003. Since the drug's introduction in 1994, there have been 51 Canadian reports of adverse hepatic events, including jaundice, hepatitis, and hepatocellular necrosis. In two of these cases the patients subsequently underwent liver transplantation (Choi, 2003). The drug remains available in the generic form as nefazodone.

Discontinuing antidepressants too quickly can lead to a withdrawal syndrome. Antidepressant withdrawal syndromes have been reported with the TCAs, the SSRIs, and the SNRIs (Perahia, Kajdasz, Desaiah, & Haddad, 2005; Stahl, 2008). The syndrome can consist of a cluster of symptoms that may include headaches; nausea; dizziness; unstable moods; gastrointestinal upset; recurrence of depression; bizarre dreams; strokelike symptoms; abnormal sensations of burning, prickling, or tingling; or auditory hallucinations. TCA-related withdrawal also can include cardiac arrhythmias (Dilsaver, Greden, & Snider, 1987). Some investigators have discussed atypical symptoms of antidepressant discontinuation, including discontinuation-associated mania (Andrade, 2004), although this is very rare in clinical practice. What is clear from the body of literature is that clinicians need to be well-informed of these potential manifestations of discontinuation syndrome to ensure comfort and safety during antidepressant withdrawal. It is critical to address the issue of potential for discontinuation syndrome with patients before prescribing the medication and during the course of the medication trial. This strategy may help to reduce a negative experience in the course of the medication trial and possibly enhance adherence to the prescribed regimen.

Although it is important to recognize the individual differences between the classes and individual antidepressants, it should be understood there are no clear directives for choosing an antidepressant based on the summary of current clinical trials in the older adult population (Alexopoulos, Katz, Reynolds, Carpenter, & Docherty, 2001). All antidepressant classes demonstrate superiority over placebo in the older adult population. The provider's responsibility in prescribing, therefore, is to choose the best particular antidepressant based primarily on the potential for adverse effects, drug-drug interactions, and cost for each individual patient.

One topic that merits some attention from clinicians is the issue of tachyphylaxis related to the use of antidepressants. This phenomenon is best described as a precipitous or insidious loss of therapeutic effect from the use of the antidepressant. It is not well-understood and there have been no studies published to document predictors of this loss of effect. Clinicians are well-advised to review the practice guidelines available from the American Psychiatric Association, including the guideline on the treatment of depression (www.psych.org) (American Psychiatric Association, 2000). These guidelines offer evidence-based guidance related to the community standard for the treatment of select psychiatric disorders, including depression.

FDA Warnings on Antidepressant Use and Suicide Risk

In 2004, the FDA issued a black box warning on antidepressants regarding the risk of suicidal thinking and behavior (Cipriani, 2005). According to the FDA, use of antidepressants in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, particularly in the first 2 months of therapy (NIMH, 2009). This warning was updated in 2007 to also include language stating that scientific data did not show this increased risk in adults older than 24, and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality. The warning statements emphasize that depression and certain other serious psychiatric disorders are themselves the most important causes of suicide (FDA, 2007) rather than particular drug-related responses. A set of guidelines from the FDA on the use of antidepressants and clinical monitoring recommendations can be found at http://www.fda.gov/cder/drug/antidepressants/antidepressants_MG_2007.pdf.

Antipsychotics

FDA Black Box Warning on the Use of Antipsychotic Medications in those with Dementia

In April 2005, the FDA informed healthcare professionals and the public about the increased risk of mortality in elderly patients receiving second-generation (atypical) antipsychotic drugs to treat dementia-related psychosis. At that time, the analyses of 17 placebo-controlled trials that enrolled 5377 elderly patients with dementia-related behavioral disorders revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Although the causes of death were varied, most of the deaths seemed to be either cardiovascular (e.g., heart failure or sudden death) or infectious (e.g. pneumonia) in nature. Based on this analysis, the FDA requested that the manufacturers of second-generation antipsychotic drugs include information about this risk in a boxed warning and the warnings section of the drugs' prescribing information. Although the initial warnings were related to second-generation antipsychotic medications, in 2005 the warning was extended to include both conventional and second-generation antipsychotic medications (Kuehn, 2005). The specifics of the 2005 Health Advisory can be found at http://www.fda.gov/cder/drug/advisory/antipsychotics.htm, and the 2008 information for healthcare professionals is also available on the FDA Web site at http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm.

Experts recommend antipsychotics in several geriatric psychiatric disorders, such as late-life schizophrenia, delusional disorder, and psychotic mood disorders (Alexopoulos, Streim, Carpenter, & Docherty, 2004). Providers must assess if symptoms presenting as these disorders are the result of treatable etiologies. These etiologies may include the use of pharmacologic agents, such as ß-blockers, anticholinergics, or steroids; dosage additions or changes of other medications; or conditions, such as fluid or electrolyte loss, or infections. Correction by addressing the underlying cause, such as removing offending agents or treating a disease state, should be the primary goal of therapy. If symptoms continue, an antipsychotic may be temporarily considered. Frequent attempts to withdraw the agent at appropriate intervals based on the disease state are important (Alexopoulos et al.). Gradual reduction is a key regarding attempts to discontinue antipsychotics. Abrupt discontinuation can lead to cholinergic rebound, withdrawal dyskinesias, and relapse or rebound syndrome.

Both conventional and second-generation antipsychotics have been clinically evaluated with older adults. The two classes of antipsychotics differ in both side-effect profiles and documented efficacy and can be considered for use in the older population. However, second-generation agents have generally been considered first line because of what previously was believed to be a more favorable side-effect profile than that of the conventional antipsychotics (Bartels et al., 2003). The second-generation agents include clozapine (Clozaril), risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify). These drugs, with dosing schedule and adverse effects, are featured in Table 6-5. The drug interactions of the second-generation antipsychotics and geriatric considerations are noted in Table 6-6. The conventional agents include haloperidol, fluphenazine, trifluoperazine, chlorpromazine, and thioridazine.

The conventional antipsychotics offer a relatively poor benefit-to-risk ratio because of significant side effect, drug–drug, and drug–disease interaction profiles in the older adult population (Kastrup, 2004). They have considerable anticholinergic and sedative properties, both of which raise serious concerns in older adults. They can lead to falls, fractures, weight loss, pressure ulcers, incontinence, urinary tract infections, and decreased cognition. In addition, they are associated with movement disorders, such as tardive dyskinesia (TD) and extrapyramidal symptoms (EPS). TD is a troubling side effect characterized by involuntary and abnormal movements. EPS can cause patients to experience restlessness, an inability to sit still, or muscle rigidity. Conventional

TABLE 6–5

Second-Generation Antipsychotics: Dosing and Adverse Effects*

Medications	*Starting Dose*	*Maintenance Dose*	*Adverse Effects*
Clozapine (Clozaril)	25 mg/day	Up to 300 to 450 mg/day over slow titration	Agranulocytosis, anticholinergic side effects, cognitive and motor impairment, orthostasis, tachycardia
Risperidone (Risperdal)	0.25 to 0.5 mg once or twice daily	0.75 to 1.5 mg/day	Extrapyramidal symptoms, anticholinergic effects, orthostasis, sedation (all increased at higher dosages), slight increased risk of stroke
Olanzapine (Zyprexa)	5 mg/day	10 to 20 mg/day	Hyperprolactinemia, dose-related somnolence, headache, diabetes, dyslipidemia, slight increased risk of stroke
Quetiapine (Seroquel)	25 mg twice daily	150 to 750 mg/day	Somnolence, dyslipidemia, diabetes, slight increased risk of stroke, seizures, thyroid dysfunction, orthostasis
Ziprasidone (Geodon)	20 mg twice daily	20 to 80 mg twice daily	QT prolongation, cognitive and motor impairment, rash, orthostasis
Aripiprazole (Abilify)	5 mg daily	10 to 30 mg/day	Headache, orthostasis, anxiety, and insomnia

*Neuroleptic malignant syndrome has been reported with all second-generation agents.

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007).

agents also cause increased prolactin secretion, which can lead to such problems as sexual and reproductive dysfunction, breast pathology, bone demineralization, depression, memory deficits, and damage to the cardiovascular endothelium (Bezchlibnyk-Butler, Jeffries, & Virani (2007).

Although the newer second-generation antipsychotics have become an attractive alternative, they are not devoid of side effects. Each drug in the class has slightly different characteristics, all of which are important to consider in the older adult population. Possible adverse effects of this class include headache, orthostatic hypotension, falls, cardiovascular effects, weight gain, dyslipidemia, diabetes, and to a lesser extent TD and EPS. As a class, however, the second-generation agents have a lower affinity for the dopamine D_2 receptor, which accounts for the relatively low incidence of EPS, TD, and prolactinemia. The faster the drug dissociates from the D_2 receptor, the lower the rates of these treatment-induced D_2-related side effects. Clozapine and quetiapine have fast dissociation from the D_2 receptor. Olanzapine and risperidone have slower dissociation and the conventional antipsychotics have even slower dissociation. Therefore, the conventional agents have the highest dopamine D_2-related side effects, followed by olanzapine and risperidone. The dopamine-related side-effect profiles of some second-generation agents are dose-dependent because of loss of specificity. For example, increasing doses of olanzapine, risperidone, and ziprasidone raise relative D_2 occupancy and can begin to resemble side-effect profiles of conventional agents at higher dosages. In older adults, this can be more problematic and occur at lower dosages than in younger age groups (Jeste, 2004).

TABLE 6–6

Second-Generation Antipsychotics: Drug Interactions and Geriatric Considerations

Medications	*Drug Interactions*	*Geriatric Considerations**
Clozapine (Clozaril)	Benzodiazepines, antihypertensives, anticholinergics, CYP1A2	Not recommended for nonpsychotic patients
Risperidone (Risperdal)	CYP2D6 and CYP3A4, increased hypotension with antihypertensives, decreased levels with inducers, St. John's wort	Oral solution can be mixed with water, orange juice, or low-fat milk but not with cola, grapefruit juice, or tea
Olanzapine (Zyprexa)	CYP1A2, CYP2D6, increased hypotension with antihypertensives, decreased levels with inducers, St. John's wort	Half-life 1.5 times that of younger adults
Quetiapine (Seroquel)	CYP3A4, clearance increased with phenytoin	No oral solution available
Ziprasidone (Geodon)	Increased hypotension with antihypertensives, other agents that affect QTc prolongation	No dosage adjustment recommended; start low and titrate slowly based on response, avoid in patients with cardiac disease
Aripiprazole (Abilify)	CYP2D6, CYP3A4, highly protein bound	Once-daily dosing, does not cause weight gain or electrocardiogram changes

*Metoclopramide (Reglan), because of its affinity for dopamine, increases extrapyramidal symptoms, whereas the effects of levodopa may be antagonized by antipsychotics.

Source: Adapted from Desai (2003); Semla (2003).

Second-generation antipsychotics have been studied much more extensively in younger populations than in older age groups and have been found to differ from conventional agents in that they have greater ability to treat negative symptoms. In 2004, Marder et al. published a consensus paper on physical health monitoring with persons treated with second-generation antipsychotics. This paper discusses the potential problems with lipid dysregulation, insulin resistance, and potential for type 2 diabetes in conjunction with these agents. In many ways, these problems are the equivalent of what TD was to the conventional antipsychotic agents, and needs to be addressed by any clinician who is working with patients receiving these agents as part of their treatment plan. There are specific guidelines for monitoring weight, lipids, and glucose, and these guidelines have become a dimension of the community standard of practice to which all clinicians are accountable. Additionally, the FDA requires that second-generation antipsychotic medications carry a warning related to risk of hyperglycemia and diabetes (Rosack, 2003). Such changes carry significant implications for the monitoring of older adults who are treated with these agents.

A great deal has been learned since 2004 because of a more concerted effort to understand the metabolic effects of the second-generation antipsychotic medications. It seems that the only medication from this generation of medications that holds significantly less liability for metabolic adverse effects is aripiprazole (Stahl, 2008). The remainder of the agents in this class has

vulnerabilities associated with risks for metabolic dysregulation. Stahl uses the analogy of a highway when looking at the trajectory of liabilities associated with second-generation antipsychotic medications. He discusses that the entrance ramp for the metabolic highway is increased appetite and weight gain associated with these medications, and how these factors combined may cause an increase in body mass index to > 25. As one moves down the highway, the process continues with obesity, insulin resistance, and dyslipidemia coupled with increases in fasting triglyceride levels. The end of the road is marked with hyperinsulinemia, leading to pancreatic beta cell failure, prediabetes, and finally diabetes.

The American Diabetes Association in conjunction with the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Society for the Study of Obesity examined the evidence related to metabolic dysregulation and put forth recommendations for clinical monitoring (ADA et al., 2004). The guidelines recommend that before the start of a second-generation antipsychotic medication a comprehensive family history of diabetes, cardiovascular disease, obesity, dyslipidemia, and hypertension needs to be taken. Weight must be checked at baseline and then at 4, 8, and 12 weeks and quarterly thereafter. Waist circumference must be measured at baseline and annually. Blood pressure and fasting glucose should be monitored at baseline, 12 weeks, and annually. Finally, fasting lipid monitoring should occur at baseline, 12 weeks, and then at 5-year intervals, providing that the results are normal. A PDF file of the monitoring recommendations can be found at http://www.ohsu.edu/medicine/residency/handouts/pharmpearls/Psychiatry%20CNS%20Neuro/MonitoringTheMetabolicEffectsOfAtypicalAntipsychotics.pdf

Clozapine has been studied for the treatment of psychotic symptoms, including those associated with dementia, and demonstrates overall benefit in over half of the older adult patients treated, especially at low doses. It has minimal effect in the striatal area, which explains its relative low potential for extrapyramidal side effects. Clozapine, however, does have other serious potential side effects in the older adult, such as seizures, hypotension, and potent anticholinergic effects. Even more limiting is the potential of clozapine-induced agranulocytosis, which can have an incidence as high as 1.3% per year (Novartis, 2002), but more commonly is cited in the range of 0.8% of patients treated with this medication and agranulocytosis may occur in patients even after years of uneventful treatment (Sedky, Shaughnessy, & Hughes, 2005). The risk of fatal agranulocytosis requiring frequent blood monitoring makes it more restrictive to use than other second-generation antipsychotic medications. Clozapine may be considered in older adults refractory to all other choices and possibly in patients with Parkinson's disease, because it does not increase the motor symptoms, like many of the other antipsychotic agents.

Risperidone affects serotonin and dopamine and has been shown to improve both negative and positive symptoms of psychoses while reducing the incidence of EPS (Jeste et al., 2000). Risperidone should be dosed as low as possible to maintain efficacy and prevent dose- related D_2 motor side effects. Risperidone has been evaluated in several open-label studies and case studies, and one large randomized controlled trial in older adults with positive benefit (De Deyn et al., 2005).

Olanzapine is thought to work through an antagonism of both dopamine and serotonin receptors. It does affect muscarinic, histamine, and α_1-receptors to a degree that explains potential anticholinergic side effects, sedation, and hypotension. Studies of olanzapine use in the older adult have shown therapeutic effects across a number of conditions not related to dementia, particularly with delirium (Ozbolt, 2008). Olanzapine can increase the potential for development of dia betes and associated problems. Olanzapine can also contribute to the development of dyslipidemia. Therefore, proper monitoring for these two conditions is necessary.

Quetiapine is thought to work through a combination of dopamine and serotonin antagonism. It has no appreciable affinity for muscarinic or benzodiazepine receptors but does cause some blockade at histamine and ($_1$-receptors. Therefore, quetiapine can cause somnolence and orthostatic hypotension. Quetiapine does have a good EPS tolerability profile across the entire dose range (AstraZeneca Pharmaceuticals LP, 2004). The most common adverse events exhibited across placebo-controlled trials included headache, somnolence, and dizziness (Tariot, Salzman, Yeung, Plutz, & Rak, 2000). Quetiapine has been shown to be effective in the treatment of psychosis in older adults and in patients with Parkinson disease. Effective doses are often lower when used in older adults (Friedman & Factor, 2000).

Ziprasidone and aripiprazole are two antipsychotic medications that have been used in the treatment of older adults with psychiatric illnesses. In general, there is no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in older adults compared to younger adults. However, dosages should still be started low and titrated slowly to therapeutic response with careful monitoring of potential side effects, such as orthostasis (Pfizer, 2002). Aripiprazole, another new antipsychotic, has common side effects of somnolence and orthostatic hypotension (Bristol-Myers Squibb, 2003; Burris et al., 2002). Aripiprazole is the first antipsychotic agent on the market whose mechanism of action includes dopamine partial agonism and serotonin antagonism. This unique mechanism of action places it in a class by itself, and it may be the first "atypical" second-generation antipsychotic agent. The alleged benefits of aripiprazole include an absence of hyperprolactinemia, reduced risk for weight gain and type 2 diabetes, and absence of dyslipidemia (Davies, Scheffler, & Roth, 2004).

It is important to note that the misuse of antipsychotics in older adults, particularly in long-term care settings, prompted the passage of OBRA in 1987 with modifications in 1990. This act mandated nursing home reform. Among its many stipulations, it stated that residents had the right to be free from chemical and physical restraints imposed for the purpose of convenience or discipline and not required to treat a medical condition. Further, there must be documented need for the use of this category of drugs to treat a specific condition. This act focused on improving quality of life and eliminating the unnecessary use of antipsychotic, anxiolytic, and sedative hypnotic drugs as a means of chemically restraining older adults in long-term care settings.

Anxiolytics

Proper treatment of anxiety in older adults requires proper diagnosis by addressing organic causes, comorbid psychiatric conditions, or a medication that causes anxiety-related side effects. There are very little evidence-based data to guide anxiolytic therapy (Bartels et al., 2003). However, antianxiety medications should be prescribed based on the suitability of the drug for an individual patient, taking into account potential side effects and compatibility with the existing medication profile (Stahl, 2008). Antidepressants may be recommended as first-line therapy for anxiety disorders, but a short course of a benzodiazepine sometimes is considered (Alexopoulos et al., 2004). If a benzodiazepine is prescribed, it is important to appreciate the potential risks associated with its use.

Benzodiazepines have a side-effect profile particularly dangerous in older adults. Benzodiazepines are likely to cause sedation and a decrease in hand-eye coordination. The outcome of benzodiazepine use at modest doses impairs driving performance in the older driver to a level similar to the legal definition of alcohol intoxication (Beers & Berkow, 2004). Ataxia, slurred speech, impaired coordination, confusion, poor concentration, memory loss, sleep disturbances, and depressive symptoms also may occur. Patients should be monitored closely for adverse effects.

OBRA guidelines for benzodiazepine use with residents of long-term care facilities are fairly specific related to use with proper diagnoses, which drugs to avoid, duration of treatment, attempts at withdrawal of medication, and maximum daily dose (OBRA, 1987). Generally, geriatric patients experience fewer adverse effects from shorter-acting drugs without active metabolites, such as alprazolam, lorazepam, and oxazepam. Longer-acting drugs, such as diazepam and chlordiazepoxide, should be avoided. Short-acting benzodiazepines are listed in Table 6-7 with the recommended dosing schedule. It is generally recommended to use low regularly scheduled doses, but as needed dosing (prn) may be beneficial in certain patients. Clinicians need to consider when and how to discontinue the antianxiety medications once they are started. A brief period of 4 to 6 weeks may be all that is required for treatment, but benzodiazepines may require an additional 3 to 4 weeks to be gradually tapered. Older adults should be aware of the need for short-term treatment with these agents, to prepare them better for proper titration off the drug at the appropriate time. Tapering a benzodiazepine too quickly can lead to rebound anxiety or even a withdrawal syndrome with possible seizures.

An alternative to benzodiazepines is buspirone (Buspar). Buspirone is less sedating than the benzodiazepines and is not addicting. Efficacy and safety of this drug is reported to be equal in older adults compared to younger adults (Semla, Beizer, & Higbee, 2003). The initial dose is 5 mg twice daily and titrated by 5 mg daily up to an average dose of 20 to 30 mg divided into two or three doses per day. Buspirone takes longer to show subjective benefit than benzodiazepines; it usually begins to show benefit after 2 weeks and maximum benefit after 4 weeks of continuous therapy. Because of this delay in effect, patients who have used benzodiazepines in the past may be resistant to using buspirone. Concomitant use of benzodiazepines with buspirone reduces the effectiveness of buspirone.

TABLE 6–7

Preferred Benzodiazepines and Dosing Schedule*

Medication (Short-Acting Benzodiazepines)	*Initial Dose (mg)*	*Recommended Maximum Daily Dose (mg)**	*Dosing in Hepatic and Renal Disease*	*Dosage Forms*
Alprazolam (Xanax)	0.125 to 0.25 BID	0.75	Decrease 50% in hepatic impairment, avoid in cirrhosis, caution in renal disease	Tablet, liquid
Lorazepam (Ativan)	0.25 to 0.5 BID	2	Caution if renal or hepatic disease	Tablet, liquid, intramuscular injection
Oxazepam (Serax)	10 BID	30	Avoid in hepatic disease, caution yet safer option in renal impairment	Tablet, capsule

* Per HCFA guidelines for residents of long-term care facilities.

Source: Adapted from Bezchlibnyk-Butler, Jeffries, & Virani (2007).

SUMMARY

Psychotropic medications are the second most commonly prescribed class of drugs in the geriatric population and the class most frequently associated with adverse drug reactions (Ives, 2001). It is essential for clinicians to recognize that good prescribing practice is a multifaceted process. This process not only involves the clinician's knowledge of pharmacotherapeutics, but takes into account patient and caregiver status, and financial concerns and insurance restrictions. The treatment of mental illness in older adults, as noted in this chapter, presents challenges unique to this patient population. By carefully considering and weighing the many factors that influence the treatment of mental illness in older adults, clinicians will evidence the very best prescribing practice as they address the mental health needs of older adults.

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