Pharmacotherapy for Mood and Anxiety Disorders

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Trevor R. Norman

Abstract

Mood and anxiety disorders are common in the elderly. They are associated with significant morbidity and mortality. Unrecognized psychiatric conditions may have a significant negative effect on treatment outcomes for somatic disorders. Psychopharmacological treatment strategies should aim to provide not only symptomatic response and remission of symptoms but also full functional recovery. While medications are the mainstay for moderate to severe conditions, the use of adjunctive psychotherapy should also be considered. The selective serotonin reuptake inhibitors have become the first-line pharmacological treatment of depression and anxiety for the elderly. Alternative options (benzodiazepines, other antidepressants, and buspirone), while effective, have drawbacks associated with their use which makes them unsuitable as first-line choices. Clinical use of the selective serotonin reuptake inhibitors requires careful consideration of the mental status of the individual patient, their physical health (robust good health for age or frailty), and the presence of somatic illness. The choice of medication and initial dose will be guided by the interaction of these factors. Careful assessment of response to and monitoring of side effects of medication is essential to ensure optimal outcomes.

Keywords

Depression • GAD • Elderly • Antidepressants • Anxiety • Benzodiazepines • Pregabalin • Tricyclics • Monoamine oxidase inhibitors • SSRIs • SNRIs • Agomelatine • Vortioxetine

T.R. Norman
Department of Psychiatry, University of Melbourne, Austin Hospital, Heidelberg, VIC, Australia
e-mail: trevorrn@unimelb.edu.au

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Introduction

It has been estimated that between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% (WHO 2015). Within the same time frame, about 80% of these older people will be living in low- and middle-income countries. The United Nations has identified the decline in fertility rates as the primary determinant of population aging. In developed countries the decline in fertility is below the population replacement rate, while in the less developed countries, fertility rates are predicted to fall below population replacement around 2050 (United Nations 2002). This lowered fertility rate coupled with an increasing life expectancy at birth (the UN estimates an increase of more than 20 years in the past five decades (United Nations 2002) implies that the elderly will increasingly consume healthcare services, including mental healthcare delivery. Much of this burden is likely to be due to high-prevalence mental disorders in later life, particularly the mood and anxiety disorders, as well as dementia.

Although the elderly currently represent a minor proportion of the population, they account for a disproportionate number of medication prescriptions. Older surveys suggested that while the elderly constituted 12% of the population, they accounted for 33% of expenditure on prescription medicines (Judge and Caird

1978). This is perhaps not surprising as aging is associated with a greater likelihood of developing a condition (or conditions) which will require ongoing medication. Polypharmacy is relatively common as a consequence of this situation. Indeed it has been estimated that one in six elderly people take three or more medications a day (Judge and Caird 1978). Later surveys suggest that the elderly take two to five prescription medications regularly while polypharmacy occurs in 20–50% of patients (Kennerfalk et al. 2002; Pizzuti et al. 2006).

The use of medications in the elderly is associated with a number of common problems including ineffectiveness, adverse drug effects, overdosage, underdosage, and drug-drug interactions due to the use of multiple medications (Herrlinger and Klotz 2001; Mallet et al. 2007**)**. Polypharmacy and age-related changes in pharmacodynamics and pharmacokinetics increase the risk of adverse effects. Furthermore, adverse drug reactions are often more serious in the elderly (Doucet and Queneau 2005; Cresswell et al. 2007) and are a frequent cause of admission to hospital. The potential for a prescribing cascade occurs when adverse effects of an originally prescribed drug are interpreted as a symptom of a new disorder and a further drug is prescribed to treat it. This new, unnecessary agent may cause additional side effects which are misinterpreted as another disorder and treated unnecessarily. For example, the use of an antipsychotic medication leads to Parkinson like symptoms which are then treated as a new disorder.

Further distinction needs to be drawn between "fit elderly" and "frail elderly" (Ahmed et al. 2007). The later subpopulation of patients represents a group for whom multiple disease states rather than age per se primarily account for alterations in drug responses (Woodhouse and O'Mahony 1997; Hubbard et al. 2008). Differences in response of the elderly, especially those over 75 years, from younger patients are an important cause of morbidity and mortality. Psychotropic medications are frequently prescribed to the elderly in both ambulatory care and in nursing homes. Prescribing in the elderly must take into account the principles of good clinical practice. Treatment must be tailored to fit each elderly individual's unique comorbidities where these exist. Table 1 outlines a number of issues to be given consideration before prescribing a medication for an elderly patient.

Metabolic, Pharmacokinetic, and Pharmacodynamic Changes in the Elderly

It is well recognized that aging brings with it alterations in physiological parameters that can affect both drug handling (pharmacokinetic) and responses to medication (pharmacodynamics). These changes have been described in detail in the past (Benedetti et al. 2007; Hilmer et al. 2007; Hutchison and O'Brien 2007; Kinirons and O'Mahony 2004; McLean and Le Couteur 2004; Schwartz 2007; Wauthier et al. 2007; Klotz 2009) and are not reiterated in detail here. Several factors, outlined in Table 2, contribute to alterations in drug kinetic differences between elderly and young subjects. Although such differences are well recognized, there is, in general and for

Table 1 Prescribing principles for the elderly

Is drug therapy required at all?	Accurate diagnosis and assessment of severity
Which drug is appropriate?	Accurate diagnosis; depression and anxiety are often symptoms not disorders; underlying organic causes evaluated?
Is the dosage correct?	Smaller doses are often required. Start low go slow
What are the undesirable effects?	Potential for postural hypotension and anticholinergic effects should be considered
Is the choice of preparation correct?	Some sub-lingual preparations are available for patients with difficulty swallowing
Can the patient living at home manage self-administration?	Simple, clear instructions for drug regimens; compliance decreases with increase in number of medications
Is the drug correctly packaged and labeled?	Use of large print for eyesight difficulties; containers easily opened due to arthritis
When can the drug therapy be ceased?	Withdrawal of medications no longer indicated; tapered withdrawal for most psychotropics

Table 2 Age-related changes potentially affecting pharmacokinetics of medications

Organ system	Physiology change with aging	Major effect	Pharmacokinetic effect
GI tract	↓Gastric secretion	Decreased transport efficiency	Onset of action may be delayed
	↓GI motility		Unlikely to be of concern on repeated administration
	↓GI blood flow		
	↑Gastric pH		
Kidney	Decreased renal blood flow	Decreased GFR	Decreased clearance
			Increased plasma elimination half-life
Liver	↓Enzyme induction	Decreased availability of drugs to the liver	Reduced hepatic clearance of drugs
	↓Hepatic mass		Increased plasma half-life
	↓Hepatic blood flow		Increased potential for drug interactions
	↓Activity in enzyme activity		
Plasma	Generally decreased proteins		Higher concentrations of free drug
Muscle	More fat, less muscle	Altered distribution	Increased Vd
			Increased elimination half-life

GFR glomerular filtration rate, *GI* gastrointestinal, *Vd* volume of distribution

psychotropic medications specifically, a lack of well-designed clinical studies to evaluate single- and repeated-dose pharmacokinetic studies in elderly populations. Evaluations of pharmacokinetic and pharmacodynamic responses to psychotropic medications rarely include elderly patients with coexisting physical disorders.

Absorption

Changes in the gastrointestinal (GI) tract with aging may affect how some drugs are absorbed. Both GI motility and GI blood flow are generally reduced with aging. Gastric acid secretion may also be reduced leading to an elevation in gastric pH. Reduced absorption may result from increased gastric pH and reduced gastric blood flow, whereas reduced motility may result in greater drug absorption. The use of antacids and proton pump inhibitors will also contribute to changes in the GI tract (Kapadia et al. 2010). Although these age-related changes in absorption may affect the onset of action of a drug following single doses, repeated administration is less likely to be affected in a clinically significant way.

Distribution

A number of factors influence the theoretical volume of distribution of a drug, including protein binding (only unbound drug is distributed), water or lipid solubility (highly lipid-soluble drugs have greater volumes of distribution), pH, and molecular size. The decline in muscle mass and increase in the proportion of body fat with aging will significantly affect drug distribution in the body. In general lipophilic agents have increased volumes of distribution in the elderly. Diazepam, which is highly fat soluble, is a case in point. Aging is associated with a reduction in total body water with a consequential effect on the volume of distribution for drugs which are water soluble.

Age-related changes in plasma protein binding are not regarded as of clinical relevance (Benet and Hoener 2002). Although mean serum albumin concentrations have been shown to decline progressively with age (Greenblatt 1979), α1-acid glycoprotein tends to increase with age (Butler and Begg 2008). Such changes have been attributed more to pathophysiology or disease states than to aging per se (Benet and Hoener 2002). Nevertheless, reductions in protein binding can result in an increased free drug concentrations which may affect pharmacological responses (Hutchison and O'Brien 2007; Mangoni and Jackson 2004**;** Greenblatt et al. 2002).

The multidrug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (*ABCB1*) gene product, P-glycoprotein (P-gp), is an efflux pump that is present in excretory organs as well as the blood-brain barrier (Taylor 2002). Potentially drug disposition might be affected by P-gp expression and activity (Lin and Yamazaki 2003). With respect to the effects of aging, there is a paucity of data on the importance of P-gp for drug distribution (Klotz 2009). Such studies which have been conducted show either no or minimal effects (Toornvliet et al. 2006).

Metabolism

Before excretion most drugs undergo biotransformation to more polar metabolites by cytochrome P450 (CYP)-dependent phase I reactions and/or phase II pathways, such as glucuronidation, acetylation, or sulfation. This drug metabolism mainly takes place in the liver (Klotz 2009). Liver size/mass (~20–30%) and hepatic blood flow

(~20–50%) decrease with age which might result in alteration of the elimination of high-clearance drugs. Hepatocyte volume remains unchanged between 20 and 95 years, while there are no age-related changes in routine clinical tests of liver function (Le Couteur et al. 2005; Herrlinger and Klotz 2001). Studies in vivo assessing the capacity of specific cytochrome enzymes in elderly versus young subjects or population kinetic studies have generally failed to demonstrate clinically significant changes in healthy elderly subjects (Klotz 2009). Nevertheless, for hepatically cleared drugs dosing is usually recommended to be reduced in elderly patients. Although adjustments are somewhat arbitrary, doses should be titrated to therapeutic outcome or adverse effects.

Elimination

Renal excretion is the primary route of elimination for most psychotropic medications. The apparent plasma half-life of elimination of drugs is increased as renal function declines. Although there are significant changes in kidney mass and the number of glomeruli decreases by about 20–30% with aging, it has been estimated that about a third of elderly patients have no decline in renal function (Klotz 2009). Indeed a small subpopulation of elderly renal function, based on creatinine clearance, may actually increase (Lindeman et al. 1985; Froissart and Rossert 2005). Changes in renal function with aging are more likely to arise due to concomitant disease states than aging *per se* (Fliser et al. 1997). Nevertheless there are some psychotropic medications for which renal elimination is important. Lithium is a case in point being subject to renal clearance only, and therefore alterations in renal function can result in inadvertent over- or underdosing if this is not taken into account.

Overview

In summary, the altered pharmacokinetics observed in most elderly patients can be attributed to physiological changes with aging. Table 2 summarizes important physiological changes with aging and their likely effects on pharmacokinetic parameters. What is perhaps best to bear in mind is not that the kinetics are different from younger patients but that there is a much greater variability in kinetic parameters seen in elderly patients than in younger patients. Furthermore concomitant disease states are likely to influence kinetics more than aging per se. Nevertheless, the dosing strategy of "start low, go slow" represents a balance between the kinetic and dynamic alterations in medication responses in the elderly.

Depression in the Elderly

While in the community-dwelling elderly population depressive symptoms are relatively common (15% according to the Epidemiological Catchment Area study (Blazer and Hughes 1987)), a much smaller subset meets full criteria for major

depressive disorder, perhaps 1–2%. In nursing homes the prevalence of depression may be much higher, up to 25% in one study (Samuels and Katz 1995). Estimates of prevalence clearly are influenced by the setting of the survey as well as the presence of chronic medical illness associated with depressive symptoms (Mock et al. 2010). Depression in the elderly is associated with significant morbidity and disability, as well as increased risk of mortality. The presentation of depression in older people is often regarded as atypical. Older people are less likely to report feelings of sadness or identify with the term "depression." Commonly patients present with complaints of anxiety, somatic symptoms, and memory loss. Hospitalized depressed patients frequently have psychotic symptoms (mood-congruent delusional beliefs with themes of persecution, nihilism, and guilt). Response and remission with treatment are often lower in the elderly with higher relapse rates as a consequence of suicidal ideation and attempts (Driscoll et al. 2007). Rates of suicide are high in the elderly, particularly elderly men, with some specific risk factors identified (divorced or single, widowers). Acts of deliberate self-harm in older patients should be managed as a "failed suicide" however trivial the attempt, as most incidents are performed with high suicidal intent (Osgood 1991).

Treatment of Depression

The mainstay of treatment for depression of moderate to severe intensity has been the use of pharmacotherapy. The efficacy and tolerability of the first-generation antidepressants (tricyclics and monoamine oxidase inhibitors), as well as the second-generation antidepressants (selective serotonin reuptake inhibitors), in older people have a reasonably robust database of controlled clinical evaluations in specific elderly populations. The so-called "third-generation" antidepressants with variable modes of action are not as well evaluated in elderly populations. The very elderly (older than 85 years) are underrepresented in clinical trials (Giron et al. 2005). Similarly, patients who reside in nursing homes and who have dementia and medical comorbidities are also generally excluded from clinical trials. This population has high rates of depression (three to five times higher than community-dwelling elderly) that is often under-recognized and undertreated, resulting in a lack of clinical evidence guiding treatment (Giron et al. 2005).

Most available tricyclic antidepressants have been evaluated in specific populations of elderly patients. Thus evidence of varied degrees of reliability suggests that amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, maprotiline, and nortriptyline are effective in relieving the symptoms of depression. It is beyond the scope of this chapter to reproduce the evidence for each of the studies associated with the clinical evaluation of these agents, but a comprehensive compendium of studies is available (Alexopoulos et al. 2005).The majority of studies are observational or evaluations based on comparison with another agent (or psychotherapy). Placebo-controlled comparisons are relatively few, probably due to ethical concerns in this population. Nevertheless, a review of 12 placebo-controlled evaluations involving tricyclic antidepressants over a mean 7-week

treatment period reported that both imipramine and nortriptyline were superior to placebo in 11 of the studies examined (Taylor and Doraiswamy 2004). The authors identified small sample sizes and lack of inclusion of common comorbid conditions as shortcomings of the extant database. Cross-trial comparisons were also difficult due to large placebo response rates and lack of controlled head-to-head comparisons. A later meta-analysis (Kok et al. 2012) also found tricyclics to be superior to placebo for response rates ($\geq$50% decrease on Hamilton Depression Rating Scale (HDRS) or Montgomery Depression rating Scale (MADRS) or a Clinical Global Impression (CGI) score of 1 or 2) but not for remission of symptoms. Since most studies did not report remission rates, this finding is unreliable due to a small sample size. The number needed to treat (NNT) from this analysis was 4.2. Alexopoulos' compilation of studies suggests that no one tricyclic antidepressant has an established superiority over any other tricyclic, at least in the group comparisons. Choice of medication from this class is likely to be influenced by the side effects of the medication and the particular needs of an individual patient, i.e., which side effects are best avoided due to concomitant medical illness or other characteristics of the patient. Secondary amine tricyclics, particularly desipramine and nortriptyline, are claimed to have some advantages for the elderly due to their less complex metabolism and milder side effects. By far the greatest set of published data in geriatric patients is for nortriptyline. In contrast the use of tertiary amine tricyclics is not recommended in late-life depression by an expert consensus statement (Alexopoulos et al. 2001). It is claimed that there is a greater likelihood of side effects and dose-limiting toxicity with these agents. While all of the medications generally have response rates equivalent to those seen in younger patients (around 60%; Wilson et al. 2001), the majority of studies do not have published data on remission rates for depression. Current management guidelines for depression suggest that remission of symptoms, rather than response, is the most desirable outcome and the targeted goal of treatment (Keller 2003). The few studies for which remission data is available suggest that the tricyclics achieve acceptable rates of remission in the longer term. Thus, a remission rate of 78% was noted during maintenance therapy for recurrent major depression in patients treated with a combination of interpersonal psychotherapy and nortriptyline (Reynolds et al. 1996). Following stabilization 15.5% of patients relapsed. Imipramine and doxepin were associated with a 45% remission rate in patients aged 55 years or older in a 26-week study (Jarvik et al. 1982).

A Cochrane Review examined the efficacy of antidepressant classes in the elderly and compared the withdrawal rates between classes of agent (Mottram et al. 2006). There were no differences in efficacy between classes of antidepressants, but there was a higher withdrawal rate associated with tricyclics due to side effect experiences. Two side effects of particular concern with elderly patients using tricyclics are the well-recognized issues of orthostatic hypotension and conduction alterations (Sloman et al. 1983). These effects are generally dose (and plasma concentration) dependent but cardiac arrhythmias are often unpredictable, while orthostatic hypotension can lead to falls with hip fractures. Partly for these reasons, a recent American Geriatric Society Beers Criteria Update Expert Panel has recommended that tricyclic antidepressants taken either alone or

in combination should be avoided (American Geriatrics Society 2015 Beers Criteria Update Expert Panel 2015).

Monoamine oxidase inhibitors were among the first antidepressants available, yet surprisingly few controlled studies have been performed in elderly groups. Both phenelzine, a nonselective inhibitor of monoamine oxidase (MAO), and moclobemide, a selective MAO-A inhibitor, have been evaluated in double-blind, placebo-controlled trials as noted in Table 3. The single trial of phenelzine showed that it was more effective than placebo and at least as effective as nortriptyline, based on the decline in the HDRS from baseline (Georgotas et al. 1986, 1987). No data was available on response or remission rates in this study. Moclobemide has been evaluated in two placebo-controlled trials. In one large trial, over 600 elderly patients with either depression or dementia were assigned to treatment with moclobemide or placebo (Roth et al. 1996). While it was reported that moclobemide was superior to placebo for depressive symptoms in both groups, few details of the response were available. In the second study, remission rates, defined as a HDRS score <10 at end point, for moclobemide were 23% compared to 33% for nortriptyline and 11% for placebo (Nair et al. 1995). The intent to treat analysis found no differences between moclobemide and placebo and marginal significance for nortriptyline. The study is compromised by a high dropout rate (~50% of treated patients in all groups) and relatively short treatment duration. Comparative or open-label studies with MAOIs in the elderly generally support their efficacy in geriatric depression. Nevertheless they are less likely to be used due to side effects, particularly postural hypotension in the elderly, and the necessity for dietary restrictions.

Recommended first-line treatment of depression in the elderly is a course of one of the selective serotonin reuptake inhibitor (SSRI) medications (Mulsant et al. 2001). These agents are regarded as having a more favorable side effect profile than other classes of antidepressants, a generally safer drug-drug interaction potential and therefore better tolerated at appropriate doses (Rajji et al. 2008). Clinical trials in the elderly have demonstrated that SSRIs are superior to placebo for the treatment of depression (Roose and Schatzberg 2005). A detailed review of the efficacy of SSRIs in elderly patients is published elsewhere (Mukai and Tampi 2009). This review concluded that SSRIs were at least as effective as tricyclics and that they were better tolerated in elderly patients. The meta-analysis of Kok et al. (2012), on the other hand, suggested that remission rates for SSRIs compared to placebo were not significantly different. For response rates however, there was a statistically significant difference from placebo and the NNT was 10 (Kok et al. 2012). The perception of the efficacy of SSRIs may be altered when studies in the very old age group are considered. For example, citalopram failed to separate from placebo in a group of patients aged >80 years (Roose et al. 2004).

Dual reuptake inhibitors provide an alternative approach for the treatment of depression in the elderly. Both venlafaxine and duloxetine have been evaluated in placebo-controlled evaluations in elderly populations. There does not appear to have been any placebo-controlled evaluations of desvenlafaxine in a specifically designed trial in an elderly group. Duloxetine has the best evidence for efficacy: both published studies suggested a statistically significant benefit of the drug at 60 mg/day

Table 3 Placebo-controlled studies of MAOIs in elderly depression

	Sample size	Mean age (yrs)	Dose mg/day	Length of randomized treatment	Primary efficacy variables	Efficacy	REF
Moclobemide							
Moclobemide	25	67	400	6 weeks	HDRS	23%	Nair et al. (1995)
Nortriptyline	27	71	75			33%	
Placebo	25	71				11% (Remission HDRS <10)	
Moclobemide	694	73.6	400	7 weeks	HDRS	MOCLO > PBO on HDRS at end point	Roth et al. (1996)
Placebo							
Phenelzine							
Phenelzine	22	>55	45	7 weeks	HDRS	PHEN = NORT > PBO on HDRS at end point	Georgotas et al. (1987)
Nortriptyline	25		75			PHEN 61.1%, NORT 61.9%; PBO 13.3% responders HDRS <10	
Placebo	28						

(Nelson et al. 2005; Raskin et al. 2007). Venlafaxine showed antidepressant efficacy in open and comparative trials, but three placebo-controlled evaluations were negative studies (Mock et al. 2010). This may have been due to the choice of formulation, immediate release versus extended release. The immediate release formulation is associated with poorer tolerability than the extended release resulting in more dropouts due to side effects and lower statistical power to detect significant differences (Mock et al. 2010).

Recent developments in depression pharmacotherapy have seen the introduction of several new medications: agomelatine, vilazodone, and vortioxetine. Both vortioxetine and agomelatine have been evaluated in limited studies in an elderly population with positive results compared to placebo. Vortioxetine (5 mg/day) was superior to placebo in elderly patients treated for 8 weeks (Katona et al. 2012). Response was achieved by 53.2% of vortioxetine patients and 35.2% of placebo patients. Remission rates were 29.2% and 19.3% for vortioxetine and placebo, respectively. Somewhat similar results were achieved with agomelatine (25–50 mg/day) over 8 weeks compared to placebo (Heun et al. 2013). Response rates were 59.5% and 38.6% for agomelatine and placebo, respectively. Remission rates were not statistically significantly different between drug and placebo. Both agomelatine and vortioxetine are generally well tolerated in the elderly at the doses used in these studies with relatively benign side effect profiles. In addition the putative beneficial effects on sleep (agomelatine) and cognition (vortioxetine) might prove advantageous for these two agents in treating elderly depressed patients. Further evaluations of these agents are required.

Expert consensus guidelines currently recommend only a limited number of antidepressants for geriatric depression. These recommendations are summarized in Table 4 along with dose ranges and particular side effect issues related to use in elderly populations.

While there is a reasonable body of evidence suggesting that antidepressants are effective in elderly depressed populations, the studies are mostly of short treatment duration. Efficacy of pharmacotherapy in continuation and maintenance therapy is less robust. Late-life depression is generally considered as a recurring disorder (Alexopoulos 2005). In the absence of continuation treatment, recurrence rates are around 50% within 4–6 months (Rajji et al. 2008). Recurrence occurred in 90% of elderly patients with major depression within 3 years of remission when maintained on placebo (Reynolds et al. 1999). Lower recurrence was observed in patients maintained on nortriptyline or interpersonal psychotherapy (IPT). A similar observation was made in patients treated with paroxetine and IPT (Reynolds et al. 2006). Recurrence rates over 2 years were 32% in those maintained on paroxetine compared to 58% in those for whom the drug was discontinued. The benefits of longer-term antidepressant treatment on mortality were supported by the PROSPECT study which showed that in practices which implemented depression care management (including antidepressants), mortality was lower over a 5-year period than in patients treated with usual care (Gallo et al. 2007).

The literature would support the necessity for 4–6 months of continuation pharmacotherapy to consolidate remission and achieve recovery. For maintenance treatment, antidepressants are recommended to be used at the same doses as for the

Table 4 Antidepressants for the treatment of late-life depression

Antidepressant	Initial daily dose	Dose ranges	Major side effects
Selective serotonin reuptake inhibitors			
Citalopram	10 mg	20–40 mg/day	Anxiety, dose-dependent QT prolongation
Escitalopram	5 mg	10–20 mg/day	Dose-dependent QT prolongation
Sertraline	25 mg	50–100 mg	Dyspepsia, tremor, weight loss
Serotonin-noradrenaline reuptake inhibitors			
Duloxetine	30 mg	60–120 mg/day	Constipation decreased appetite, fatigue, hyperhidrosis, diarrhea
Desvenlafaxine	50 mg	50–100 mg/day	Hyperhidrosis, dizziness, insomnia, constipation, decreased appetite, fatigue, vomiting, sexual dysfunction
Venlafaxine	37.5 mg	75–225 mg/day	Abnormal dreams, anorexia, dizziness, nervousness, hyperhidrosis, tremor, sexual dysfunction
Tricyclic antidepressants			
Desipramine	25 mg	75–100 mg at night	Abdominal cramps, nausea, vomiting, asthenia, insomnia, weakness, headache, lethargy, agitation
Nortriptyline	25 mg	50–75 mg at night	Sedation, weight gain, lowered seizure threshold, fatigue
Noradrenergic/specific serotonergic antidepressants			
Mirtazapine	7.5 mg at night	15–30 mg at night	Dry mouth, sedation, arthralgia, somnolence, increased appetite, weight gain, dizziness, constipation
Monoamine oxidase inhibitors			
Moclobemide	75 mg bid	300–600 mg bid	Sleep disturbance, anxiety, restlessness, tremor, vomiting, hypotension
Newer antidepressants			
Agomelatine	25 mg at night	25–50 mg at night	Increases ALT and/or AST, headache
Vortioxetine	5 mg	5 mg/day	Nausea, diarrhea, dry mouth, headache, hyperhidrosis

acute treatment phase. For a single severe episode of depression, drug treatment should continue for at least 1 year, while in patients with three or more lifetime episodes, maintenance treatment is recommended to continue for longer than 3 years (Alexopoulos 2005). The value of maintenance pharmacotherapy appears to be greater in older patients with more severe forms of depression. In psychotic depression patients who achieve remission after treatment with an antidepressant and an antipsychotic, the general consensus is that the antipsychotic drug be continued for 6 months. For patients in whom electroconvulsive therapy is effective, continuation or maintenance therapy should consist of an antidepressant not yet tried by the patient and a mood stabilizer. Continuation or maintenance electroconvulsive therapy is another option (Alexopoulos 2005).

Clearly, further studies for the management of depression in older patients are needed in order to develop reliable and practical guidelines as well as to evaluate thoroughly the efficacy of newer agents in the elderly. Studies of the "old-old" as well as those that include comorbid medical illnesses and cognitive impairment are also required.

Anxiety in the Elderly

The prevalence of anxiety disorders among older adults (10–20%) surpasses that of other old age conditions such as dementias (8%) and major depressive disorder (1–3%) (Reiger et al. 1988). Although anxiety disorders are the most common psychiatric disorder through the life span, they are often difficult to diagnose or missed entirely (Cassidy and Rector 2008). The vast majority of presentations (~90%) are accounted for by either generalized anxiety disorder (GAD) or a specific phobia (Krasucki et al. 1999). Obsessive-compulsive (OCD), post-traumatic stress (PTSD), and panic disorders account for the remaining 10% of the anxiety disorders of the elderly (Cassidy and Rector 2008). More recently a survey among aged care residents found the overall rate of anxiety disorders ranged from 3.2% to 20% (Creighton et al. 2016). Generalized anxiety disorder and specific phobias were the most common disorders, while clinically significant anxiety symptoms were more frequent than threshold disorders.

Data on risk factors for the development of an anxiety disorder in old age are limited. Nevertheless a review of the literature has suggested that the following factors increase the likelihood of developing an anxiety disorder in late age: (a) being female; (b) having several chronic medical conditions; (c) being single, divorced, or separated (compared to being married); (d) lower education; (e) impaired subjective health; (f) stressful life events; (g) physical limitations in daily activities; (h) adverse events in childhood; and (i) neuroticism (Wolitzky-Taylor et al. 2010).

A recent survey of longitudinal studies of anxiety disorders in the elderly identified their chronicity (Sami and Nilforooshan 2015). Furthermore, the disorders are associated with a high relapse rate with up to 39–52% relapse in 3–6 years. There was a substantial conversion to depression and anxiety-depression over their natural course. Remission rates in depressive anxiety were shown to be lower than pure depression in 3- and 6-year follow-up (Schoevers et al. 2005; Steffens and McQuoid 2005) indicating anxiety-depression had a worse prognosis than depression or anxiety alone. A further significant finding was that anxiety disorders in community settings are undertreated.

Treatment of Anxiety Disorders

Controlled clinical evaluation of pharmacological treatments for anxiety disorders in late life is sparse with guidelines based on extrapolation of evaluations in younger age groups (Krasucki et al. 1999).

Benzodiazepines are more effective than placebo in the studies which have been conducted in elderly populations. In outpatients with a primary diagnosis of anxiety neurosis, oxazepam was superior to placebo over a 4-week study period (Koepke et al. 1982). The drug was well tolerated. Similarly ketazolam (15 mg/day) was superior to placebo over a 15-day treatment period for generalized anxiety disorder (Bresolin et al. 1988). Response to treatment was achieved by 83% of the ketazolam-treated patients and 43% of the placebo patients ($P < 0.01$). The partial benzodiazepine agonist abecarnil was evaluated in outpatients with anxiety over a 6-week period (Small and Bystritsky 1997). Abecarnil (3.0–7.0 mg/day) was superior to placebo in reducing anxiety at weeks 2–4 and 6. A higher dose of the drug (7.5–17.5 mg/day) although effective was not well tolerated. The efficacy of **alpidem** (25–50 mg t.i.d.), administered for 3 weeks in anxious elderly patients (65–80 years), was significantly ($p < 0.01$) superior to placebo (Frattola et al. 1992). Psychomotor and mnemonic performances were not impaired by alpidem. Benzodiazepines are still widely prescribed for anxiety disorders despite a small database of placebo-controlled evaluations and their association with well-known serious problems for the elderly: hip fracture, impaired cognitive and psychomotor function, dependence, and withdrawal (Cassidy and Rector 2008). In a survey of mental health utilization by 55–85-year-olds, 25.3% of those with anxiety disorders were prescribed benzodiazepines, whereas 3.8% reported being prescribed antidepressants (de Beurs et al. 1999). Benzodiazepine use is not a favorable prognostic factor – patients who require benzodiazepines are significantly less likely to remit than those who do not take benzodiazepines (Steffens and McQuoid 2005). Risks to the elderly from long-term use of benzodiazepines suggest that their use should be limited to the short term. As late-life GAD is a chronic condition, benzodiazepines do not appear to be an appropriate option for its treatment (Lenze et al. 2003).

The high level of comorbidity of GAD and depression and the observation that late-onset generalized anxiety is frequently secondary to depression suggest that antidepressant medication should be the treatment of choice for many older adults who present with GAD. Limited evaluations in older populations have shown antidepressants to be effective for the treatment not only of GAD but of panic disorder as well (Wolitzky-Taylor et al. 2010). Citalopram, sertraline, and venlafaxine ER have all demonstrated efficacy for reducing anxiety among elderly patients. Compared to CBT or a waitlist control, sertraline had a greater effect on symptoms for older patients with GAD, panic disorder, agoraphobia, and social anxiety disorder(Schuurmans et al. 2006). Pooled data from five placebo-controlled trials evaluating the efficacy of venlafaxine ER for GAD in younger and older adults found similar response rates between the two groups (66% older versus 67% younger) (Katz et al. 2002).

Buspirone, a 5HT1A partial agonist, is an alternative option for the treatment of anxiety in the elderly. It has demonstrated efficacy over placebo and comparable efficacy to benzodiazepines in younger populations. However, its usefulness in treating elderly populations is unclear since it has a slow onset of action and is reported to be less effective for those previously treated with a benzodiazepine (Flint 2005). The safety and efficacy of pregabalin were evaluated in the treatment of generalized

anxiety disorder in people 65 years and older in a double-blind, randomized, placebo-controlled, 8-week trial (Montgomery et al. 2008). Flexible doses of 150–600 mg/day pregabalin were associated with a greater reduction in anxiety ratings than placebo. Discontinuations due to adverse events were similar for pregabalin and placebo. Pregabalin was a safe and effective treatment of GAD in older patients.

Other medication options for late-life anxiety include mirtazapine and atypical antipsychotics, but there are no studies in specific elderly anxious populations.

A meta-analysis of studies in GAD reported that elderly patients benefited from pharmacotherapy but that the benefits were no greater than with psychotherapy (Goncalves and Byrne 2012). There is a growing body of evidence that cognitive behavioral therapy (CBT) is the most appropriate treatment for anxiety disorders in the elderly (Barrowclough et al. 2001). Benzodiazepine use has been shown to decline with CBT reducing the risk of falls and fall-related deaths in this age group. Enhanced models of CBT for older individuals, modified to better meet the needs of older adults, have been shown to be more effective than standard CBT in an individual or group format (Mohlman et al. 2003). The use of CBT in the elderly is not discussed further here.

Pharmacotherapy Side Effects of Concern in the Elderly

Treatment of psychiatric disorders in the elderly with medication involves risks of adverse reactions and side effects. Benzodiazepines are well known for their psychomotor and cognitive impairing effects as well as the withdrawal syndrome as discussed above. In addition benzodiazepines and hypnotic agents are respiratory depressants. Behavioral disinhibition may also occur with benzodiazepines, which makes them less suitable for controlling agitation and aggressive outbursts in elderly demented patients. The general consensus is that benzodiazepines should be avoided in elderly patients wherever possible. The side effects of concern with these agents are therefore not discussed further. Since antidepressants are more likely to be prescribed, there are some significant issues for their use in elderly patients.

The selection of a particular antidepressant can be influenced by the mundane issues of pharmacokinetic and pharmacodynamic considerations. Both paroxetine and fluoxetine are effective in the elderly, but are not good first-line choices due to the long half-life of elimination of fluoxetine and the significant anticholinergic effects associated with the use of paroxetine. The anticholinergic effects of TCA antidepressants preclude their use in patients with preexisting glaucoma, urinary retention, and hypertrophy of the prostate or cognitive impairment. Furthermore, their cardiovascular effects and toxicity on overdose suggest a contraindication in patients with a recent history of myocardial infarction, cardiac conduction defects, and orthostatic hypotension. The necessity for dietary restrictions, due to interaction with tyramine in certain foods, as well as their orthostatic effects limits the usefulness of monoamine oxidase inhibitors in the elderly (Alamo et al. 2014).

Mortality by All Causes

The risk of all-cause mortality with antidepressant use is increased in the elderly (Gallo et al. 2007). Poorer self-care and noncompliance with medications used in the treatment of conditions such as diabetes and heart disease are associated with comorbid depression (Alamo et al. 2014). This may also contribute to greater mortality. The association between antidepressant treatment and risk of adverse outcomes was examined in a cohort study of people aged 65 with depression in over 500 general practices in the UK (Coupland et al. 2011). SSRIs (54.7%), TCAs (31.6%), MAOIs (0.2%), and other antidepressants (13.5%) were prescribed. The adjusted hazard ratio for all-cause mortality was highest for the group of other antidepressants.

Hyponatremia and Inappropriate ADH Secretion

Excessive secretion of antidiuretic hormone (ADH) can be caused by antidepressants, notably SSRIs and venlafaxine leading to hyponatremia (De Picker et al. 2014). Hyponatremia is associated with significant morbidity, such as lethargy, headache, confusion, convulsions, and coma, and can occasionally cause death. The estimated prevalence of hyponatremia in elderly patients receiving SSRIs ranges from 12% to 25% (Alamo et al. 2014). A more recent systematic review supported the predominant involvement of SSRIs and SNRIs as well as mirtazapine in case reports and clinical studies evaluating hyponatremia in older adults (Viramontes et al. 2016).

Bleeding Risks Related to Antidepressant Drugs

Excessive bleeding is of concern for patients receiving SSRIs and SNRIs including elderly patients. SSRI use is associated with roughly doubled odds of upper gastrointestinal (GI) bleeding; bleeding at other sites has been less commonly described (Andrade et al. 2010). Concomitant use of NSAIDs, anticoagulants, and antiplatelet agents increases the risk of SSRI-associated GI bleeding. On the other hand, the risk is decreased by concurrent use of proton pump inhibitors.

More recently antidepressant use has been associated with a higher cerebral micro-bleed incidence than nonuse (Akoudad et al. 2016). When stratified by affinity for the serotonin transporter, intermediate serotonin affinity antidepressant use was associated with an increased risk of developing micro-bleeds. Both SSRIs and non-SSRI antidepressant use were associated with increased micro-bleed incidence.

Cardiovascular Risks Related to Antidepressant Drugs

Antidepressant-related cardiovascular adverse effects are well known, especially as related to TCA overdoses (Sloman et al. 1983). The tricyclic pharmacological effects of muscarinic blockade, noradrenaline reuptake inhibition, and quinidine-like effects

are thought to be responsible for their cardiovascular effects. In addition TCAs affect the electric conduction of the heart such that they tend to slow conduction; prolong PR, QRS, and QT intervals; as well as induce heart block and arrhythmias in the elderly. An increased relative risk of 2.2 for myocardial infarction was associated with antidepressant use compared to nonuse in a cohort study (Cohen et al. 2000). Adjusting for age, gender, baseline heart disease, diabetes, hypertension, hyperlipidemia, anxiety, and cancer, users of TCAs had a higher relative risk than users of SSRIs. The difference was attributed to the inhibitory effect of SSRIs on platelet aggregation. SSRIs are recommended in patients with cardiovascular disease, while sertraline has been found to be safe in patients with a history of acute myocardial infarction or unstable angina (Alamo et al. 2014). Nevertheless, SSRIs are not without attendant cardiovascular risks in the elderly. A widely used surrogate marker of drug cardiotoxicity is prolongation of the QTc interval (Roden 2004). Both citalopram and its congener, escitalopram, have been associated with a dose-dependent increase in the QTc interval (Cooke and Waring 2013). This prompted a warning from the US FDA that citalopram should not be used in doses exceeding 20 mg/day for patients with hepatic impairment, older than 60 years, for CYP2C19 poor metabolizers, or for those taking concomitant CYP2C19 inhibitors (US Food and Drug Administration).

Orthostatic hypotension is also of concern in the elderly as it is associated with an increased risk of falls and fractures (Alamo et al. 2014). This is in part due to the blockade of α1-adrenergic receptors by TCAs and MAOIs. Drugs with noradrenergic reuptake effects are associated with tachycardia and slightly raised blood pressure or even hypertension at higher doses. The SNRI antidepressants duloxetine and venlafaxine are particularly implicated.

Risk of Antidepressant Overdose

Rates of suicide are generally higher in the elderly, particularly in the population 85 years and older (Osgood 1991). Although antidepressants may reduce the overall suicide rate, they are frequently used in overdose in a suicide attempt. The relative toxicity of antidepressants was determined in an observational study of prescriptions, poisoning deaths, and nonfatal self-poisoning episodes in England and Wales (Hawton et al. 2010). Of the TCAs, dothiepin and doxepin had the greatest toxicity based on overdose deaths both relative to prescriptions and nonfatal self-poisonings. Venlafaxine appeared to be less toxic than the TCAs but more toxic than the SSRIs and mirtazapine. Of the five SSRIs examined, citalopram was more toxic than the other four.

Although considered safer than TCAs on overdose, SSRIs may result in a serotonin syndrome, particularly when combined with another serotonergic agent. Additionally, early in treatment SSRIs may be associated with a paradoxical increase in anxiety and suicidal ideation. Patients should be monitored closely in the early stages of treatment for the emergence of akathisia which has been associated with an increased suicide behavior.

Risk Due to Anticholinergic Effects

Negative effects on the physical health and quality of life of elderly patients may be due to side effects experienced because of the antimuscarinic effects of some antidepressants, especially TCA and paroxetine. Peripheral effects of dry mouth, blurred vision, urinary hesitancy, and constipation are well known. In the central nervous system, confusion and delirium may occur in elderly patients due to cholinergic blockade. In those with an underlying dementia, this risk is exacerbated.

Sexual Dysfunction

Depression and pharmacological treatments of depression are associated with sexual dysfunction in both men and women. Sexual dysfunction is frequently cited as a reason for noncompliance with or a discontinuation of treatment (Clayton et al. 2014). Decreased quality of life is also associated with sexual dysfunction. SSRIs and SNRIs inhibit desire, cause erectile dysfunction, decrease vaginal lubrication, as well as impair orgasm (Conaglen and Conaglen 2013). Variable effects depending on the putative mechanism of action are seen with TCAs. All inhibit sexual desire and orgasm, but clomipramine, a more selective serotonergic agent, causes orgasmic difficulties, whereas nortriptyline causes more erectile dysfunction with less effect on orgasm. MAOIs are also associated with sexual dysfunction, although moclobemide was reported to increase sexual desire. Variable negative effects on all aspects of sexual function are associated with other antidepressants such as venlafaxine and mirtazapine. Initial reports suggest that both agomelatine and vortioxetine do not have significant sexual adverse effects in the elderly (Katona et al. 2012). However, evaluation of the sexual effects of these agents requires further investigation.

Risk of Osteoporosis

The use of antidepressants at therapeutic doses is associated with decreased bone mineral density (BMD) and increased fall and fracture risk (Bruyere and Reginster 2014). A cohort study in elderly women on SSRIs reported greater bone loss at the hip, which was class specific as TCAs did not appear to have this effect (Cizza et al. 2009). Identification of the serotonin transporter on osteoblasts suggests that a direct effect on bone mass is biologically plausible. The risk of fractures might differ among different antidepressants. A dose-dependent increase in fracture risk was associated with most SSRIs. TCAs with the greatest sedating effects, e.g., amitriptyline and clomipramine, were associated with fractures, whereas imipramine and nortriptyline were not. The clinical evidence suggests that antidepressants in general should be considered among agents which are risk factors for osteoporotic bone fractures.

Withdrawal Syndrome

Discontinuation or withdrawal syndromes for antidepressants and benzodiazepines are well recognized.

It has been estimated that between 15% and 44% of chronic benzodiazepine users experience withdrawal symptoms after ceasing medication (Lugoboni and Quagli 2014). The withdrawal syndrome is characterized by a number of emergent symptoms, particularly anxiety and depressed mood, but may also include perceptual changes, paranoia, and seizures in the most severe cases. Seizures are more likely to be associated with the prolonged use of high doses (>50 mg equivalents of diazepam). The use of short half-life benzodiazepines (alprazolam in particular is associated with withdrawal syndrome) and abrupt cessation of medication is more likely to produce a withdrawal syndrome. Management of benzodiazepine withdrawal involves an individually devised tapering of the drug combined with switching to an equivalent dose of a long half-life drug (usually diazepam) before commencement of tapering. Other medications such as antiepileptics or pregabalin might be useful but have not been evaluated in sufficient clinical studies for firm recommendations. Occasionally management of withdrawal syndrome may require hospitalization, and the use of supportive psychotherapy is always appropriate.

SSRIs, like TCAs and MAOIs, are associated with a well-recognized syndrome following discontinuation or dose reduction (Olver et al. 1999). Commonly the withdrawal syndrome is characterized by flu-like symptoms. Rarely extrapyramidal syndromes and mania/hypomania can occur (Haddad and Anderson 2007). Common features of withdrawal are an abrupt onset within days of cessation of the drug, a relatively short duration when untreated and rapid resolution on reinstatement of the antidepressant. Withdrawal symptoms can be attenuated or prevented by using an individualized tapering schedule at the end of treatment. Noncompliance with medication during treatment might also be associated with withdrawal symptoms potentially confused as relapse of the underlying condition. Usually symptoms are of mild intensity and short lived. Severe symptoms may require symptomatic treatment or reinstatement of the antidepressant. There are some differences between medications with respect to withdrawal. For example, paroxetine appears to have the highest and fluoxetine the lowest incidence of withdrawal symptoms. Other SSRIs are associated with an intermediate incidence. SNRIs are also associated with a withdrawal syndrome similar in presentation to that of the other antidepressants. Venlafaxine has been most often associated with a withdrawal phenomenon.

Drug-Drug Interactions: Pharmacotherapy in Elderly

Older age is associated with a greater likelihood of somatic illness to which patients with psychiatric disorders are not immune. Thus polypharmacy is likely to be the rule rather than the exception. Such polypharmacy leads to the potential for drug-drug interactions at both the pharmacokinetic and pharmacodynamic level. The medications which are used to treat psychiatric conditions are, for the most part,

Table 5 Benzodiazepine drug interactions

Drug	Clinical effects
Antacids	Decreased absorption single doses; doubtful relevance repeated dosing
Anticholinergic agents	As above
Cimetidine	Inhibition of metabolism; possible increased side effects
Alcohol, CNS depressants	Lower tolerance to alcohol; additive effects on psychomotor performance
Succinylcholine	Prolonged muscular blockade
Disulfiram	Inhibition of metabolism; increased clinical effects
Rifampicin	Increased metabolism; decreased clinical efficacy
L-DOPA	Exacerbation of Parkinsonian symptoms[a]
Digoxin	Increased plasma digoxin concentrations[a]
Lithium	Hypothermia[a]
Phenytoin	Changes in phenytoin concentration; dubious clinical significance

[a]Based on case reports alone

extensively metabolized by liver enzymes (P450 system), while some are well-recognized inhibitors of individual cytochrome enzymes. Phase II conjugative metabolism is a related metabolic system which has been implicated in drug-drug interaction. The family of uridine 5-diphosphate glucuronosyltransferases (UGTs) is the most prominent of these enzymes. P-glycoprotein (P-gp) an ATP-dependent, extruding transporter resides in the plasma membrane of the gut where it is an important regulator of absorption. P-gp is also present at the blood-brain barrier, where it is an important gateway for preventing various substances accessing the CNS. An extensive discussion of interactions is not provided here, but a few are highlighted since they are likely to be important in considering the choice of medication for depression and anxiety treatments in the presence of comorbidity. More extensive reviews are available in the published literature (e.g., Spina and Scordo 2002).

Some interactions observed with benzodiazepines are summarized in Table 5. The most important clinical interaction is that with alcohol and other CNS depressants, where psychomotor performance might be impaired leading to falls and fractures (*vide supra*) with the attendant risk of mortality due to medical complications.

TCAs and MAOIs are associated with significant interactions with other agents of which the most relevant for the elderly are likely to be with drugs used to treat cardiovascular disorders (Spina and Scordo 2002). The effectiveness of older antihypertensive agents (guanethidine, debrisoquine, bethanidine, bretylium, clonidine, methyldopa) is often reduced by TCAs due to competitive antagonism at similar receptor sites. Calcium channel blockers may affect the metabolism of some TCAs. Both MAOIs and TCAs are mild to moderate inhibitors of some of the P450 enzymes, while TCAs are inhibitors of P-gp. The combination of TCA and MAOI has sometimes proven fatal possibly due to the development of a serotonin syndrome.

Table 6 Effect of antidepressants on cytochrome P450 enzymes

	Cytochrome enzyme inhibition				
Drug	2D6	1A2	2D6	2C9	2D6
Tricyclics					
Amitriptyline	+	++	0	+	+++
Clomipramine	+	++	0	+	+++
Desipramine	+	0	0	0	+
Doxepin	+	+	0	+	+++
Dothiepin	+	+	0	+	+++
Nortriptyline	+	0	0	0	+
SSRIs					
Citalopram	++	0	0	0	0
Escitalopram	++	0	0	0	0
Fluoxetine	+++	0	+	++	+++
Fluvoxamine	+	+++	++	+++	+++
Paroxetine	+++	0	0	0	0
Sertraline		0	0	0	0
SNRIs					
Desvenlafaxine	++	0	0	0	0
Duloxetine	++	0	0	0	0
Venlafaxine	+	0	0	0	0
Recent Agents					
Agomelatine	0	0	0	0	0
Vortioxetine	0	0	0	0	0

Adapted from Gilman (2007)
+ Unlikely to be of clinical significance
++ May be clinically significant depending interacting agents
+++ Large clinical effect possible with some other agents

The effect of SSRIs on cytochrome P450 enzymes is more extensively investigated than for TCAs or MAOIs. Table 6 shows the effect of the different SSRIs on the various cytochrome subtypes. Despite the opportunities for a multiplicity of potential interaction events, the data on clinically significant interactions with these agents is sparse (DeVane 2006). However as pointed out a "lack of evidence does not equate to evidence of absence." Among the SSRIs escitalopram and sertraline have the lowest risk for interactions with other agents metabolized by the cytochrome system. Pharmacodynamic interactions are somewhat less predictable, and vigilance in prescribing, particularly in elderly patients on multiple medications, is always warranted.

Conclusions

Assessment of psychiatric disorders in the elderly requires that potentially contributing factors such as primary medical causes, medications, and dementia should be identified as potential confounders of diagnosis. As with all prescribing the risk and

benefits of the use of medications needs to be judiciously assessed taking into account the patients' physical as well as their mental health.

SSRIs are broad-spectrum agents effective in both depression and anxiety. Furthermore, they are generally well tolerated, have a good safety profile on overdose, and are relatively free of drug-drug interactions. They have become the preferred first-line treatment of depression and anxiety in the elderly. Nevertheless there are some nuances in their clinical application which needs to take into account the differences in their side effects, safety on longer-term administration, and potential for drug-drug interactions.

TCAs and MAOIs are probably less suited to use in the elderly due to their generally lower tolerability and lower cardiovascular safety. Other antidepressant agents including the SNRIs and mirtazapine also have side effect and longer-term safety issues which would make them second-line treatment in the elderly. The newer agents such as agomelatine, vortioxetine, and vilazodone appear, from limited clinical evaluations, to have efficacy in the short-term treatment of depression in the elderly with relatively benign side effect profiles. However there is still much to learn about the use of these drugs in specific elderly populations.

Benzodiazepines must be prescribed judiciously to the elderly due to increased risk of falls, cognitive impairment, and the withdrawal syndrome.

Cross-References

- ▶ Anxiety in Late Life
- ▶ Depression in Late Life: Etiology, Presentation, and Management
- ▶ Elderly Suicide and Suicide Prevention
- ▶ Physical Comorbidities and Mood Disorders in Older Adults
- ▶ Psychological Interventions for Older Adults: Evidence-Based Treatments for Depression, Anxiety, and Carer Stress

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