Chapter 20. Psychopharmacology © American Psychiatric Publishing

http://dx.doi.org/10.1176/appi.books.9781615370054.ds20

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Pharmacological intervention in late life requires special care. Older patients are more susceptible to drug-induced adverse events. Most concerning, several psychotropic medications have been associated during the past decade with serious adverse events, including increased mortality risk. Older persons are also more likely to experience adverse effects, including cardiac effects such as prolonged QTc, arrhythmias, and sudden death; peripheral and central anticholinergic effects such as constipation, urinary retention, delirium, and cognitive dysfunction; antihistaminergic effects such as sedation; and antiadrenergic effects such as postural hypotension that not only interfere with basic activities but also lead to falls and fractures. In addition, older patients might develop adverse effects such as hyponatremia, bleeding, and altered bone metabolism. Increased susceptibility to these various adverse effects in elders may be a result of the pharmacokinetic and pharmacodynamic changes associated with aging, such as diminished glomerular filtration, changes in the density and activity of target receptors, reduced liver size and hepatic blood flow, and decreased cardiac output (Pollock et al. 2009; Uchida et al. 2009) (Table 20–1).

Physiological changes in elderly persons associated with altered pharmacokinetics

Organ system	Change	Pharmacokinetic consequence
Circulatory system	Decreased concentration of plasma albumin and increased α1-acid glycoprotein	Increased or decreased free concentration of drugs in plasma
Gastrointestinal tract	Decreased intestinal and splanchnic blood flow	Decreased rate of drug absorption
Kidney	Decreased glomerular filtration rate	Decreased renal clearance of active metabolites
Liver	Decreased liver size; decreased hepatic blood flow; variable effects on cytochrome P450 isozyme activity	Decreased hepatic clearance
Muscle	Decreased lean body mass and increased adipose tissue	Altered volume of distribution of lipid-soluble drugs, leading to increased elimination half-life

Source. Adapted from Pollock BG: "Psychotropic Drugs and the Aging Patient." Geriatrics 53 (suppl 1): S20–S24, 1998. Used with permission.

Illnesses that affect many elderly persons (e.g., diabetes) further diminish the processing and removal of medications from the body. In addition, polypharmacy and the associated risk of drug interactions add another level of complexity to pharmacological treatment in older patients. Poor adherence to treatment regimens—which can be a result of impaired cognition, confusing drug regimens, or lack of motivation or insight associated with the psychiatric disorder being treated—is a significant obstacle to effective and safe pharmacological treatment. Finally, psychotropic medications are not as extensively studied in elders as in younger individuals or in patients without comorbid medical illness (Mulsant 2014; Pollock et al. 2009). New methodologies such as population pharmacokinetics can help to address the lack of information about dosage and drug-drug interactions (Jin et al. 2010). Nonetheless, even with currently available

knowledge, medications cause considerable morbidity in elders. In a study by Laroche et al. (2007), 66% of the admissions to an acute geriatric medical unit were preceded by the prescription of at least one inappropriate medication; even among patients taking appropriate medications, the prevalence of adverse drug reactions was 16%.

Despite these challenges, psychiatric disorders can be treated successfully in late life with psychotropic drugs. In this chapter, we summarize relevant geriatric data published as of November 2014 on the efficacy, tolerability, and safety of the major psychotropic drugs.

Antidepressant Medications

Six selective serotonin reuptake inhibitors (SSRIs) are available in the United States: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. They are approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder (all except fluvoxamine) and several anxiety disorders (generalized anxiety disorder: escitalopram, paroxetine; obsessive-compulsive disorder: fluoxetine, fluvoxamine, paroxetine, sertraline; panic disorder: fluoxetine, paroxetine, sertraline; posttraumatic stress disorder: paroxetine, sertraline; and social anxiety disorder: paroxetine, sertraline in adults). In older adults, SSRIs remain first-line antidepressants (Sonnenberg et al. 2008) because of their broad spectrum of action, high efficacy (Mukai and Tampi 2009; Pinquart et al. 2006; Tedeschini et al. 2011), ease of use, good tolerability, and relative safety (Mulsant et al. 2014). More than 40 randomized controlled trials (RCTs) of SSRIs involving more than 6,000 geriatric patients with depression have been published (Table 20–2). However, as with most drugs, few clinical trials of SSRIs have been conducted under “real-life” geriatric situations (e.g., in long-term-care facilities) or in very old patients. Overall, published trials support the efficacy and tolerability of SSRIs in older patients with major depression (Tedeschini et al. 2011). These patients are at high risk for relapse and recurrence, and maintenance therapy with escitalopram or paroxetine has been shown to be effective in their prevention (Gorwood et al. 2007; Reynolds et al. 2006). Many open studies and some small controlled trials in special populations also have concluded that SSRIs are reasonably efficacious, safe, and well tolerated in older patients with mild cognitive impairment (Devanand et al. 2003; Reynolds et al. 2011), minor depression (Lavretsky et al. 2010; Rocca et al. 2005), schizophrenia (Kasckow et al. 2001), cardiovascular disease (Glassman et al. 2002; Serebruany et al. 2003), cerebrovascular disease (Y. Chen et al. 2007; Murray et al. 2005; Rampello et al. 2004; Rasmussen et al. 2003; Robinson et al. 2000, 2008), Parkinson’s disease (Barone et al. 2006; Devos et al. 2008), or other medical conditions (Arranz and Ros 1997; Evans et al. 1997; Goodnick and Hernandez 2000; Karp et al. 2005; Lotrich et al. 2007; Trappler and Cohen 1998), as well as in family dementia caregivers with minor or major depression (Lavretsky et al. 2010).

Selective Serotonin Reuptake Inhibitors

Summary of published randomized controlled trials of selective serotonin reuptake inhibitors for the acute treatment of geriatric depression

Medication	No. of published trials (cumulative no. of older participants)	Dosages studied (mg/day)	Comments
Citalopram	7a (1,343)	10–40	Citalopram was more efficacious than placebo in one of two trials and as efficacious as amitriptyline and venlafaxine. It was better tolerated than nortriptyline but associated with a lower remission rate. Several trials included patients with stroke and dementia.

Medication	No. of published trials (cumulative no. of older participants)	Dosages studied (mg/day)	Comments
Escitalopram	2b (781)	10–20	In one failed trial, escitalopram and fluoxetine were well tolerated but not superior to placebo. In another trial, escitalopram did not differ from placebo.
Fluoxetine	13c (2,092)	10–80	Fluoxetine was more efficacious than placebo in two of five trials and as efficacious as amitriptyline, doxepin, escitalopram, paroxetine, sertraline, trimipramine, and venlafaxine. In patients with dysthymic disorder, fluoxetine was marginally superior to placebo. In patients with dementia of the Alzheimer's type, fluoxetine did not differ from placebo.
Fluvoxamine	4d (278)	50–200	Fluvoxamine was more efficacious than placebo and as efficacious as dothiepin, imipramine, mianserin, and sertraline.
Paroxetine	9e (1,474)	10–60	Paroxetine was more efficacious than placebo and as efficacious as amitriptyline, bupropion, clomipramine, doxepin, fluoxetine, and imipramine. Paroxetine was less efficacious than venlafaxine in older patients (n = 30) who had previously failed to respond to two other antidepressants. Mirtazapine was marginally superior to paroxetine. In very old long-term-care patients with minor depression, paroxetine was not more efficacious but was more cognitively toxic than placebo. One trial included patients with dementia.
Sertraline	11f (1,948)	50–200	Sertraline was more efficacious than placebo and as efficacious as amitriptyline, fluoxetine, fluvoxamine, imipramine, nortriptyline, and venlafaxine. Sertraline was better tolerated than imipramine and venlafaxine. Greater cognitive improvement occurred with sertraline than with nortriptyline or fluoxetine. Some trials included long-term-care patients. In one small single-site trial, sertraline was more efficacious than placebo for the treatment of depression associated with Alzheimer's dementia. However, this finding was not replicated in a larger multicenter trial.

aAllard et al. 2004; Andersen et al. 1994; Kyle et al. 1998; Navarro et al. 2001; Nyth and Gottfries 1990; Nyth et al. 1992; Roose et al. 2004b; Rosenberg et al. 2007.

bBose et al. 2008; Kasper et al. 2005.

cAltamura et al. 1989; Devanand et al. 2003; Doraiswamy et al. 2001; Evans et al. 1997; Feighner and Cohn 1985; Finkel et al. 1999; Kasper et al. 2005; Petracca et al. 2001; Schatzberg and Roose 2006; Schöne and Ludwig 1993; Taragano et al. 1997; Tollefson et al. 1995; Wehmeier et al. 2005.

Medication	No. of published trials (cumulative no. of older participants)	Dosages studied (mg/day)	Comments
dPhanjoo et al. 1991; Rahman et al. 1991; Rossini et al. 2005; Wakelin 1986. eBurrows et al. 2002; Dunner et al. 1992; Geretsegger et al. 1995; Guillibert et al. 1989; Katona et al. 1998; Mazeh et al. 2007; Mulsant et al. 2001b; Rapaport et al. 2003; Schatzberg et al. 2002; Schöne and Ludwig 1993. fBondareff et al. 2000; Cohn et al. 1990; Doraiswamy et al. 2003; Finkel et al. 1999; O. V. Forlenza et al. 2001; Lyketsos et al. 2003; Newhouse et al. 2000; Oslin et al. 2000, 2003; Rosenberg et al. 2010; Rossini et al. 2005; Schneider et al. 2003; Sheikh et al. 2004a; Weintraub et al. 2010.			

Two published placebo-controlled trials of citalopram (Lenze et al. 2005) and escitalopram (Lenze et al. 2009) support the efficacy of SSRIs in older patients with generalized anxiety disorder. The use of SSRIs to treat other anxiety disorders is based on small open trials (Flint 2005; Lenze et al. 2002; Sheikh et al. 2004b; Wylie et al. 2000) or extrapolation from studies in younger adults.

Several published studies, including three RCTs, suggest that citalopram may be efficacious in the treatment of behavioral disturbances associated with dementia, including not only agitation and disinhibition but also delusions and hallucinations (Nyth and Gottfries 1990; Nyth et al. 1992; Pollock et al. 1997, 2002, 2007; Porsteinsson et al. 2014). However, all these studies used citalopram doses above the maximum of 20 mg/day recommended by the FDA in older patients (U.S. Food and Drug Administration 2012). In the most recent and largest placebo-controlled trial, older patients with dementia randomized to citalopram up to 30 mg/day had longer QTc and more cognitive impairment than those randomized to placebo (Porsteinsson et al. 2014). The evidence supporting the use of other SSRIs in the treatment of noncognitive symptoms associated with dementia is much weaker: there is only one small (N = 40) published positive randomized trial supporting the use of escitalopram in the treatment of behavioral and psychotic symptoms (Barak et al. 2011). Some open studies and small single-site controlled trials also supported the use of SSRIs for the treatment of depression associated with Alzheimer's dementia (Katona et al. 1998; Lyketsos et al. 2003; Nyth and Gottfries 1990; Nyth et al. 1992; Olafsson et al. 1992; Petracca et al. 2001; Taragano et al. 1997). However, a larger multicenter trial failed to confirm these results; in this study, sertraline was not more efficacious and was less well tolerated than placebo for the treatment of depression in Alzheimer's disease (Rosenberg et al. 2010; Weintraub et al. 2010). Another multicenter study also showed no differences in the efficacy of sertraline, mirtazapine, or placebo in treating depression in patients with Alzheimer's disease, but the tolerability of either drug was worse than placebo (Banerjee et al. 2011). In a double-blind placebo-controlled discontinuation study in 128 patients with dementia and neuropsychiatric symptoms (but no depressive disorder), discontinuation of an SSRI that had been prescribed for at least 3 months was associated with a worsening of depressive symptoms compared with continuing the SSRI (Bergh et al. 2012).

Available data from head-to-head randomized comparisons indicate that all SSRIs currently available have similar efficacy and tolerability in the treatment of depression (Gartlehner et al. 2011) (see Table 20–2). Nevertheless, in older patients, experts now favor the use of escitalopram or sertraline over citalopram, fluvoxamine, fluoxetine, or paroxetine (Mulsant et al. 2014) because of favorable pharmacokinetic profiles (Table 20–3) and lower potential for clinically significant drug interactions (Table 20–4) or for other adverse effects. Notably, a warning has been issued by the FDA against the use of dosages of citalopram above 40 mg/day in any person and above 20 mg/day in people older than age 60 years because of a risk of prolonged QTc and torsades de pointes (Castro et al. 2013; U.S. Food and Drug Administration 2012; Wenzel-Seifert et al. 2011).

Selective Serotonin Reuptake Inhibitors

Pharmacokinetic properties of second-generation antidepressants

Medication	Half-life (days), including active metabolites	Proportionality of dosage to plasma concentration	Risk of uncomfortable discontinuation symptoms	Efficacious dosage range in elderly (mg/day)a
Selective serotonin reuptake inhibitors				
Citalopram	1 –3	Linear across therapeutic range	Low	20b
Escitalopram	1 –2	Linear across therapeutic range	Low	10–20
Fluoxetine	7 –10	Nonlinear at higher dosages	Very low	20–40
Fluvoxamine	0.5–1	Nonlinear at higher dosages	Moderate	50–300
Paroxetine	1	Nonlinear at higher dosages	Moderate	20–40
Sertraline	1 –3	Linear across therapeutic range	Low	50–200
Serotonin-norepinephrine reuptake inhibitors				
Desvenlafaxine	0. 5	Linear up to 600 mg/day	High	50
Duloxetine	0.5	Linear across therapeutic range	Moderate	60–120
Levomilnacipran	0.5	Linear across therapeutic range	Moderate	40–120
Venlafaxine XR	0.2	Linear across therapeutic range	High	75–300
Other second-generation antidepressants				
Bupropion	1	Linear across therapeutic range	Very low	150–400 (SR)

Medication	Half-life (days), including active metabolites	Proportionality of dosage to plasma concentration	Risk of uncomfortable discontinuation symptoms	Efficacious dosage range in elderly (mg/day)a
				150–450 (XL)
Mirtazapine	1 –2	Linear across therapeutic range	Moderate	15–45
Trazodone	5 –9	Linear across therapeutic range	Low	50–600 (see text)
Vilazodone	1	Linear across therapeutic range	Moderate	20–40
Vortioxetine	2 –3	Linear across therapeutic range	Low	5–20

Note. SR = sustained release; XL = extended release; XR = extended release.

aStarting dosage is typically half of the lowest efficacious dosage; all the selective serotonin reuptake inhibitors can be administered in single daily doses except fluvoxamine, which should be given in two divided doses.

bIn August 2011, the U.S. Food and Drug Administration issued a drug safety communication updated in March 2012, stating the following: "20 mg per day is the maximum recommended dose for patients with hepatic impairment, who are greater than 60 years of age, who are CYP 2C19 poor metabolizers, or who are taking concomitant cimetidine (Tagamet), because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes" (http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm).

Selective Serotonin Reuptake Inhibitors

Second-generation antidepressants' inhibition of cytochrome P450 (CYP) and potential for causing or being involved in significant drug-drug interactions

					Potential for causing or being involved in clinically significant drug-drug interactions	
Medication	CYP1A2	CYP2C9 and 2C19	CYP2D6	CYP3A4	Causing	Being involved
Selective serotonin reuptake inhibitors						
Citalopram	+	0	+	0	Low	Low (2C19 inhibitors)
Escitalopram	+	0	+	0	Low	Low (2C19 inhibitors)

					Potential for causing or being involved in clinically significant drug-drug interactions	
Medication	CYP1A2	CYP2C9 and 2C19	CYP2D6	CYP3A4	Causing	Being involved
Fluoxetine	+	++	+++	++	High	High
Fluvoxamine	+++	+++	+	++	High	High
Paroxetine	+	+	+++	+	Moderate	Moderate
Sertraline	+	+	+	+	Low	Low
Serotonin-norepinephrine reuptake inhibitors						
Desvenlafaxine	0	0	0	0	Minimal	Minimal
Duloxetine	0	0	+	+	Low	Low (1A2 and 2D6 inhibitors)
Levomilnacipran, milnacipran	0	0	0	0	Low	Low
Venlafaxine	0	0	0	0	Low	Low (2D6 inhibitors)
Other second-generation antidepressants						
Bupropion	0	0	++	0	Low	Moderate (2B6 inhibitors)
Nefazodone	0	+	0	+++	High	High
Trazodone	0	0	0	0	Low	Moderate (3A4 inhibitors and inducers)
Vilazodone	0	0	0	0	Low	Low (3A4 inducers and inhibitors)
Vortioxetine	0	0	0	0	Low	Low (2D6 inhibitors and 3A4 inducers)
Note. 0 = minimal or no inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = strong inhibition.						

Some data also suggest that citalopram and sertraline may be more beneficial in terms of cognitive improvement (Burrows et al. 2002; Doraiswamy et al. 2003; Furlan et al. 2001; Jorge et al. 2010; Newhouse et al. 2000; Savaskan et al. 2008). However, more recent data suggest that citalopram—like other SSRIs—may have deleterious cognitive effects in

some older patients (Culang et al. 2009) or in patients with dementia (Porsteinsson et al. 2014), and executive dysfunction is associated with a lower or slower improvement from citalopram, escitalopram, or other SSRIs (Manning et al. 2013; Sneed et al. 2010).

In older patients, SSRI starting dosages (see Table 20–3) are typically half the minimal efficacious dosage in younger adults, and the dosage is usually doubled after 1 week. All of the SSRIs can be administered in a single daily dose except fluvoxamine, which should be given in two divided doses. Even though frail older patients typically tolerate these drugs relatively well (Oslin et al. 2000), some patients experience some gastrointestinal distress (e.g., nausea) during the first few days of treatment. Significant hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a potentially dangerous adverse effect that is observed almost exclusively in elderly individuals and typically during the first couple of weeks of treatment (Coupland et al. 2011; Fabian et al. 2004).

SSRIs, as well as other serotonergic drugs, may directly affect platelet activation (Pollock et al. 2000), and they are associated with an increase in the risk of cerebral, gastrointestinal, or postsurgical bleeding (Auerbach et al. 2013; Hung et al. 2013; Looper 2007; Löppönen et al. 2014; Mortensen et al. 2013; Shin et al. 2014; Wang et al. 2014). They act synergistically with other medications that increase the risk of bleeding, such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, or warfarin. Thus, SSRIs should be used cautiously in older patients taking these medications, and the prophylactic use of acid-suppressing agents should be considered in some high-risk patients (de Abajo and García-Rodríguez 2008; Yuan et al. 2006).

SSRIs also can be associated with bradycardia and should be started with caution in patients with low heart rates (e.g., patients taking β-blockers). SSRIs rarely cause extrapyramidal symptoms (Mamo et al. 2000), and they are well tolerated by most patients with Parkinson's disease (P. Chen et al. 2007). The risk of falls and hip fracture does not differ among different classes of antidepressants (Liu et al. 1998), but there is concern that chronic use of SSRIs and other serotonergic drugs may contribute to the risk of fractures through their direct effects on bone metabolism (Diem et al. 2007; Garfield et al. 2014; Richards et al. 2007; Shea et al. 2013).

A large pharmacoepidemiological study in patients age 66 years or older found that SSRIs, compared with non-SSRI antidepressants, are associated with a greater risk for suicide during the first month of therapy (Juurlink et al. 2006). However, the absolute risk was low, which suggests that there may be a vulnerable subgroup at risk for an idiosyncratic response. By contrast, a very large meta-analysis and controlled data available to the FDA indicated a substantial reduction in the risk for suicidal ideation in older patients taking SSRIs compared with those taking placebo (Barbui et al. 2009; Friedman and Leon 2007; Nelson et al. 2007).

As of November 2014, the FDA has approved four serotonin-norepinephrine reuptake inhibitors (SNRIs) for the treatment of major depressive disorder in adults: desvenlafaxine, duloxetine, levomilnacipran, and venlafaxine. Duloxetine and venlafaxine have also been approved for the treatment of generalized anxiety disorder, duloxetine for diabetic peripheral neuropathic pain and fibromyalgia, and venlafaxine XR (extended release) for panic disorder and social anxiety disorder. A fifth SNRI, milnacipran, is indicated solely for the treatment of fibromyalgia. Because of their favorable side-effect profile in younger individuals and their dual mechanism of action (Chalon et al. 2003; Harvey et al. 2000), SNRIs are the preferred alternatives to SSRIs in both younger and older patients (Alexopoulos et al. 2001; Cooper et al. 2011; Mulsant et al. 2014). Some early meta-analyses suggested that venlafaxine may be associated with a higher rate of remission than SSRIs (e.g., Shelton et al. 2005; Smith et al. 2002; Stahl et al. 2002; Thase et al. 2001, 2005a); however, a number of more recent meta-analyses and head-to-head trials have contradicted these results or challenged their clinical significance in both younger patients (Bradley and Lenox-Smith 2013; Cipriani et al. 2009, 2012; Gartlehner et al. 2011; Hansen et al. 2005; Lam et al. 2010; Papakostas et al. 2007; Rush et al. 2006b, 2008; Schueler et al. 2011; Thaler et al. 2012; Vis et al. 2005) and older patients (Mukai and Tampi 2009; Nelson et al. 2008; Rajji et al. 2008). Also,

the risk-benefit ratio of SNRIs may differ in younger and older patients and may change the relative desirability of these medications in the treatment of older patients.

The efficacy, tolerability, and relative safety of SNRIs in the treatment of late-life depression are supported by 11 published controlled trials involving about 1,700 older patients (9 trials with venlafaxine and 2 with duloxetine; Table 20–5). Two additional analyses of geriatric data pooled from randomized placebo-controlled trials conducted in mixed-age adults support the efficacy of desvenlafaxine and duloxetine for late-life depression (Kornstein et al. 2010a; Nelson et al. 2005). In a series of randomized comparisons of desvenlafaxine with escitalopram or placebo in perimenopausal and postmenopausal women ages 40–70 years with major depressive disorder, desvenlafaxine and escitalopram had similar efficacy and tolerability (Kornstein et al. 2010b; Soares et al. 2010) and desvenlafaxine was more efficacious than placebo (Clayton et al. 2013; Kornstein et al. 2014). Additional data from open-label studies and case series support the efficacy of SNRIs in older individuals, including those with atypical depression (Roose et al. 2004a), treatment-resistant depression (Mazeh et al. 2007; Whyte et al. 2004), dysthymic disorder (Devanand et al. 2004), poststroke depression (Dahmen et al. 1999), generalized anxiety disorder (Katz et al. 2002), chronic pain syndromes (Grothe et al. 2004), stress urinary incontinence (Mariappan et al. 2005), or pain symptoms associated with geriatric depression (Karp et al. 2010; Raskin et al. 2007; Wohlreich et al. 2009).

Serotonin-Norepinephrine Reuptake Inhibitors

Summary of published randomized controlled trials of second-generation antidepressants other than selective serotonin reuptake inhibitors for the acute treatment of geriatric depression

Medication	No. of published trials (cumulative no. of older participants)	Dosages studied (mg/day)	Comments
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	0	NA	No published geriatric randomized trial as of November 2014.
Duloxetine	2b (681)	20–60	Duloxetine was more efficacious and as well tolerated as placebo in one trial (in this trial, duloxetine also showed efficacy on pain and cognitive measures). In a second trial, duloxetine was more efficacious than placebo on secondary measures but not on the primary efficacy measure and duloxetine was less well tolerated.
Levomilnacipran, milnacipran	0	NA	No published geriatric randomized trial as of November 2014.
Venlafaxine	9d (1,032)	50–300	Venlafaxine did not differ from placebo in one trial. Venlafaxine was as efficacious as citalopram, clomipramine, dothiepin, fluoxetine, nortriptyline, and sertraline and was more efficacious than paroxetine (in 30 older patients who had previously failed to respond to two other antidepressants) and trazodone. It was less well tolerated than placebo, fluoxetine, and sertraline; tolerated

Medication	No. of published trials (cumulative no. of older participants)	Dosages studied (mg/day)	Comments
			as well as citalopram and dothiepin; and better tolerated than clomipramine, nortriptyline, and trazodone.
Other second-generation antidepressants			
Bupropion	2a (163)	100–450	Bupropion was as efficacious as imipramine and paroxetine.
Mirtazapine	2c (370)	15–45	Mirtazapine was as efficacious as low-dose (total daily dose = 30–90 mg) amitriptyline and marginally superior to paroxetine.
Vilazodone	0	NA	No published geriatric randomized trial as of November 2014.
Vortioxetine	0	NA	No published geriatric randomized trial as of November 2014.

Note. NA = not applicable.

aBranconnier et al. 1983; Doraiswamy et al. 2001; Weihs et al. 2000.

bRaskin et al. 2007; Wohlreich et al. 2009; Oakes et al. 2013; Robinson et al. 2014.

cHøyberg et al. 1996; Schatzberg et al. 2002.

dAllard et al. 2004; Gastó et al. 2003; Kok et al. 2007; Mahapatra and Hackett 1997; Mazeh et al. 2007; Oslin et al. 2003; Schatzberg and Roose 2006; Smeraldi et al. 1998; Trick et al. 2004.

To our knowledge, the only published data on the use of levomilnacipran or milnacipran in geriatric patients come from one small (N = 92) randomized placebo-controlled trial of milnacipran for the prevention of poststroke depression (Tsai et al. 2011). Results suggest that milnacipran was well tolerated and was more efficacious than placebo in preventing poststroke depression. In a post hoc pooled analysis of five placebo-controlled RCTs of levomilnacipran in patients with major depressive disorder, the 106 patients who were 60 years of age and older experienced a remission rate that was comparable to the remission rate of midlife patients (Montgomery et al. 2008).

SNRIs do not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes and thus are unlikely to cause clinically significant drug-drug interactions (Oganesian et al. 2009; Spina et al. 2012) (see Table 20–4). However, venlafaxine and duloxetine are metabolized by CYP2D6, and their concentration can increase markedly in genetically poor metabolizers or in patients who are taking drugs that inhibit this isoenzyme (Whyte et al. 2006). The concentration of duloxetine also can be increased by drugs that inhibit CYP1A2. Dose adjustments of SNRIs are not recommended on the basis of age, but SNRIs should be used with caution in older patients with renal or liver disease (Dolder et al. 2010).

SNRIs inhibit the reuptake of serotonin. Thus, they share the side-effect profile of SSRIs, including not only nausea, diarrhea, headaches, and excessive sweating but also sexual dysfunction (Montejo et al. 2001), SIADH and hyponatremia (Kirby et al. 2002), bleeding (de Abajo and García-Rodríguez 2008; Löppönen et al. 2014), serotonin syndrome (McCue

and Joseph 2001; Perry 2000), changes in bone metabolism (Garfield et al. 2014; Shea et al. 2013), and discontinuation symptoms (Montgomery et al. 2009). SNRIs are also associated with adverse effects that can be linked to their action on the adrenergic system, including dry mouth, constipation, urinary retention, increased ocular pressure, cardiovascular problems, and transient agitation (Aragona and Inghilleri 1998; Benazzi 1997; Dolder et al. 2010). These adverse effects appear to be dose dependent (Clayton et al. 2009; Liebowitz and Tourian 2010; Thase 1998) and are usually self-limiting. However, the cardiovascular effects of SNRIs are of special concern in the elderly. SNRIs can cause not only some increase in blood pressure (Clayton et al. 2009; Thase 1998; Thase et al. 2005c; Zimmer et al. 1997) but also clinically significant orthostatic hypotension, syncope, electrocardiographic changes, arrhythmia, acute ischemia, and death in overdose (Clayton et al. 2009; Davidson et al. 2005; Johnson et al. 2006; Lessard et al. 1999; Reznik et al. 1999). At present, it is not known whether the cardiovascular risks of most of the various SNRIs differ; however, the bulk of the available data implicates venlafaxine as more of a problem for patients. In the United Kingdom, the National Institute for Clinical Excellence has recommended that venlafaxine should not be prescribed to patients with preexisting heart disease, that an electrocardiogram should be obtained at baseline, and that blood pressure and cardiac functions should be monitored in those patients taking higher doses (National Collaborating Centre for Mental Health 2004). Overall, some data in adult patients suggest that SNRIs may be less well tolerated than escitalopram and sertraline (Cipriani et al. 2009), and a randomized trial conducted under double-blind conditions in older nursing home residents found that venlafaxine was less well tolerated than sertraline, without evidence for an increase in efficacy (Oslin et al. 2003). In a large observational study, venlafaxine was associated with a higher risk of fracture, stroke, or all-cause mortality than other commonly prescribed antidepressants (Coupland et al. 2011); however, in the absence of randomization, one cannot rule out that this association was due to confounding factors that could not be controlled for.

In conclusion, it seems prudent not to use SNRIs as first-line agents in older patients but to reserve SNRIs for those whose symptoms do not respond to one or two SSRIs (Alexopoulos et al. 2001; Mulsant et al. 2001a, 2014) or those who present with depression and chronic pain (Karp et al. 2010; Raskin et al. 2007; Wohlreich et al. 2009). This recommendation is congruent with the results from small geriatric studies (Cooper et al. 2011; Karp et al. 2008; Mazeh et al. 2007; Whyte et al. 2004) and with the results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al. 2006a, 2006b, 2008). In this large study, mixed-age patients who had failed to respond to a first-line SSRI had similar outcomes when the next treatment step was to augment the SSRI with sustained-release bupropion or buspirone, switch to another SSRI, or switch to an agent from another class (i.e., bupropion or venlafaxine XR). The following steps included using a combination of venlafaxine XR and mirtazapine with outcomes similar to those associated with switching to the monoamine oxidase inhibitor (MAOI) tranylcypromine (Rush et al. 2006a, 2006b, 2008). One should be cautious when combining venlafaxine and mirtazapine in older patients with cardiovascular disease given the recent warning that mirtazapine can cause prolongation of QT and torsades de pointes, in particular when it is combined with other drugs that can also prolong the QT interval (Health Canada Advisory 2014).

Other Second-Generation Antidepressants

Only limited controlled data support the efficacy and safety of bupropion, nefazodone, or mirtazapine in older populations, and to our knowledge, as of November 2014, there are no published data on the use of vilazodone or vortioxetine in geriatric patients (see Table 20–5). Because of their usually favorable side-effect profiles and their different mechanisms of action, bupropion and mirtazapine are often used as monotherapy in older individuals who cannot tolerate SSRIs or SNRIs, or as monotherapy or in combination in older individuals who do not respond to SSRIs or SNRIs (Alexopoulos et al. 2001; Buchanan et al. 2006; Mulsant et al. 2001b, 2014).

Bupropion

Published data supporting the safety and efficacy of bupropion in geriatric depression are limited to small controlled trials (see Table 20–5) and one small open study (Steffens et al. 2001). Expert consensus favors the use of bupropion—

alone or as an augmentation agent—in older depressed patients whose symptoms have not responded to SSRIs or who cannot tolerate them (Alexopoulos et al. 2001; Buchanan et al. 2006; Mulsant et al. 2001a, 2014). In particular, bupropion can be helpful for patients who complain of nausea, diarrhea, unbearable fatigue, or sexual dysfunction during SSRI treatment (Nieuwstraten and Dolovich 2001; Thase et al. 2005b). Although augmentation with bupropion has been reported to be helpful in patients who were partial responders to SSRIs or venlafaxine (Bodkin et al. 1997; Spier 1998), the safety of this combination in older patients has not been established (Joo et al. 2002). Controlled data on the use of bupropion in individuals with heart disease (Kiev et al. 1994; Roose et al. 1991), in smokers (Tashkin et al. 2001), and in persons with neuropathic pain (Semenchuk et al. 2001) confirm clinical experience that bupropion is relatively well tolerated by medically ill patients. Bupropion is contraindicated in patients who have or are at risk for seizure disorders (e.g., poststroke patients). However, the sustained-release preparation of bupropion appears to be associated with a very low incidence of seizure, comparable to that of other antidepressants (Dunner et al. 1998). Bupropion also has been associated with the onset of psychosis in case reports (Howard and Warnock 1999), and the prudent action is to avoid this medication in psychotic patients or in agitated patients at risk for the development of psychotic symptoms. The propensity of bupropion to induce psychosis in at-risk patients has been attributed to its action on dopaminergic neurotransmission (Howard and Warnock 1999). The same mechanism has been hypothesized to underlie the association of bupropion with gait disturbance and falls in some patients (Joo et al. 2002; Szuba and Leuchter 1992).

Bupropion is a moderate inhibitor of CYP2D6 (Kotlyar et al. 2005) (see Table 20–4). It appears to be metabolized by CYP2B6 (Hesse et al. 2004), and adverse effects of bupropion such as seizures or gait disturbance may be more likely in individuals who take drugs that inhibit CYP2B6, such as fluoxetine or paroxetine (Joo et al. 2002).

Mirtazapine

The antidepressant activity of mirtazapine has been attributed to its blockade of α2 autoreceptors, resulting in a direct enhancement of noradrenergic neurotransmission and an increase in the synaptic levels of serotonin (5-hydroxytryptamine [5-HT]), indirectly enhancing neurotransmission mediated by serotonin type 1A (5-HT1A) receptors. In addition, like the antinausea drugs granisetron and ondansetron, mirtazapine inhibits 5-HT2 and 5-HT3 receptors. Thus, mirtazapine could be particularly helpful for individuals who do not tolerate SSRIs because of sexual dysfunction (Gelenberg et al. 2000; Montejo et al. 2001), tremor (Pact and Giduz 1999), or severe nausea (Pedersen and Klysner 1997). In one case series, mirtazapine was used successfully to treat depression in 19 mixed-age oncology patients who were receiving chemotherapy (Thompson 2000). It also has been combined with SSRIs (Pedersen and Klysner 1997); however, these combinations should be used cautiously because they have been associated with a serotonin syndrome in an older patient (Benazzi 1998). The STAR*D study found that a combination of mirtazapine and venlafaxine XR had modest efficacy in patients with treatment-resistant depression, comparable to the efficacy of the MAOI tranylcypromine (Rush et al. 2006a); however, only a few STAR*D participants were elderly, and the safety of this combination has not been established in older patients.

No published placebo-controlled trials and only two comparator-controlled trials of mirtazapine in geriatric depression have been done (see Table 20–5). Consistent with this paucity of controlled data, experts favor the use of mirtazapine as a third-line drug in older depressed patients who cannot tolerate or whose symptoms have not responded to SSRIs or venlafaxine (Alexopoulos et al. 2001). Mirtazapine also has been used to treat depression in frail nursing home patients (Roose et al. 2003) and in older patients with dementia (Raji and Brady 2001), but there are concerns about its effect on cognition. It has been shown to impair driving performance in two placebo- and active comparator–controlled trials in healthy volunteers (Ridout et al. 2003; Wingen et al. 2005) and to cause delirium in older patients with organic brain syndromes (Bailer et al. 2000). This deleterious effect on cognition is possibly a result of mirtazapine's antihistaminergic and sedative effects. Other adverse effects of mirtazapine include weight gain with lipid increase (Nicholas et al. 2003), hyponatremia (Cheah et al. 2008), and, very rarely, neutropenia or even agranulocytosis (Hutchison 2001). In a large

observational study in older primary care patients treated for depression, mirtazapine was associated with a higher risk of stroke and mortality than other commonly prescribed antidepressants (Coupland et al. 2011); however, in the absence of randomization, one cannot rule out that this association was due to confounding factors that could not be controlled for. In March 2014, Merck Canada issued a warning endorsed by Health Canada that mirtazapine can cause QT prolongation and torsades de pointes in association with overdose or when other risk factors for QT prolongation are present (e.g., in patients with cardiovascular disease or when combined with other medications that can cause QT prolongation) (Health Canada Advisory 2014).

Trazodone

Trazodone is indicated for the treatment of major depressive disorder, but it is now almost exclusively used off-label as a hypnotic or a sedative agent (Bossini et al. 2012) due to its sedative effect associated with antagonism of the 5-HT2A receptor and, to a lesser extent, the 5-HT2B, 5HT1A, and α1 receptors. To minimize adverse effects, doses should be kept low (e.g., 50–150 mg at bedtime) when trazodone is used as a hypnotic agent. Some evidence going back to the early 1990s indicates that trazodone at low to moderate doses (50–300 mg/day) has an efficacy comparable to that of haloperidol in the treatment of agitation or aggression in patients with dementia (Henry et al. 2011; Houlihan et al. 1994; Sultzer et al. 1997; Teri et al. 2000). In a unique small (N = 30) RCT, trazodone (50 mg given at 10 p.m.) was well tolerated, and it was more efficacious than placebo in the treatment of sleep disturbances of patients with Alzheimer's disease (Camargos et al. 2014).

At doses typically used to treat depression (300–600 mg/day), trazodone antagonism of α1-adrenergic receptors may cause dry mouth, orthostatic hypotension (with syncope), QT prolongation or arrhythmias, and priapism (which is rare in older adults). Like other psychotropic medications, trazodone has been associated with hyponatremia and it can be involved in a serotonergic syndrome, in particular when combined with SSRIs or SNRIs or other medications that also affect the serotonergic system. In a large observational study in older primary care patients treated for depression, trazodone was associated with the highest risk of all-cause mortality among 11 commonly prescribed antidepressants (Coupland et al. 2011); however, in the absence of randomization, one cannot rule out that this association was due to confounding factors that could not be controlled for. Trazodone is mostly metabolized by CYP3A4. Therefore, its dose should be reduced when it is coprescribed with medications that inhibit this liver enzyme (see Table 20–4), and drinking a large quantity of grapefruit juice should be discouraged in patients taking trazodone.

Nefazodone

Given the absence of any controlled trials of nefazodone in treating geriatric depression, mediocre outcomes in an open study (Saiz-Ruiz et al. 2002), potentially problematic drug-drug interactions caused by its strong inhibition of CYP3A4 (see Table 20–4), and reports that the incidence of hepatic toxicity or even liver failure is 10- to 30-fold higher with nefazodone than with other antidepressants (Carvajal García-Pando et al. 2002), nefazodone should not be used in older patients.

Vilazodone and Vortioxetine

Vilazodone is a newer antidepressant that acts as both a serotonin reuptake inhibitor and a partial agonist at the 5-HT1A receptor, with negligible noradrenergic or dopaminergic effects. In clinical trials in adults, the most common adverse effects were diarrhea, nausea, and headache. Vortioxetine is the newest antidepressant available in the United States. It has a complex multimodal mechanism but predominantly seems to be a serotonin reuptake inhibitor (Berhan and Barker 2014). In clinical trials in adults, its most common adverse effects were nausea, constipation, and vomiting. The full prescribing information for vortioxetine (Physicians' Desk Reference 2014) does not recommend dosage adjustments in older people and reports that in a study of 300 cognitively intact adults ages 64–88 with recurrent major depressive disorder, patients randomized to vortioxetine 5 mg/day experienced a greater reduction in depressive symptoms than

those randomized to placebo. However, as of November 2014, given the absence of published randomized clinical trials or open studies of vilazodone or vortioxetine in geriatric patients, it is prudent to avoid their use in older patients (Mulsant et al. 2014; Schiff et al. 2011).

Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Tricyclic antidepressants (TCAs) and MAOIs have become third- and fourth-line drugs in the treatment of late-life depression because they are less well tolerated than SSRIs, they have a narrow therapeutic range, and their use requires special precautions (Mulsant et al. 2001a; Rajji et al. 2008; von Wolff et al. 2013; Wilson and Mottram 2004). The tertiary-amine TCAs—amitriptyline, clomipramine, doxepin, and imipramine—can cause significant orthostatic hypotension and anticholinergic effects, including cognitive impairment, and they should be avoided in elderly persons (American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012; Beers 1997). The secondary amines desipramine and nortriptyline are preferred in older patients (Mulsant et al. 2014). They have a lower propensity to cause orthostasis and falls, in addition to having linear pharmacokinetics and more modest anticholinergic effects (Chew et al. 2008). Their relatively narrow therapeutic index (i.e., the plasma level range separating efficacy and toxicity) necessitates monitoring of plasma levels and electrocardiograms in older patients. A single dose is given at bedtime; 5–7 days after initiation of desipramine at 50 mg or nortriptyline at 25 mg, plasma levels should be measured and dosages adjusted linearly, with targeted plasma levels of 200–400 ng/mL for desipramine and 50–150 ng/mL for nortriptyline. These narrow ranges ensure efficacy while decreasing risks of cardiac toxicity and other side effects. Like the tertiary-amine TCAs, desipramine and nortriptyline are type 1 antiarrhythmics: they have quinidine-like effects on cardiac conduction and should not be used in patients who have or are at risk for cardiac conduction defects (Roose et al. 1991). Most anticholinergic side effects of desipramine or nortriptyline (e.g., dry mouth, constipation) resolve with time or usually can be mitigated with symptomatic treatment (Rosen et al. 1993). TCAs have been associated with cognitive worsening compared with placebo (Reifler et al. 1989) and with less cognitive improvement than occurs with sertraline (Bondareff et al. 2000; Doraiswamy et al. 2003) or other SSRIs.

Even though MAOIs have been found to be efficacious in older depressed patients (Georgotas et al. 1986), and they may have a special role in patients with atypical or treatment-resistant depression, these medications are now rarely used in older patients (Shulman et al. 2009). This is in large part because they can cause significant hypotension or life-threatening hypertensive or serotonergic crises as a result of dietary or drug interactions. When MAOIs are used in older individuals whose symptoms have typically failed to respond to SSRIs, SNRIs, and TCAs, phenelzine is preferred to tranylcypromine because it has been more extensively studied in older patients (Georgotas et al. 1986). A typical starting dosage would be 15 mg/day, with a target dosage of 45–90 mg/day in three divided doses. Patients need to follow dietary restrictions (Shulman and Walker 2001) and to inform any health care providers (including pharmacists) that they are taking an MAOI. Another option is the selegiline transdermal patch, which was developed to deliver selegiline blood concentrations sufficient to inhibit monoamine oxidase A and B (MAO A and MAO B) in the brain without inhibiting MAO A in the gastrointestinal tract, thereby reducing the risk of hypertensive crisis (Nandagopal and DelBello 2009). No geriatric data are available, but dietary restrictions are not needed at the 6-mg/24-hour dosage; however, they are recommended with higher dosages (Robinson and Amsterdam 2008), and potentially lethal drug interactions remain a concern.

Psychostimulants

Even though some clinicians prescribe psychostimulants for the treatment of late-life mood disorders, this practice has minimal empirical support. A few small double-blind trials suggested that methylphenidate is generally well tolerated and modestly efficacious for medically burdened depressed elders (Satel and Nelson 1989; Wallace et al. 1995). Methylphenidate also has been used for the treatment of apathy and anergia associated with late-life depression or dementia (Herrmann et al. 2008). A small study suggested that methylphenidate can be used in older depressed patients

to augment SSRIs, which inhibit dopamine release and may contribute to apathy and fatigue (Lavretsky et al. 2006). The wakefulness-promoting agent modafinil and its R-enantiomer armodafinil appear to induce a calm alertness through nondopaminergic mechanisms. These agents have been used to target apathy and fatigue in patients taking SSRIs (Dunlop et al. 2007; Fava et al. 2007; Goss et al. 2013) and as adjunctive treatment for negative symptoms of schizophrenia (Lindenmayer et al. 2013), but there are almost no published geriatric data for these drugs (Darwish et al. 2011; Varanese et al. 2013). Caution is advised regarding the possible exacerbation by methylphenidate and other psychostimulants of anxiety, psychosis, anorexia, or hypertension and potential interactions with warfarin. Experience with other dopaminergic medications, such as pergolide, piribedil, pramipexole, and ropinirole, in elderly patients has been limited, but there have been several encouraging controlled trials in patients with Parkinson's disease and depression (Aiken 2007; Barone et al. 2006, 2010; Rektorová et al. 2003) and in elderly patients with cognitive impairment (Nagaraja and Jayashree 2001).

Antipsychotic Medications

In older adults, as in other age groups, atypical antipsychotics are now being prescribed as first-line drugs for the treatment of psychotic symptoms of any etiology. Studies support the efficacy of these agents in the treatment of late-life schizophrenia and late-onset psychoses (Scott et al. 2011; Suzuki et al. 2011) and in the treatment of behavioral and psychological symptoms of dementia (Maher et al. 2011; Maher and Theodore 2012). However, use of these agents in patients with dementia is being questioned (Ballard and Corbett 2010; Mulsant 2014; Salzman et al. 2008). In 2005, two highly publicized reports and an FDA warning indicated a nearly twofold increase in the rate of deaths in older patients with behavioral and psychological symptoms of dementia treated with atypical antipsychotics when compared with placebo (Kuehn 2005; Schneider et al. 2005). These reports have led to a reexamination of the safety of both conventional and atypical antipsychotics in older patients. Over the past decade, a series of studies have emphasized their association with mortality (Ballard et al. 2009; Langballe et al. 2014; Ray et al. 2009; Wang et al. 2005), stroke (Gill et al. 2005; Herrmann et al. 2004), severe hyperglycemia in patients with diabetes (Lipscombe et al. 2009), fractures (Liperoti et al. 2007), and venous thromboembolism (Kleijer et al. 2010). The relative safety of atypical compared with conventional antipsychotics remains unclear: atypical antipsychotics appears to be associated with lower mortality than typical antipsychotics (Langballe et al. 2014; Schneider et al. 2005) and they may cause fewer falls (Hien et al. 2005; Landi et al. 2005) and fewer extrapyramidal symptoms (Lee et al. 2004; Meagher et al. 2013; Rochon et al. 2005; van Iersel et al. 2005); however, they may cause more cerebrovascular events (Percudani et al. 2005), venous thromboembolism (Liperoti et al. 2005), and pancreatitis (Koller et al. 2003). Given the increased recognition of the risks associated with the use of antipsychotics in older patients, clinicians need to consider their potential risks and benefits for each individual patient (Gauthier et al. 2010; Rabins and Lyketsos 2005). Antipsychotics should be prescribed only to patients who have failed to respond to nonpharmacological interventions or alternative medications (Ballard and Corbett 2010; Mulsant 2014; Sink et al. 2005). When antipsychotics are prescribed to older patients, the minimal effective dose should be used for the shortest possible duration (Tsuboi et al. 2011). Their long-term use is justified when they are used to treat schizophrenia, bipolar disorder, and possibly major depressive disorder with psychotic features; discontinuation should be attempted in stable patients with other disorders. Although antipsychotics can be discontinued safely in most older patients with dementia, their discontinuation can be associated with poor outcomes, in particular in older patients who had presented with more severe agitation or psychosis (Declercq et al. 2013).

Risperidone

Of the atypical antipsychotics currently available in the United States, risperidone has the most published geriatric data for a variety of conditions (Schneider et al. 2005, 2006a; Sink et al. 2005; Suzuki et al. 2011). The efficacy and tolerability of risperidone in the treatment of behavioral and psychological symptoms of dementia have been reported in several randomized placebo-controlled trials (e.g., Brodaty et al. 2003; De Deyn et al. 1999, 2005b; Katz et al. 1999; Schneider et al. 2006a, 2006b; Sink et al. 2005); in randomized comparisons with haloperidol (Chan et al. 2001; De Deyn et al. 1999;

Suh et al. 2004), promazine and olanzapine (Gareri et al. 2004), and olanzapine (Fontaine et al. 2003; Mulsant et al. 2004); and in many uncontrolled studies or large case series. The efficacy of risperidone in the treatment of agitation or psychosis is further supported by a placebo-controlled trial showing that individuals with Alzheimer's disease whose agitation or psychosis had responded acutely to risperidone experienced an increased risk of relapse when they were switched to placebo after 4 months (hazard ratio 1:9) or 8 months (hazard ratio 4:9) compared with those who remained on risperidone (Devanand et al. 2012). Taken together, these data support risperidone as a first choice among antipsychotics for the treatment of patients with dementia and distressing psychosis or severe agitation. However, the substantial risks associated with the use of risperidone and other atypical antipsychotics in these patients—including increased mortality (number needed to harm = 87) and stroke (number needed to harm = 53) (Maher and Theodore 2012; Maher et al. 2011)—should lead to caution.

The efficacy and tolerability of risperidone in the treatment of late-life schizophrenia are supported by one randomized comparison with olanzapine (Harvey et al. 2003; Jeste et al. 2003) and one randomized open-label study of crossover from conventional antipsychotics to risperidone or olanzapine (Ritchie et al. 2003, 2006). The parallel study showed similar efficacy between olanzapine and risperidone but more weight gain and less cognitive improvement with olanzapine. In the crossover study, patients switched to olanzapine were more likely to complete the switching process and to show an improvement in psychological quality of life. The results from these two controlled trials are supported by a large body of uncontrolled data in older patients with schizophrenia and other psychotic disorders (e.g., Davidson et al. 2000; Madhusoodanan et al. 1999). In addition, an analysis of 57 patients with schizophrenia ages 65 years and older who participated in randomized studies of the long-acting injectable ("depot") risperidone (Risperdal Consta) found that it was well tolerated and produced significant symptomatic improvements (Lasser et al. 2004).

One randomized comparison with haloperidol (Han and Kim 2004) and some uncontrolled data (e.g., Mittal et al. 2004; Parellada et al. 2004) support the efficacy and tolerability of risperidone in the treatment of delirium (Wang et al. 2013). In another RCT, a significantly lower incidence of delirium was observed in patients given a single 1-mg dose of risperidone just after cardiac surgery than in those given placebo (Prakanrattana and Prapaitrakool 2007; Zhang et al. 2013). However, there have been several case reports of delirium induced by risperidone. One small randomized comparison with clozapine (N = 10) (Ellis et al. 2000) and several open trials of low-dose risperidone in the treatment of Parkinson's disease and drug-induced psychosis or Lewy body dementia have had inconsistent results, with clear worsening of parkinsonian symptoms in some studies (e.g., Culo et al. 2010; Ellis et al. 2000; Leopold 2000). Thus, risperidone should be used with great caution in the treatment of these disorders (Parkinson Study Group 1999).

As with other atypical antipsychotics, the efficacy and tolerability of risperidone in younger patients with bipolar disorder (and possibly other mood disorders) (Andreescu et al. 2006) are well established. However, given the risks associated with antipsychotics, experts continue to favor the use of mood stabilizers as first-line agents for older patients with bipolar disorder, except in the presence of severe mania or mania with psychosis, in which case they favor combining risperidone, olanzapine, or quetiapine with a mood stabilizer (Sajatovic et al. 2005b, 2013; Young et al. 2004).

Commonly reported side effects of risperidone include orthostatic hypotension (on initiation of treatment) and extrapyramidal symptoms that are dose dependent (Katz et al. 1999). At a given dosage, concentrations of risperidone (and possibly its active metabolite paliperidone or 9-hydroxyrisperidone) seem to increase with age (Aichhorn et al. 2005). Therefore, typical dosages should be between 0.5 and 2 mg/day for older patients with dementia and lower than 4 mg/day for older patients without dementia. Of all the atypical antipsychotics, risperidone appears to be the most likely to be associated with hyperprolactinemia (Kinon et al. 2003). Risperidone causes only moderate electroencephalographic abnormalities (Centorrino et al. 2002), and it is rarely associated with cognitive impairment, probably because of its low affinity for muscarinic receptors (Chew et al. 2006; Harvey et al. 2003; Mulsant et al. 2004). Like other antipsychotics, risperidone can cause weight gain, diabetes, or dyslipidemia. It is more likely to do so than are

aripiprazole and ziprasidone but less likely than are clozapine, olanzapine, and quetiapine (American Diabetes Association et al. 2004; Feldman et al. 2004; Zheng et al. 2009).

Paliperidone

Paliperidone is the active 9-hydroxy metabolite of risperidone, and therefore some of its pharmacological action, efficacy, and side effects are similar to those of risperidone. Its once-daily extended-release formulation takes 24 hours to reach a maximum concentration, and its clearance is not affected by hepatic impairment or CYP2D6 metabolism but is affected by renal function. It is the only medication indicated for the treatment of schizoaffective disorder in the United States. Its efficacy and tolerability in the treatment of older patients with psychosis is supported by data from 125 subjects ages 65 years and older who participated in three 6-week registration trials that led to the medication's approval by the FDA for the treatment of schizophrenia (e.g., Davidson et al. 2007; Kane et al. 2007). Otherwise, limited available data support the efficacy and safety of paliperidone in the treatment of older patients with schizophrenia (Madhusoodanan and Zaveri 2010): in a 6-week randomized placebo-controlled trial followed by a 24-week open-label extension, 114 patients ages 65 years and older (mean age of 70) received paliperidone 3–12 mg/day or placebo. Discontinuation due to adverse events and weight gain were similar in the two groups. Half of the patients treated with paliperidone experienced prolactin elevation, but it was not related to any adverse event. Changes in efficacy measures were similar in the two groups (Tzimos et al. 2008). Paliperidone has not yet been systematically studied in older patients with bipolar disorder or dementia, and doses remain speculative for these populations. The availability of a long-acting injectable form of paliperidone that requires only monthly injections is an attractive option for patients who require a long-acting injectable antipsychotic (González-Rodríguez et al. 2014; Rado and Janicak 2012), but its more widespread use is impeded by a paucity of geriatric data.

Next to risperidone, olanzapine has the most published geriatric data. Its efficacy and tolerability in the treatment of behavioral and psychological symptoms of dementia have been reported in several randomized placebo-controlled trials (e.g., Clark et al. 2001; De Deyn et al. 2004; Schneider et al. 2006b; Street et al. 2000) and in randomized comparisons with haloperidol (Verhey et al. 2006), promazine or risperidone (Gareri et al. 2004), and risperidone (Fontaine et al. 2003; Mulsant et al. 2004). However, a meta-analysis of published and nonpublished placebo-controlled trials of olanzapine in the treatment of behavioral and psychological symptoms of dementia concluded that "olanzapine was not associated with efficacy overall" (Schneider et al. 2006a, p. 205). More recently, a 2011 review published by the U.S. Agency for Healthcare Research and Quality focusing on data available since 2006 concluded that—like aripiprazole and risperidone—olanzapine is associated with statistically significant small benefits for older patients with behavioral disturbances associated with dementia (Maher and Theodore 2012; Maher et al. 2011).

The efficacy and tolerability of olanzapine in the treatment of late-life schizophrenia have been confirmed in two randomized comparisons with haloperidol (Barak et al. 2002; Kennedy et al. 2003) and two randomized comparisons with risperidone (Harvey et al. 2003; Jeste et al. 2003; Ritchie et al. 2003, 2006). In one RCT in patients with delirium, olanzapine and haloperidol were found to have comparable efficacy (Skrobik et al. 2004). In another RCT, a significantly lower incidence of delirium was observed in patients given 5 mg of olanzapine just before and just after joint replacement surgery compared with patients given placebo; however, when delirium occurred, it was longer and more severe in patients who had received olanzapine (Larsen et al. 2010; Zhang et al. 2013). Caution is needed when using olanzapine in patients with delirium because some controlled trials have reported some cognitive worsening in patients with dementia while taking olanzapine (Kennedy et al. 2005; Mulsant et al. 2004), and several case reports of delirium induced by olanzapine have been published. Similarly, the need for caution when olanzapine is used to treat psychosis in patients with Parkinson's disease or Lewy body dementia is reinforced by two comparative trials (Breier et al. 2002; Goetz et al. 2000) and several open trials or case series (e.g., Marsh et al. 2001; Molho and Factor 1999; Parkinson Study Group 1999; Walker et al. 1999) that have reported a significant worsening of motor symptoms in these patients.

The evidence supporting the efficacy and safety of olanzapine in younger patients with bipolar disorder and other mood disorders (Andreescu et al. 2006; Shelton et al. 2001; Thase 2002) is strong. One large published trial in which more than half of the randomized patients were age 65 years and older supports the efficacy and tolerability of olanzapine in the treatment of major depressive disorder with psychotic features (Meyers et al. 2009). Otherwise, there is a paucity of data relevant to older individuals with mood disorders (Sajatovic et al. 2005a, 2005b; Young et al. 2004). Similarly, very few geriatric data are available on the rapidly dissolving or the intramuscular preparations of olanzapine (Belgamwar and Fenton 2005).

On review of all evidence available in 2004, a consensus conference concluded that among the atypical antipsychotics, clozapine and olanzapine were associated with the highest risk for diabetes and caused the greatest weight gain and dyslipidemia (American Diabetes Association et al. 2004). Limited geriatric data show a similar higher risk of metabolic problems in older patients (Feldman et al. 2004; Micca et al. 2006; Zheng et al. 2009). Other common side effects include sedation and gait disturbance. Extrapyramidal symptoms appear to be dose dependent and are rare at the lower dosages typically used in older patients (5–10 mg/day). Olanzapine also has been associated with electroencephalographic abnormalities (Centorrino et al. 2002), and its strong blocking of the muscarinic receptor (Chew et al. 2005, 2006; Mulsant et al. 2003) (Table 20–6) may explain why it has been associated with the following: constipation in a large series of long-term-care patients (Martin et al. 2003); an inverted dose-response relationship, with lower efficacy in older agitated or psychotic patients with dementia randomized to 15 mg/day than in those randomized to 5 mg/day, suggesting that higher doses may be toxic in these patients (Street et al. 2000); a differential cognitive effect from risperidone in randomized trials involving older patients with schizophrenia (Harvey et al. 2003) or dementia (Mulsant et al. 2004); worsening of cognition in a large placebo-controlled trial in older nonagitated, nonpsychotic patients with Alzheimer's disease (Kennedy et al. 2005); and frank delirium in some clinical cases. Individuals who are older, female, or nonsmokers or who are taking a drug that inhibits CYP1A2 (e.g., fluvoxamine or ciprofloxacin) have higher concentrations of olanzapine and may be at higher risk for adverse effects (Gex-Fabry et al. 2003). Because of olanzapine's adverse-effect profile, experts do not recommend it as a first-line antipsychotic in older patients at special risk for anticholinergic or metabolic adverse effects (Bell et al. 2010).

Olanzapine

Receptor blockade of atypical antipsychotics

	D2	5-HT2	M1	α1
Aripiprazole	*	++	0	+
Asenapine	+++	+++	0	+++
Clozapine	+	++	+++	+
Iloperidone	+++	++++	0	++++
Lurasidone	+++	++	0	++
Olanzapine	++	+++	++	+
Paliperidone	+++	+++	0	++

	D2	5-HT2	M1	α1
Quetiapine	+	++	+	+
Risperidone	+++	++++	0	+++
Ziprasidone	++	++	0	+

Note. Receptor types: α1 = α-adrenergic type 1; D2 = dopamine type 2; 5-HT2 = 5-hydroxytryptamine (serotonin) type 2; M1 = muscarinic type 1.

0 = none; + = minimal; ++ = intermediate; +++ = high; ++++ = very high.

*High-affinity partial agonist.

Quetiapine

Results of several randomized placebo-controlled trials of quetiapine in older patients with behavioral and psychological symptoms of dementia are inconclusive (Cheung and Stapelberg 2011; Schneider et al. 2006a). For instance, in a large trial of 333 institutionalized participants, quetiapine 200 mg/day (but not 100 mg/day) differed from placebo on global impressions and positive symptom ratings but not on the important primary outcome measures of agitation and psychosis (Zhong et al. 2007).

Several uncontrolled or unblinded studies suggest that quetiapine may have a role in the treatment of older patients with primary psychotic disorders (e.g., Madhusoodanan et al. 2000; Tariot et al. 2000; Yang et al. 2005). Similarly, two small RCTs (Devlin et al. 2010, 2011; Tahir et al. 2010) and several other small studies (e.g., Kim et al. 2003; Pae et al. 2004; Sasaki et al. 2003) suggest that quetiapine may be effective for the treatment of delirium.

Because of its low propensity to cause extrapyramidal symptoms, quetiapine is often used as a first-line antipsychotic in older patients with Parkinson's disease, dementia with Lewy bodies, or tardive dyskinesia (Fernandez et al. 2002; Poewe 2005); however, quetiapine was not found to be efficacious in these patients in two double-blind trials (Kurlan et al. 2007; Rabey et al. 2007).

Quetiapine also has FDA approval for the treatment of acute mania and depression associated with bipolar disorder in adults and as adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults. Relevant published data from geriatric patients with bipolar disorder are limited (Carta et al. 2007; Tadger et al. 2011). By contrast, in one geriatric randomized placebo-controlled trial of a flexible dose (50–300 mg/day) of quetiapine in 338 older patients with major depression, remission and response rates were remarkably high (56% and 64%, respectively) and significantly higher than those with placebo (23% and 30%, respectively). Adverse events observed in more than 10% of the patients randomized to quetiapine included somnolence, headache, dry mouth, and dizziness (Katila et al. 2013).

There have been several case reports of SIADH and serotonin syndrome in older patients treated with quetiapine (e.g., Atalay et al. 2007; Kohen et al. 2007). Like other antipsychotics, quetiapine can also cause somnolence or dizziness (Jaskiw et al. 2004; Katila et al. 2013; Yang et al. 2005), but the incidence of these adverse effects can be minimized by a slower dose titration. The risk for weight gain, diabetes, or dyslipidemia associated with quetiapine appears similar to the risk associated with the use of risperidone but lower than the risk associated with the use of clozapine or olanzapine (American Diabetes Association et al. 2004; Feldman et al. 2004).

Clozapine

Clozapine is still considered the drug of choice for younger patients with treatment-refractory schizophrenia, and one small case series suggested that it can be similarly helpful in older patients for the treatment of primary psychotic disorders refractory to other treatments (Sajatovic et al. 1997). An RCT comparing clozapine and chlorpromazine in older patients with schizophrenia (Howanitz et al. 1999) and one large case series (Barak et al. 1999) also supported the use of clozapine in moderate dosages (i.e., approximately 50–200 mg/day) in older patients with primary psychotic disorders. The strongest published geriatric studies of clozapine are focused on the treatment of drug-induced psychosis in patients with Parkinson's disease (Ellis et al. 2000; Goetz et al. 2000; Parkinson Study Group 1999). The results of these studies suggest that clozapine at low dosages (12.5–50 mg/day) could be the preferred treatment for this condition (Parkinson Study Group 1999). However, the use of clozapine in older individuals is severely limited because of its significant hematological, anticholinergic (including severe constipation and ileus associated with fatalities), neurological (e.g., seizures), cognitive, metabolic, and cardiac adverse effects (Alvir et al. 1993; Bishara and Taylor 2014; Centorrino et al. 2002; Chew et al. 2006; Hibbard et al. 2009; O'Connor et al. 2010; Rajji et al. 2010).

Aripiprazole

Aripiprazole has partial dopamine type 2 (D2) receptor agonist properties (i.e., in high dopaminergic states it acts as an antagonist, and in low dopaminergic states it acts as an agonist). This may explain why it is unlikely to cause extrapyramidal side effects or prolactin elevation (associated with osteoporosis), even at high D2 receptor occupancy (Mamo et al. 2007). It has only moderate affinity to the adrenergic α1 receptor and histamine H1 receptor and negligible affinity to the muscarinic receptor (Chew et al. 2006). As a result, orthostatic hypotension and antihistaminergic and anticholinergic adverse effects are less likely to occur than with other atypical agents. However, akathisia may be a common side effect in older patients (Coley et al. 2009; Sheffrin et al. 2009). Several randomized placebo-controlled trials of aripiprazole in older patients with behavioral and psychological symptoms of dementia have been published (De Deyn et al. 2005a; Mintzer et al. 2007; Streim et al. 2008). Recent expert opinions (De Deyn et al. 2013; Herrmann et al. 2013b) are congruent with a meta-analysis of these trials that concluded that "efficacy on rating scales was observed by meta-analysis for aripiprazole" (Schneider et al. 2006a, p. 191) and with a 2011 review published by the U.S. Agency for Healthcare Research and Quality that reached a similar conclusion (Maher and Theodore 2012; Maher et al. 2011).

Aripiprazole is approved by the FDA for the treatment of manic or mixed episodes associated with bipolar disorder and as an adjunctive treatment for major depressive disorder. Lenze, Mulsant, Reynolds, and their collaborators have completed a large federally funded randomized placebo-controlled trial of aripiprazole augmentation of venlafaxine XR in older patients with major depression who did not respond to venlafaxine XR monotherapy (300 mg/day). As of November 2014, the results of this study had not yet been published. However, two small prospective open studies (Sajatovic et al. 2008; Sheffrin et al. 2009) and analyses of pooled geriatric data (Steffens et al. 2011; Suppes et al. 2008) support the efficacy and tolerability of aripiprazole augmentation in older patients with major depression that does not respond fully to an antidepressant.

Ziprasidone

On the basis of ziprasidone's lower effect on glucose, lipids, and weight (American Diabetes Association et al. 2004) and its lack of affinity for the muscarinic receptor (Chew et al. 2006) (see Table 20–6) and thus its low potential to cause cognitive impairment, ziprasidone is an attractive medication for older patients with psychosis. However, geriatric data on oral ziprasidone remain limited (Berkowitz 2003; Wilner et al. 2000). Three published studies on the use of intramuscular ziprasidone found no adverse cardiovascular or electrocardiographic changes in a small number of older patients (Greco et al. 2005; Kohen et al. 2005; Rais et al. 2010). However, after thioridazine, ziprasidone remains the antipsychotic that is most likely to be associated with QT prolongation (Wenzel-Seifert et al. 2011). Thus, in the absence

of systematic geriatric studies, ziprasidone should be used with caution in older patients and should be avoided in patients with cardiac disease or in those who take other drugs associated with QT prolongation.

Newer Atypical Antipsychotics

In recent years, three other atypical antipsychotics have been approved by the FDA for use in schizophrenia: asenapine, iloperidone, and lurasidone. Except for two case series of 11 and 15 older patients with bipolar disorder treated with asenapine (Baruch et al. 2013; Sajatovic et al. 2014), there is an almost total absence of published geriatric data for these three medications (Guay 2011; Rado and Janicak 2012). Coupled with their lack of clear advantages over other atypical antipsychotics and some potential disadvantages (Guay 2011), this absence of data precludes making any recommendations for the use of these three newer antipsychotics in older patients (Schiff et al. 2011).

Mood Stabilizers

As a class, mood stabilizers are high-risk medications for older patients. There is a paucity of controlled studies and an abundance of concerns regarding the drugs' potential toxicity, problematic side effects, and drug interactions. Beyond their approved indications, anticonvulsants are also used in the management of agitation accompanying dementia. Currently, no consensus exists as to which drug should be preferred as a first-line mood stabilizer in older individuals with bipolar disorder or secondary mania (Sajatovic et al. 2005b; Shulman 2010; Young et al. 2004). However, the neuroprotective properties of lithium (Foland et al. 2008; Germaná et al. 2010; Hajek et al. 2012a, 2012b; Macritchie et al. 2010) and the favorable cognitive effects of lamotrigine (Gualtieri and Johnson 2006) make them attractive agents for older patients with bipolar disorder (D'Souza et al. 2011; Sajatovic et al. 2013).

Lithium

Lithium continues to be used in older patients for the treatment of bipolar disorder (D'Souza et al. 2011; Shulman 2010) or, less commonly, as an augmentation agent in treatment-resistant depression (Cooper et al. 2011; Flint and Rifat 2001; Ross 2008) and for the prevention of depressive relapse following electroconvulsive therapy (Sackeim et al. 2001). Several publications have described the design and the characteristics of the participants in the first RCT of the pharmacotherapy of manic or mixed episodes in older patients with bipolar disorder (Al Jurdi et al. 2012; Beyer et al. 2014; Young et al. 2010). Although the results of this randomized comparison of the efficacy and tolerability of divalproex and lithium have been reported at several scientific meetings, they have not yet been published. Available data from open and controlled trials suggest that lithium is efficacious in the acute treatment and prophylaxis of mania in older patients (D'Souza et al. 2011; Sajatovic et al. 2005a; Shulman 2010); however, age-related reductions in renal clearance and decreased total body water significantly affect the pharmacokinetics of lithium in older patients, increasing the risk of toxicity (D'Souza et al. 2011). Medical comorbidities common in late life—such as impaired renal function, hyponatremia, dehydration, and heart failure—further exacerbate the risk of toxicity (D'Souza et al. 2011; Sajatovic et al. 2006, 2013). Thiazide diuretics, angiotensin-converting enzyme inhibitors, and NSAIDs may precipitate toxicity by further diminishing the renal clearance of lithium. Lithium toxicity can produce persistent central nervous system impairment or be fatal: it is a medical emergency that requires careful correction of fluid and electrolyte imbalances and that may require administration of mannitol (or even hemodialysis) to increase lithium excretion.

Older patients require lower lithium dosages than do younger patients to produce similar serum lithium levels, and their lithium levels, electrolytes, and thyroid-stimulating hormone should be monitored regularly (D'Souza et al. 2011; Rej et al. 2014a). Also, older persons are more sensitive to neurological side effects of lithium and experience them at lower lithium levels. This sensitivity may be a consequence of increased permeability of the blood-brain barrier and subtle changes in sodium-lithium countertransport, resulting in a higher ratio of brain-to-serum concentration in older patients than in younger patients (Forester et al. 2009). Neurotoxicity may manifest as coarse tremor, slurred speech, ataxia, hyperreflexia, and muscle fasciculations. In vitro, lithium has moderate anticholinergic activity (Chew et al. 2008). This

may explain why cognitive impairment has been observed with levels well below 1 mEq/L and why frank delirium has been reported with levels as low as 1.5 mEq/L (Sproule et al. 2000). Consequently, treatment in older patients may require lithium levels to be kept as low as 0.4–0.8 mEq/L. In addition, despite the absence of definite evidence, concerns about the association between long-term use of lithium and renal disease and the possible causal role of lithium in this association remain (Rej et al. 2014b). Despite its potential toxicity, lithium remains an important drug in the treatment of bipolar disorder and treatment-resistant depression in late life because of its potential effect on suicidality (Müller-Oerlinghausen and Lewitzka 2010) and its potential neuroprotective properties (Foland et al. 2008; Germaná et al. 2010; Hajek et al. 2012a, 2012b; Macritchie et al. 2010).

Anticonvulsants

Anticonvulsants are used as alternatives to lithium in the treatment of bipolar disorder (Young et al. 2004) and as third-line alternatives to antipsychotics and SSRIs for the management of agitation associated with dementia (Herrmann et al. 2013b). There may be a subgroup of patients with bipolar disorder with dysphoria or rapid cycling who respond poorly to lithium but do well with anticonvulsants (Post et al. 1998).

Divalproex

Divalproex, a compound of sodium valproate and valproic acid in an enteric-coated form, is a broad-spectrum anticonvulsant approved by the FDA for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. It also may be efficacious in the treatment of bipolar depression (Bond et al. 2010). Small case series have suggested that divalproex is relatively well tolerated by older patients with bipolar disorder (Kando et al. 1996; Noaghiul et al. 1998). Nonetheless, it should not be used in patients with dementia because of six negative placebo-controlled trials showing that compared with placebo, divalproex is not more effective but is more toxic—including potential neurotoxicity and cognitive toxicity—in older patients with dementia and agitation (Herrmann et al. 2013b; Sink et al. 2005; Tariot et al. 2005, 2011). Sedation, nausea, weight gain, and hand tremors are common dose-related side effects. Reversible thrombocytopenia can occur in up to half of the elderly patients taking divalproex and may ensue at lower total drug levels than in younger patients (Fenn et al. 2006). Other dose-related adverse effects include reversible elevations in liver enzymes and transient elevations in blood ammonia levels. However, liver failure and pancreatitis are rare. Divalproex has other metabolic effects of concern to aging patients, such as increases in bone turnover and reductions of serum folates, with concomitant elevations in plasma homocysteine concentrations (Sato et al. 2001; Schwaninger et al. 1999).

The pharmacokinetics of valproate vary according to formulation, and valproic acid, divalproex sodium, and its extended-release (ER) preparation are not interchangeable. Valproate is metabolized principally by mitochondrial β-oxidation and secondarily by the cytochrome P450 system; typical half-lives are in the range of 5–16 hours and are not affected by aging alone. Concomitant administration of valproate will increase concentrations of carbamazepine, diazepam, lamotrigine, phenobarbital, and primidone. Conversely, concurrent administration of carbamazepine, lamotrigine, phenytoin, and topiramate may decrease levels of valproate. Fluoxetine and erythromycin may potentiate the effects of valproate. Changes in protein binding as a result of drug interactions are no longer considered clinically important beyond causing the misinterpretation of total (i.e., free and bound) drug levels (Benet and Hoener 2002). Because valproate binding to plasma proteins is generally reduced in the elderly, use of free drug levels correlates better with adverse effects (Fenn et al. 2006).

Lamotrigine

Lamotrigine is approved by the FDA for the maintenance treatment of bipolar I disorder to prevent mood episodes (depressive, manic, or mixed episodes) and it is considered a first-line agent for the treatment of bipolar depression in adults (Fenn et al. 2006). Pooled geriatric data from two randomized placebo-controlled trials support the efficacy of

lamotrigine in preventing bipolar depression in older patients (Sajatovic et al. 2005a, 2007). Open studies and case reports suggest a role for lamotrigine in the treatment of bipolar depression (Sajatovic et al. 2011), and possibly bipolar mania and dementia-related agitation as well (Sajatovic et al. 2007).

In contrast with many other mood stabilizers and antidepressants, lamotrigine does not seem to be associated with weight gain or to cause significant drug interactions. It is also less likely than other mood stabilizers to be associated with cognitive impairment (Gualtieri and Johnson 2006). Typically, lamotrigine is well tolerated, but somnolence and rashes have been observed in older patients. Rashes are the most common reason for discontinuation, but their incidence is less frequent with lamotrigine than with carbamazepine (Fenn et al. 2006). Severe rashes, including Stevens-Johnson syndrome or toxic epidermal necrolysis, have been observed in about 0.3% of adult patients (Messenheimer 1998). At the first sign of rash or other evidence of hypersensitivity (e.g., fever, lymphadenopathy), lamotrigine should be discontinued, and the patient should be evaluated. The incidence of rashes can be reduced by using a low initial dose and a slow titration.

Because valproate increases lamotrigine concentration, the initial and target doses need to be halved in patients who are receiving divalproex and the titration of lamotrigine needs to be slowed down. Conversely, carbamazepine approximately halves lamotrigine concentrations, and the initial lamotrigine dose needs to be doubled in patients who are receiving carbamazepine.

Carbamazepine and Oxcarbazepine

The extended-release formulation of carbamazepine is approved by the FDA for the acute treatment of manic and mixed episodes associated with bipolar disorder. In a placebo-controlled trial in 51 nursing home patients, carbamazepine also was shown to be efficacious in treating agitation and aggression associated with dementia (Tariot et al. 1998). Common side effects in older patients include sedation, nausea, dizziness, rash, ataxia, neutropenia, and hyponatremia. Older patients are also at risk for agranulocytosis, aplastic anemia, hepatitis, and problematic drug interactions (Fenn et al. 2006). Carbamazepine is primarily eliminated by CYP3A4, and its clearance is reduced with aging. Its interactions with other drugs are protean: carbamazepine concentrations are increased to potential toxicity by CYP3A4 inhibitors such as macrolide antibiotics, antifungals, and certain antidepressants (see antidepressants that inhibit CYP3A4 in Table 20–4). CYP3A4 inducers—such as phenobarbital, phenytoin, and carbamazepine itself—lower the concentration of carbamazepine and the concentrations of many drugs metabolized by this isoenzyme, including lamotrigine, valproate, some antidepressants, and antipsychotics (Fenn et al. 2006). Oxcarbazepine, the 10-keto analogue of carbamazepine, is a less potent CYP3A4 inducer and less likely to be involved in drug interactions. Although oxcarbazepine has been studied in a small number of younger patients with bipolar disorder, there is a paucity of data pertaining to older psychiatric patients (Sommer et al. 2007). Therefore, its use cannot be recommended in older patients.

Gabapentin and Pregabalin

Although gabapentin has been used in bipolar disorder, trials have not borne out its effectiveness, and only small case series or case reports of its use in dementia are available (Sommer et al. 2007). Nonetheless, it has a generally favorable side-effect profile and modest anxiolytic and analgesic effects, particularly for neuropathic pain. Gabapentin does not bind to plasma proteins and is not metabolized, being eliminated by renal excretion. In patients with renal impairment, neurological adverse effects such as ataxia, involuntary movements, disorganized thinking, excitation, and extreme sedation have been noted. Even in the absence of renal dysfunction, elderly patients may be prone to excessive sedation. Therefore, in the elderly, initial dosages of 100 mg twice daily are more prudent than the 900 mg/day recommended as a starting dosage for younger patients with epilepsy. Pregabalin is a structural congener of gabapentin. It has an improved pharmacokinetic profile and it is approved by the FDA not only for the treatment of epilepsy (as adjunctive therapy for adult patients with partial-onset seizures) but also for neuropathic pain associated with diabetic

peripheral neuropathy and spinal cord injury, postherpetic neuralgia, and fibromyalgia. Some published pooled geriatric data from 11 placebo-controlled trials show that pregabalin 150–600 mg/day is associated with clinically meaningful pain relief in older patients with painful diabetic neuropathy or postherpetic neuralgia (Semel et al. 2010). In these studies pregabalin's main adverse effects are dizziness, somnolence, and peripheral edema, and they are dose related. In addition, a placebo-controlled trial (Montgomery et al. 2008) and some open data (Karaiskos et al. 2013) support the off-label use of 150–600 mg/day of pregabalin in older patients with generalized anxiety disorder.

Topiramate

Early reports of the efficacy of topiramate in younger patients with bipolar disorder have not been confirmed by subsequent studies (Sommer et al. 2007). In younger patients, topiramate is one of the few psychotropic medications that have been associated with weight loss. However, it also has been associated with cognitive impairment that can be severe enough to interfere with functioning (Gualtieri and Johnson 2006). Additionally, because of the paucity of data pertaining to use of topiramate in older psychiatric patients (Sommer et al. 2007), its use cannot be recommended in these patients.

Anxiolytics and Sedative-Hypnotics

The SSRIs and SNRIs have displaced benzodiazepines as first-line pharmacotherapy for anxiety in late life, whereas benzodiazepine receptor agonist hypnotics (i.e., eszopiclone, zaleplon, zolpidem) and the intermediate half-life benzodiazepine lorazepam have become the most commonly used hypnotics.

Benzodiazepines and Benzodiazepine Receptor Agonists

In older patients, detrimental effects of benzodiazepines and benzodiazepine receptor agonists frequently outweigh any short-term symptomatic relief that they may provide and they should be avoided (American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012). Even single small doses of diazepam, nitrazepam, and temazepam cause significant impairment in memory and psychomotor performance in older subjects (Nikaido et al. 1990; Pomara et al. 1989). Even benzodiazepines with shorter half-lives increase the risk of falls and hip fractures in frail elderly patients (Ray et al. 2000). More recently, benzodiazepines have also been linked to adverse respiratory outcomes in older patients with chronic obstructive pulmonary disease (Vozoris et al. 2014) and to an increased risk for Alzheimer's dementia (Billioti de Gage et al. 2014). Although benzodiazepine receptor agonists are perceived as being safer, they also have been associated with falls and hip fractures (Wang et al. 2001) or cognitive impairment and traffic accidents (Glass et al. 2005; Gustavsen et al. 2008; Leufkens et al. 2009). Finally, both benzodiazepines and benzodiazepine receptor agonists are associated with a significantly increased risk of mortality in older patients (Kripke et al. 2012; Weich et al. 2014).

Nevertheless, benzodiazepines may be used for the prevention of alcohol withdrawal or as a temporary adjunctive treatment for anxiety- or depression-related sleep disturbance when the primary pharmacotherapy is an antidepressant. Relative contraindications include heavy snoring (because it suggests sleep apnea), dementia (because such patients are at increased risk for daytime confusion, impairment in activities of daily living, and daytime sleepiness), and the use of other sedating medications or alcohol. Benzodiazepines with long half-lives (chlorazepate, chlordiazepoxide, clonazepam, diazepam, flurazepam, halazepam, and quazepam) are probably associated with more adverse effects and therefore should be avoided (Ballokova et al. 2014; Fick et al. 2003; Hemmelgarn et al. 1997). Also, several drugs with shorter half-lives (i.e., alprazolam, triazolam, midazolam, eszopiclone, zaleplon, and zolpidem) undergo phase 1 hepatic metabolism by CYP3A4 that is subject to specific interactions and age-associated decline (Freudenreich and Menza 2000; Greenblatt et al. 1991). Sedatives with very short half-lives also may increase the likelihood that confused elderly patients will awake in the middle of the night to stagger off to the bathroom. Lorazepam and oxazepam do not undergo phase 1 hepatic metabolism, have no active metabolites, have acceptable half-lives that do not increase with age, and

are not subject to drug interactions. Lorazepam is available in appropriately small doses (0.5-mg pills) and is well absorbed intramuscularly. It is preferred for inducing sleep because oxazepam has a relatively slow and erratic absorption.

Buspirone

The anxiolytic buspirone, a partial 5-HT1A agonist, is rarely used. Nevertheless, it may be beneficial for some patients with generalized anxiety disorder or as an augmentation agent in treatment-resistant depression (Flint 2005; Trivedi et al. 2006). It appears to be well tolerated by elderly patients without the sedation or addiction liability of the benzodiazepines (Steinberg 1994). Therefore, it may be helpful for some older patients who are prone to falls, confusion, or chronic lung disease. Nonetheless, buspirone may take several weeks to exert an anxiolytic effect, has no cross-tolerance with benzodiazepines, and may cause dizziness, headache, or nervousness (Strand et al. 1990). It is of limited use for panic or obsessive-compulsive disorders. The pharmacokinetics of buspirone are not affected by age or gender, but coadministration with verapamil, diltiazem, erythromycin, or itraconazole will substantially increase buspirone concentrations, and its combination with serotonergic medications may result in the serotonin syndrome (Mahmood and Sahajwalla 1999).

Cognitive Enhancers

In addition to memantine (discussed in the next subsection), four cholinesterase inhibitors have received FDA approval for the symptomatic improvement of Alzheimer's disease. Table 20–7 describes three of these drugs: donepezil, galantamine, and rivastigmine. The fourth, tacrine, is no longer recommended because of its potential hepatotoxic effects.

Cholinesterase Inhibitors

	Clearance	Dosing	Significant adverse effects	Pharmacodynamics
Donepezil	Half-life = 70–80 hours; CYP3A4, CYP2D6	5–10 mg/day in one dose; start at 5 mg at bedtime	Mild nausea, diarrhea, bradycardia	Reversible acetylcholinesterase inhibition
Galantamine, galantamine ER	Half-life = 7 hours; CYP2D6, CYP3A4	8–24 mg/day divided into two doses; start at 8 mg/day twice daily	Moderate nausea, vomiting, diarrhea, anorexia, tremor, insomnia	Reversible acetylcholinesterase inhibition; nicotinic modulation may increase acetylcholine release
Rivastigmine, rivastigmine patch	Half-life = 1.25 hours; renal	6–12 mg/day divided into two doses; start at 1.5 mg twice daily. For patch, start at 4.6 mg/day and increase after 4 weeks to 9.5 mg/day. Retitrate if drug is stopped.	Severe nausea, vomiting, anorexia, weight loss, sweating, dizziness	Pseudoirreversible acetylcholinesterase inhibition; also butylcholinesterase inhibition

Note. CYP = cytochrome P450; ER = extended release.

Cholinesterase inhibitors produce modest improvements in cognition and function in patients with Alzheimer's disease (Hansen et al. 2008; Herrmann et al. 2013b), including those with severe Alzheimer's disease (Herrmann et al. 2013b; Howard et al. 2012; Winblad et al. 2006). Therefore, a trial with a cholinesterase inhibitor is recommended in most patients with Alzheimer's disease; in the absence of convincing evidence that one of the three cholinesterase inhibitors is more effective than the others, the selection of a specific drug is based on its pharmacokinetic and adverse effects profile (see Table 20–7) (Herrmann et al. 2013b). Cholinesterase inhibitors have modest benefit of uncertain clinical significance in vascular dementia (Kavirajan and Schneider 2007). They may also have a role in the management of other cognitive disorders, such as Lewy body dementia (Gustavsson et al. 2009; Rolinski et al. 2012), dementia with Parkinson's disease (Herrmann et al. 2013b: Rolinski et al. 2012), frontotemporal dementia (Herrmann et al. 2013b), mild cognitive impairment (Diniz et al. 2009; Doody et al. 2009), and cognitive impairment associated with late-life depression (Reynolds et al. 2011). Available data are not consistent, however, and there is no agreement on the role of cholinesterase inhibitors in the treatment or prevention of behavioral or psychological symptoms associated with dementia (Freund-Levi et al. 2014; Gauthier et al. 2010; Herrmann et al. 2013b; Howard et al. 2007; Lockhart et al. 2011; Rodda et al. 2009; Sink et al. 2005).

No evidence suggests that cholinesterase inhibitors alter the underlying neuropathology of Alzheimer's disease or its eventual progression. Indeed, a rapid symptomatic deterioration may occur when cholinesterase inhibitors are discontinued (Scarpini et al. 2011). In patients with diminished cognitive reserve, even small anticholinergic effects can substantially impair cognition (Mulsant et al. 2003; Nebes et al. 2005). Drugs with potent anticholinergic effects directly antagonize cholinesterase inhibitors (Chew et al. 2008; Modi et al. 2009). Thus, it is imperative that unnecessary anticholinergic medications be discontinued before initiating a cholinesterase inhibitor (Lu and Tune 2003; Modi et al. 2009).

The main adverse effects of cholinesterase inhibitors are concentration dependent and result from their central and peripheral cholinergic actions. Nausea, diarrhea, weight loss, bradycardia, syncope, and nightmares are associated with all of the cholinesterase inhibitors and may lead to their discontinuation (see Table 20–7; Gill et al. 2009; Hernandez et al. 2009; Park-Wyllie et al. 2009); gastrointestinal adverse effects may be less frequent with donepezil (Mayeux 2010). However, despite theoretical concerns, the use of cholinesterase inhibitors appears to be safe in patients with chronic airway disorders (Thacker and Schneeweiss 2006). Finally, in a placebo-controlled study in older patients with a major depressive disorder receiving maintenance antidepressant pharmacotherapy, donepezil was associated with a higher rate of recurrence of depression than placebo (Reynolds et al. 2011). With these adverse effects in mind, clinicians should be aware of the drugs' specific pathways of elimination and potential pharmacokinetic drug interactions with CYP2D6 or CYP3A4 inhibitors and with CYP3A4 inducers when prescribing donepezil and galantamine (Pilotto et al. 2009; Seritan 2008). Rivastigmine is affected by renal function, and FDA warnings have emphasized the need for careful dose titration (and retitration if restarting) to prevent severe vomiting (Birks et al. 2009).

NMDA Receptor Antagonist

Memantine, an N-methyl-d-aspartate (NMDA) receptor antagonist, has FDA approval for the treatment of moderate to severe Alzheimer's disease. As an uncompetitive antagonist with moderate affinity for NMDA receptors, memantine may attenuate neurotoxicity without interfering with glutamate's normal physiological actions. In placebo-controlled clinical trials in patients with moderate to severe Alzheimer's disease, memantine was associated with modest delay in deterioration of cognition and activities of daily living, when administered alone (Reisberg et al. 2003) or in combination with donepezil (Tariot et al. 2004). However, in a study of patients with moderate or severe Alzheimer's disease, memantine and donepezil were found to have similar efficacy with respect to cognitive outcomes and activities of daily living. Furthermore, there were no significant benefits of the combination of donepezil and memantine over donepezil alone (Howard et al. 2012). Thus, combining a cholinesterase inhibitor and memantine is not recommended (Herrmann et al. 2013b). As with data on the cholinesterase inhibitors, data on memantine are not consistent and thus there is no

agreement on the role of memantine in the treatment or prevention of behavioral or psychological symptoms associated with dementia (Gauthier et al. 2008; Herrmann et al. 2011, 2013a, 2013b; Lockhart et al. 2011; Rive et al. 2013; Wilcock et al. 2008). However, memantine may have a role in the treatment of Parkinson's disease dementia and Lewy body dementia (Aarsland et al. 2009; Emre et al. 2010; Matsunaga et al. 2013).

Memantine is well tolerated, although it may cause confusion in some patients (Kavirajan 2009). It does not appear to be implicated in drug-drug interactions, but it is excreted by the kidneys, and its dosage needs to be reduced in patients with significant impairment in renal function.

Conclusion

Substantial evidence now exists to guide the use of psychotropic medications in older persons. Most available data pertain to: the use of SSRI or SNRI antidepressants in the treatment of major depressive disorders; the use of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia; and the use of cognitive enhancers in the treatment of cognitive impairment due to Alzheimer's disease. Existing data support the short-term and long-term efficacy and the relative safety of SSRI and SNRI antidepressants in the treatment of most older individuals with a major depressive disorder or an anxiety disorder. In contrast, the risks associated with the use of antipsychotics outweigh their potential benefits in many older persons presenting with behavioral and psychological symptoms of dementia. Cognitive enhancers appear relatively safe in older individuals with dementia but their efficacy is modest. Pharmacoepidemiological data show that benzodiazepines continue to be prescribed to a larger number of older individuals despite their toxicity. Empirical data to guide the use of mood stabilizers or antipsychotics in older persons with bipolar disorder or schizophrenia are lacking. Similarly, better data are needed to inform the selection, sequencing, and combination psychotropic medications in older persons whose symptoms do not respond to first-line pharmacological interventions.

Key Points

Substantial evidence supports the short-term and long-term efficacy and the relative safety of SSRI and SNRI antidepressants in the treatment of most older persons with a major depressive disorder or an anxiety disorder.

In contrast, the risks associated with the use of antipsychotics outweigh their potential benefits in many older persons presenting with behavioral and psychological symptoms of dementia.

Cognitive enhancers appear relatively safe in older persons with dementia but their efficacy is modest.

Pharmacoepidemiological data show that benzodiazepines continue to be prescribed to many older persons despite their toxicity.

Empirical data to guide the use of mood stabilizers or antipsychotics in older persons with bipolar disorder or schizophrenia are lacking.

Similarly, better data are needed to inform the selection, sequencing, and combination of psychotropic medications in older persons whose symptoms do not respond to first-line pharmacological interventions.