Age-Adjusted Psychiatric Treatment for the Older Patient

Howard H. Fenn
James A. Bourgeois
Catharine Birtley Fenn
Editors

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Dedicated to
W. Thomas Birtley
Arthur Cary Fenn, MD

Preface

> Willy Loman never made a lot of money. His name was never in the paper. He's not the finest character that ever lived. But he's a human being, and a terrible thing is happening to him. So attention must be paid. He's not to be allowed to fall into his grave like an old dog. Attention, attention must be finally paid to such a person. You called him crazy—
> [From Act 1, *Death of A Salesman*, a play in two acts by Arthur Miller, (Miller A. Death of a Salesman, Viking Penguin, Inc. 1949)]

In this classic American tragedy, Linda, the wife of Willy Loman, is talking to her two self-involved sons about the decline of her husband of over 40 years. Willy is in his mid-60s and has spent over 30 years as an on-the-road salesman. He is struggling now with diminished career options, displacement by younger salesmen, financial stressors, and failing health. He is pained by unfulfilled expectations for his two irresponsible, grown sons. He has managed stressors primarily by distorting or ignoring reality with unrealistic fantasies of success. Linda reveals that she found a hose with which Willie has been planning suicide with gas, but she has kept this secret so as not to humiliate him.

Near the end of the play, Willy's fantasies begin to morph into delusions. He hallucinates a figure from his past who reminds him of missed opportunities.

In the last scene, Willy dies off-stage in a burst of self-destructive behavior, planting a garden in the middle of the night. His cause of death is never revealed, but an acute myocardial infarction or stroke are most likely.

With an *age-adjusted* approach to his psychiatric condition, perhaps Willy might have responded to gentle questions and concern from his primary care clinician, who might have identified suicidal impulses, and would have encouraged more adaptive coping, or referred him to a pastor or a psychotherapist. If Willy were living in the current age of pharmacotherapy, his mood and outlook could have improved with 100 mg daily of sertraline. A small dose of 1 mg risperidone daily might have ameliorated the severity of delusions. A thorough medical work-up could have diagnosed coronary artery disease, hypertension, and hyperlipidemia, prompting preventive interventions such as healthier diet, lipid-lowering atorvastatin, lisinopril, and possibly an anticoagulant.

Willy might have stabilized psychiatrically and medically. He could have retired and lived into his 80s. Even if he eventually developed a vascular major neurocognitive disorder (MNCD) with neuropsychiatric symptoms

(NPS), he could have been treated with interventions to minimize any adverse effects.

These are the goals, using *age-adjusted* psychiatric treatment, to which the chapters in this book aspire. But that is not the tragedy that Arthur Miller wrote.

Anyway, who would be interested in a play entitled *Life of a Salesman*?

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Caveat: Medication Use

Many medications discussed in this book are recommended for psychiatric symptoms beyond any initial US FDA-approved indications. This *off-label* use, based upon clinical experience and randomized clinical trials, is inherent in geriatric psychiatry practice. In part, this is because the necessary medication trials have often not included geriatric subjects. For example, many medications used to treat behavioral and psychiatric symptoms of dementia (BPSD) have US-FDA indications only for bipolar disorder, psychosis, and/or depressive disorders. Whether with FDA indication or not, the *age-adjusted* ethic encourages *carefully dosed and closely monitored* treatment for a wide range of psychiatric illnesses.

Psychiatric diagnoses are consistent with the Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR, American Psychiatric Publishing; 2022.

Acknowledgments

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Herbert Ochitill, MD, enduring colleague and friend, for consultation and support throughout this process.

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Introduction

1

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Abstract

The principles of age-adjusted clinical practice and the goals of this book are discussed. The need for a review from this perspective is supported by evidence from clinical experience and scientific literature of excessive polypharmacy, deprescribing initiatives, and non-pharmacological interventions. It is emphasized that the theme of the book is to better accommodate medication use with the physiological changes of aging as well as to include non-pharmacological interventions in geriatric treatment planning.

The principles of *age-adjusted* treatment are not new. The advice for prescribing to the aging patient has always been to "start low, go slow." This book fleshes out that dictum, based upon research evidence, clinical experience, and trends we have noticed in the literature. Over the years, however, we have observed and participated in practices which, though common, can be counterproductive to the geriatric patient. Examples are as follows:

- Focusing on psychiatric symptoms without attention to contributing factors
- Minimizing the impact of chronic pain, sleep deprivation, sensory limitations, personal loss, physical limitations, infection, dehydration, and drug–drug interactions
- Starting medications before trying non-pharmacological interventions
- Overlooking prior treatments, their efficacy, adverse effects, or outcomes
- Re-prescribing psychotropic medications without reviewing indications or effectiveness
- Employing doses and formulations without adjustments for aging pharmacokinetics and pharmacodynamics
- Carrying forward psychiatric diagnoses without re-evaluating their validity

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An *age-adjusted* approach seeks to:

- First rule out or treat any systemic medical conditions associated with the psychiatric symptoms
- Search history for prior psychiatric symptoms, treatments, responses, and outcomes
- Consider delirium as a possible contributor before focusing on other psychiatric syndromes, especially in frail patients with pre-existing neurocognitive disorders
- Use lower-than-usual medication doses for geriatric patients who may have a therapeutic response at lower doses
- Avoid delirium-promoting CNS active agents (e.g., benzodiazepines, Z-drugs, anticholinergics, antihistamines) when treating *other* psychiatric illnesses
- Include *non*-pharmacological modalities as first-line options
- Change medications or doses one at a time
- Avoid unnecessary polypharmacy

This approach is not characterized as *holistic, integrative, alternative, or non-traditional.* Rather, it endorses medication interventions when needed as part of a comprehensive treatment plan. A combination of psychotherapeutic interventions, non-pharmacological modalities, *and* judiciously managed medications can improve quality of life and avoid the adverse effects of aging on medication use.

Each chapter begins with a complex case example, based upon clinical experience, which illustrates the topic. It then reviews current evidence-based evaluation and treatments. *Age-Adjusted Recommendations,* distilled from the literature, are offered at the end of each chapter. The intent is to provide actionable advice to *supplement*, but not *supplant,* good clinical judgment which can improve quality of life by managing psychiatric symptomatology and minimizing adverse results.

A growing body of evidence in medical literature supports this theme. Greater than 50% of patients aged 57–85 years use five or more medications according to the National Institute on Drug Abuse (NIDA) (Charlesworth et al. 2015). Many risks of inappropriate polypharmacy have been articulated (Rothchild 2021). Excessive use of psychotropic medications for residents of nursing homes and other geriatric treatment settings is well known (Cool et al. 2014). As a result, *deprescribing* protocols, applicable to the aged patient, have been developed (Martinez et al. 2017). Benefits of cognitive-behavioral therapies (CBT) and other supportive therapy models (STM) have been validated by RCT evidence as safe and effective interventions for many psychiatric illnesses (Ruesch et al. 2017). Finally, telemedicine, technology-assisted monitoring, and digital technologies are facilitating early detection of behavioral symptoms, cognitive deficits, and other markers of decline (Gould et al. 2020).

This topic is timely. In societies across the globe, the proportion of aging adults is growing faster than any other age group, due to declining fertility rates combined with longer life expectancy (World Health Organization 2012). Regrettably, the number of health care practitioners per capita with specialized geriatric training has not kept up with this increasing need (Grady and Singleton 2011).

Experienced clinicians as well as trainees from various disciplines, generalists, and geriatric specialists, will all inevitably treat greater numbers of aged patients who have psychiatric symptoms. This enlarging group of health care practitioners is the audience to whom this book is directed.

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Part I

Foundations of Evaluation and Treatment

Geriatric Pharmacology Overview

2

Poh Choo How, Barbara R. Sommer, and Glen Xiong

Abstract

This age of pharmacology and geriatric psychiatry requires an appreciation for the pharmacology of aging. Suboptimal prescribing, which affects 25% of those aged 65–69 years and 45% of those aged 70–79 (Charlesworth et al., J Gerontol A Biol Sci Med Sci 70:989–995, 2015), can result in increased risk of adverse effects.

This chapter reviews common medication adverse effects and risks as well as approaches which can minimize their frequency and severity. The *effectiveness* of pharmacological treatments for specific conditions is covered in the other chapters. We review factors such as inappropriate polypharmacy, as well as unnecessary, ineffective, or harmful medications and their potential for harm. Risks are significant especially for geriatric patients, for whom the physiological changes of aging, in combination with the high prevalence of chronic medical conditions, alter (1) the ways that medications are processed *by the body* (pharmacokinetics) and (2) the effects of medications *on the body* (pharmacodynamics).

Case Example: Drug–Drug Interactions and Adverse Effects

A 65-year-old computer scientist complained of forgetfulness, distractibility, slight gait instability, intermittent paresthesias of one lower extremity, and "mental fogginess." He sought neurological consultation to rule out Alzheimer's disease. The symptoms began within the previous 5 years but worsened over the past year. His mood was demoralized and apprehensive, as these symptoms impacted his work performance.

He had been treated for bipolar II disorder for 15 years, ever since an episode of dysphoria and apparent "hyperactivity," which in hindsight was because he increased his time at work, in the context of a prolonged, contentious divorce. Details of the original mood episode had not been re-examined, and the patient had not experienced any subsequent mood symptoms. His prescriber continued the original medication regimen for prevention of relapse: carbamazepine (CBZ) 400 mg twice daily and lamotrigine 400 mg daily. Fluoxetine 20 mg daily was added to his regimen 1 year earlier to treat the presumed relapse of bipolar II disorder, major depressive episode, and the fluoxetine was increased to 40 mg daily when dysphoria did not resolve.

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At consultation, the CBZ level was found to be 16 mcg/mL (therapeutic range 4–12). The lamotrigine level was thought to be subtherapeutic because its hepatic metabolism had been induced by carbamazepine. A neurological examination found no evidence of stroke, focal findings, nor of a neurodegenerative disorder. A Montreal Cognitive Assessment (MoCA) was scored at 29/30. It was hypothesized that subjective cognitive symptoms, intermittent incoordination, and paresthesias were related to CBZ toxicity.

Carbamazepine was tapered and discontinued over the course of 2 months. No mood symptoms re-emerged; he became less depressed and apprehensive as his "mental fogginess" and functioning improved. Paresthesias were resolved. Fluoxetine was tapered to 10 mg daily, and lamotrigine was discontinued.

Discussion

CBZ is an autoinducer of CYT P450 3A4, which can increase drug metabolism and reduce the serum level of lamotrigine (Table 2.1). In this case, the addition fluoxetine (an CYP 450 3A4 inhibitor) *inhibited* CBZ metabolism, raising its concentration and related adverse effects of sedation and ataxia. The prior diagnosis of bipolar II disorder was re-examined, and no history of hypomania or mania could be confirmed. A new diagnosis of *adjustment disorder with mixed anxiety and depressed mood* was offered. Discontinuation of CBZ did not result in a relapse of depressive symptoms, hypomania, or other evidence of bipolar II disorder. This permitted tapering and discontinuation of fluoxetine and lamotrigine. The patient began engaging in Cognitive Behavioral Therapy (CBT) which helped him manage stressors at work.

Table 2.1 Drug–drug interactions and adverse effects of polypharmacy in older adults

General adverse effects of polypharmacy
- Reduced adherence to treatment regimen
- Drug–drug interactions (see specifics below)
- Diminished ability for daily functioning
- Cognitive impairment
- Falls
- Malnutrition
- Urinary symptoms

Medications/ drug–drug interactions	Effects
Proton-pump inhibitors	Decreased absorption of other medications (can administer at different times to avoid interaction)
NSAIDs, diuretics, ACE inhibitors, and lithium	Decreased renal clearance of lithium and increased risk of lithium toxicity
SSRIs and opioids	Increased risk of serotonin syndrome
SSRIs and NSAIDs/ anticoagulants	Increased risk of GI and CNS bleeds
SSRIs and antipsychotics	Decreased metabolism of antipsychotics due to CYT P450 inhibition, increased half-lives of antipsychotics
Opioids and antipsychotics	Increased risk of CNS and respiratory depression
Carbamazepine	Increased and decreased levels of other medications
Valproic acid and lamotrigine	Decreased metabolism and increased half-life of lamotrigine, increased risk of Stevens-Johnson syndrome
Benzodiazepines	Increased risk of falls, fractures, cognitive impairment
Benzodiazepines and opioids	Increased risk of respiratory depression
Tricyclic antidepressants	Increased risk of delirium due to anticholinergic effects
Beta-blockers	Increased risk of bradycardia, orthostatic hypotension, loss of consciousness
Steroids	Increased risk of depressive disorder and other mood changes

Sources: Charlesworth et al. (2015), Lea et al. (2013) and Obreli-Neto et al. (2012)

Pharmacokinetics in Aging

The processes by which the body manages a drug constitute *pharmacokinetics*. Age-related changes impact metabolism, distribution, and elimination, and to a much lesser extent absorption. (Summarized in Table 2.2).

Absorption

Differences in drug solubility and changes in gastrointestinal (GI) function in aging individually affect the absorption of orally administered medications. Most medications are poorly soluble, and absorption is decreased in the aged by a combination of lower saliva production and decreased gastric acid secretion, leading to increased gastric pH (Carlo and Alpert 2015). The anticholinergic burden of medications can contribute to dry mouth, which affects sublingual and oral-dissolving tablet formulations. Co-administration of proton-pump inhibitors, antacids, and antihistamines can also diminish absorption.

Some medications need to be administered with food to stimulate gastric secretions and

Table 2.2 Pharmacokinetic changes with aging

Pharmacokinetic process	Drug–drug interactions	Implications	Clinical applications
Absorption ↓ Gastric emptying time ↓ Intestinal motility ↓ Gastric acid secretion ↑ Gastric pH	Antacids, proton-pump inhibitors, and H2 blockers increase gastric pH Anticholinergic burden (AB) of contributing to dry mouth, low saliva production	Reduced medication absorption, longer time to steady state or effective serum drug levels	Longer interval before titration and dose changes Use different medication formulations to promote absorption Changing medication administration time so as not to overlap with proton-pump inhibitors or antacids
Distribution ↓ *Vd* of hydrophilic drugs ↑ *Vd* of hydrophobic drugs Hypoalbuminemia decreases *Vd* of protein-bound medications leading to increased levels of free medications	Diuretics further decrease VOD of hydrophilic medications	Increase/decrease *Vd*	Dosage adjustment required with increase in age Close monitoring of free medication levels, especially medications with narrow therapeutic indices (e.g., lithium) Monitor for changes in *Vd* with dehydration, diuresis, third-spacing (e.g., ascites, pleural effusion), vomiting, and diarrhea
Metabolism ↓ Hepatic mass and microsomal metabolic capacity	Many medications are inhibitors and inducers of CYT P450 activity Some drugs bypass the phase I process and go directly to phase II (e.g., lorazepam, oxazepam, temazepam, and lamotrigine) Some drugs bypass liver enzymes altogether and are excreted directly through the kidney (e.g., lithium)	Increased/decreased drug metabolism Increased/decreased medication concentration and half-life	Close monitoring of drug levels Decrease polypharmacy and check for drug–drug interactions Dosage reduction of hepatically metabolized medications Administer active metabolite when appropriate/available Consider consultation with a pharmacist
Elimination ↓ GFR with age	Use of NSAIDs and antihypertensive drugs further affect renal function	Decreased elimination of medications, leading to longer half-lives	Dose reduction in patients with renal failure

enhance absorption (e.g., ziprasidone, lurasidone). Gastric emptying time and intestinal motility also decrease in the aged individual and can be further reduced by anticholinergic and opioid medications or pro-kinetic agents (Carlo and Alpert 2015). Poor nutritional status can impede the absorption of medications especially in frail elderly and nutritionally compromised patients who have a lower expression of epithelial transporters. Medical co-morbidities which interfere with absorption include poorly controlled heart failure (due to decreased GI blood flow, hepatic congestion, and GI edema), diabetic gastroparesis, and Parkinson's disease.

Aging thereby delays absorption and attainment of steady-state levels although eventually serum levels may be comparable to those in younger individuals. Medications may need to be titrated more slowly to avoid large increases in serum levels. Long-acting injectable (LAI) APs are beneficial because absorption of oral medications is potentially decreased, along with poor medication adherence. LAIs were found to be superior to oral antipsychotics to prevent re-hospitalization in geriatric patients with schizophrenia (Lin et al. 2020).

Distribution

Volume of distribution (*V*d) comprises the specific body compartments to which a medication is distributed. During aging, there is an increase in the percentage of body fat (on average 30% more than in young adults) and thus an increase in the *V*d for *hydrophobic* medications (Carlo and Alpert 2015). As a result, hydrophobic medications (e.g., long-acting injectable antipsychotics) take a longer time to reach steady-state levels and are eliminated at a slower rate. In contrast, a decrease in the percentage of body water in geriatric individuals results in a decrease in the *V*d for *hydrophilic* medications (e.g., lithium carbonate). Thus, lower doses, and dose reductions, of *hydrophilic* medications may be required to achieve therapeutic levels in older adults. Close monitoring of changes in *V*d is warranted because older adults are more susceptible to medication toxicity from sudden changes in fluid dynamics (Table 2.2).

Many medications are highly protein bound by albumin and alpha-1-glycoprotein. Changes in protein binding can lead to increase in free (active) medication fractions which result in clinical effects. For example, valproic acid (VPA) is highly bound to albumin. Routine laboratory studies of VPA calculate levels of this protein-bound medication which is not significantly different from free medication levels when albumin levels are normal. In cases of protein malnutrition with hypoalbuminemia, VPA levels may *appear* abnormally low or subtherapeutic, even though *free* medication levels may be disproportionately elevated (Dore et al. 2017). This may lead clinicians to raise the VPA dose, which ultimately increases the free fraction concentration and the risk of VPA toxicity. In the setting of hypoalbuminemia, *free* VPA levels are more clinically useful because they reflect a more accurate picture of VPA activity.

Metabolism

Most medications are metabolized by the liver through *phase I oxidation* via cytochrome P450 enzymes, followed by *phase II glucuronidation* which further increases their solubility in order to be excreted by the kidney. Phase II metabolism is not generally affected by *normal* aging but is significantly reduced in *frail* geriatric individuals (Khan and Roberts 2018).

Hepatic mass decreases by up to 20% in the aged, and cellular metabolic activity in liver microsomes diminishes (Stader et al. 2019); both changes compromise medication metabolism. Hepatic insufficiency further lowers the rate of medication metabolism and increases the risk of accumulation of unmetabolized medications (increased half-life) and adverse reactions. In such cases, medication metabolites with bioactive properties (e.g., paliperidone, desvenlafaxine), may offer advantages over their respective parent medications.

Antiepileptics, among other medications, can induce and/or inhibit cytochrome P450 enzymes. If two or more medications are present, medication levels and half-lives can be difficult to assess; pharmacist consultation and drug–drug interac-

tion (DDI) applications provide guidance to minimize risk of adverse DDIs.

Elimination

Renal mass decreases by 20–30% by the seventh decade of life, and glomerular filtration rate (GFR) decreases by 35% (Stader et al. 2019). This increases half-lives of medications and metabolites eliminated through the kidney, and requires dose adjustment, especially in those with renal pathology. Extra caution is warranted for nephrotoxic medications that can decrease GFR (e.g., nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors) or contribute to dehydration (e.g., diuretics).

Pharmacodynamics in Aging

The effects that medications exert on the body constitute *pharmacodynamics.* Age-related changes modify pharmacodynamics in ways that either enhance or decrease the impact of the medication. This is mediated by medication binding to targeted receptors, enzymes, or other proteins with biological functions and second messenger systems. Differences due to age can be attributed to changes in the affinity of the receptor to the medication and the number and rate of turnover of receptors available for medication binding.

Although there is a great variation among individuals, receptor density in general *declines* with normal aging (Knudsen 2003). For pharmacodynamic reasons, lower initial starting doses and lower target doses in older patients can often achieve the same therapeutic effects as higher doses in younger patients. For example, half the target dose of benzodiazepines may achieve sedation in individuals ≥65 years of age compared to younger patients (American Geriatrics Society Beers Criteria Update Expert Panel 2019).

Lower receptor density in the aged individual can increase susceptibility to adverse medication effects. Reduction in cholinergic receptors in the central nervous system, for example, can make geriatric patients more likely to experience central adverse reactions to anticholinergic drugs (e.g., cognitive impairment, delirium). In the case of antipsychotics (APs), lower target doses are also recommended due to increased risk of extrapyramidal symptoms and associated falls. Reducing AP doses by up to 40% has been shown to increase D2 receptor availability and overall cognitive abilities in geriatric patients with schizophrenia while maintaining adequate symptom management (Rajji et al. 2017). For antidepressants also, lower target doses decrease the risk of cognitive impairment, falls, bleeding, syndrome of inappropriate antidiuretic hormone (SIADH), and cardiovascular events (Darowski et al. 2009).

Blood–Brain Barrier (BBB)

Tightly apposed endothelial cells, specialized to impede constituents in the peripheral circulation from entering the cerebrospinal fluid (CSF), constitute the BBB. This structure serves not only as a wall separating the brain from substances in the periphery but is an important contributor to normal neuronal function (Marques et al. 2013). When intact, around 98% of small molecules cannot get into the brain, excluding many that could otherwise treat central nervous system (CNS) diseases, though psychotropic medications, which often consist of small, lipid-soluble molecules, usually cross through the BBB easily (Pardridge 2007; Zlokovic 2008).

Aging is the most common risk factor for disruptions of the BBB, which may occur even in the absence of co-morbidities such as hypertension (Montagne et al. 2015). Some studies of aging wild-type mice show an influx of pro-inflammatory substances such as *tumor necrosis factor alpha* (TNF-α), and it has been hypothesized that in humans, a permeable BBB may ultimately lead to neurogenerative disorders such as Alzheimer's disease (AD) and vascular dementia (Elahy et al. 2015; Zlokovic 2008). A study of aged adults found that BBB leakage begins specifically in the hippocampal region and is more marked in those with mild cognitive impairment than in subjects with normal cognition (Montagne et al. 2015). Neurodegenerative disorders may in turn increase BBB permeability further, thus cre-

ating a feedback loop (Elahy et al. 2015). Continued disruptions to the BBB may increase the risk of peripherally acting medications to freely enter the cerebrospinal fluid (CSF). Theoretically, peripherally acting anticholinergic medications, such as glycopyrrolate, could give rise to similar CNS effects as atropine (Zlokovic 2008).

Psychotropic Medications in Geriatrics: Adverse Events and Safety

Drug–drug interactions and inappropriate polypharmacy can increase the risk of adverse effects in the geriatric patient due to declining hepatic metabolism, diminished renal function, and/or changes in pharmacodynamics due to decreased brain volume. Polypharmacy has been associated with a decline in cognitive, physical, and emotional capabilities (Khezrian et al. 2019). The Beers Criteria offer guidelines of Potentially Inappropriate Medication (PIM) use in older adults. Table 2.3 summarizes common adverse events associated with psychotropic medications in older adults, for example, difficulty of swallowing in the oldest-old and frail patient but can have serious consequences in terms of choking and proper delivery of medications. Some formulations, such as wafers for mirtazapine, liquid/citrate solutions for lithium, for example, or tinier doses should be considered.

Antidepressants (ADs)

Prescriptions for antidepressants among individuals aged 65 and older have increased significantly since 2001, raising concerns about inappropriate use (Maust et al. 2017). A cohort study of >60,000 individuals ≥65 years of age reported that use of *any* AD was associated with higher all-cause mortality, attempted suicide/self-harm, stroke/transient-ischemic attacks, fracture, and epilepsy/seizures compared to when ADs *were not used* (Coupland et al. 2011).

Improvement in symptoms of depression or anxiety, as seen as adjustment disorders, can often be accomplished with non-pharmacological approaches (see Chaps. 14 and 15). In addition, aging adults and the oldest-old are vulnerable to medications which may have a direct effect on mood and behavior, such as corticosteroids (mood effects), beta-adrenergic blockers (reduced energy), or benzodiazepines and opioids (sedation, delirium) (Nørgaard et al. 2020).

Various ADs have been associated with specific adverse events (Table 2.3). Monoamine oxidase inhibitors (MAOIs) should be avoided in aging adults due to the risk of hypertensive crises, especially in combination with tyramine-rich foods. Similar caution accrues to tricyclic antidepressants (TCAs) due to strong anticholinergic properties, sedation, and orthostatic hypotension (risk of falls), although doxepin at a dose of ≤6 mg/day is considered safe (American Geriatrics Society Beers Criteria Update Expert Panel 2019). The selective serotonin reuptake inhibitor (SSRI) paroxetine has relatively high anticholinergic properties among SSRIs. Some SSRIs, such as fluoxetine, paroxetine, and fluvoxamine, are strong inhibitors of cytochrome P450 enzymes, and can prolong the half-life of their substrates. Sertraline, citalopram, and escitalopram are weaker inhibitors of cytochrome P450 enzymes and have lower risk of causing drug–drug interactions compared to other SSRIs.

Vortioxetine has an efficacy and side effect profile similar to other SSRIs. This medication may decrease the rate of age-related cognitive impairment and enhance the treatment of depressive disorders in patients with Alzheimer's disease (Cumbo et al. 2019; Deardorff and Grossberg 2014; Lenze et al. 2020). A trial of vortioxetine vs. sertraline in elderly patients with MDD found no differences in efficacy or safety (Borhannejad et al. 2020). Vilazodone and levomilnacipran have comparable safety and tolerability profiles compared to SSRIs and SNRIs, respectively. Significant safety concerns in the aging patient have *not* been reported for esketamine nasal spray although the study was funded by the manufacturer (Ochs-Ross et al. 2019).

Table 2.3 Cautions and common adverse events of psychotropic medications

Category of medication	Adverse effects/increased risk of
Antidepressants	Serotonin syndrome SIADH/hyponatremia (SIADH can also be due to polydipsia) Falls Cardiac complications Serotonin syndrome Sexual side effects Gastrointestinal bleeding Discontinuation syndrome
MAOIs	Hypertensive crisis when combined with tyramine-rich foods
TCAs	Anticholinergic adverse effects, delirium risk, sedation, and orthostatic hypotension
SSRIs	GI bleeds, falls, and hip fractures Many are inhibitors of CYT P450, increases half-life of other drugs (drug–drug interactions) Avoid paroxetine due to anticholinergic properties and increased risk of antidepressant discontinuation syndrome due to short half-life (REF)
SNRIs	GI bleeds, falls, and hip fractures (use duloxetine with caution in those with renal failure; avoid in hepatic disease) Antidepressant discontinuation syndrome
Bupropion	Dose adjustments needed in renal and hepatic failure
Mirtazapine	Dose adjustments needed in renal and hepatic failure
Antipsychotics	Stroke and mortality in those with a neurocognitive disorder Sedation Cognitive impairment Falls Neutropenia Orthostatic hypotension Cardiac complications Metabolic syndrome
First generation (FGA)	EPS, NMS, TD, dystonia, QTc prolongation with haloperidol
Second generation (SGA)	Metabolic syndrome Quetiapine has serotonin partial agonist activity and can increase the risk of serotonin syndrome when combined with serotonergic antidepressants QTc prolongation with risperidone, ziprasidone, quetiapine, clozapine
Mood stabilizers	Sedation Cognitive impairment
Lithium	Decreased *Vd* with age, monitor levels and renal function closely, delirium risk, hypo/hyperthyroidism, hyperparathyroidism
Antiepileptic agents	Hyperammonemic encephalopathy (valproic acid/VPA) Hyponatremia/SIADH (carbamazepine, oxcarbazepine, VPA) Increased blood levels of other medications
Benzodiazepines and Z-drugs	Cognitive impairment, falls, fractures, delirium, and motor vehicle accidents
Opioids	Sedation, respiratory depression
Stimulants	Cardiac complications and mortality
Cognitive enhancers/ cholinesterase inhibitors	Mortality (especially rivastigmine). May precipitate mania/psychosis
Anticholinergics	Delirium, cognitive impairment, urinary retention, constipation, dry mouth, blurred vision

Sources: Coupland et al. (2011), Gorgas et al. (2019) and American Geriatrics Society Beers Criteria Update Expert Panel (2019)

Adverse Effects in Antidepressants

Serotonin syndrome (SS) or serotonin toxicity. The pathophysiology of aging suggests increased vulnerability to SS due to an increased polymorphism and declines in expression and inducibility of CYT P450 enzymes. Impaired renal function and a reduction of renal clearance can result in hyper-serotonergic states with the use of serotonergic agents.

Medications which directly or indirectly increase central serotonin neurotransmission at postsynaptic receptors, 5-hydroxytryptamine 1A (5-HT1A) and 5-hydroxytryptamine 2A (5-HT2A) can produce SS. Psychotropic and non-psychotropic medications (such as tramadol) impact serotonin receptors, resulting in excessive levels of serotonin (Hede and Devillé 2019). SS can be precipitated when multiple serotonergic agents are combined or with high doses of a single serotonergic agent. Timing of dosage, frequency of administration, drug–drug interactions, and drug overdose, as well as inadequate washout periods between serotonin-enhancing medications, can contribute to excess serotonin levels (Wang et al. 2016).

Because it is a direct response to increased levels of serotonergic activity, SS can be identified with a thorough review of medications. SS often presents on a continuum with nonspecific clinical stages, but if not noticed and managed early, its progression can lead to organ failure and death (Boyer and Shannon 2005).

The *Hunter Toxicity Criteria* specify symptoms which identify SS (Dunkley et al. 2003), and Table 2.4 summarizes the stages of SS from mild, moderate, to severe. While SS remains a clinical diagnosis (Francescangeli et al. 2019), rigid adherence to the diagnositc criteria may leave SS undetected in old age where it may manifest as nonspecific and common symptoms such as confusion, anxiety, or restlessness.

The differential diagnosis of SS is extensive (Table 2.4), and initial treatment is focused on supportive measures in a medical emergency/inpatient hospital setting. Serotonergic medication(s) should be discontinued, and rarely, serotonin antagonists, such as cyproheptadine, may be needed.

Table 2.4 Symptoms and stages of serotonin syndrome

Symptoms of serotonin syndrome		
Delirium	Autonomic instability	Neuromuscular hyperactivity
Agitation Pressured speech Confusion	Tachycardia Shivering Mydriasis Diaphoresis	Hyperreflexia Clonus Tremor Mydriasis
Risk factors History of exposure to a serotonergic medication Presence of one or more of the following: 1. Spontaneous clonus 2. Inducible clonus with agitation and diaphoresis 3. Ocular clonus with agitation and diaphoresis 4. Tremor and hyperreflexia 5. Hyperthermia with temperature over 38 °C/100.4 °F		
Differential diagnosis • Neuroleptic malignant syndrome • Malignant hyperthermia • Toxic levels of sympathomimetics, anticholinergics, lithium, and other substances • Alcohol/other sedative-hypnotic withdrawal • Meningitis		
Stages of serotonin syndrome		
Mild	Mild symptoms of neuromuscular excitation and autonomic dysfunction that do not necessarily lead to delirium. Symptoms of toxicity can begin within 1 h of a precipitating event, such as an overdose, in approximately 30% of patients, and within 6 h in 60% (Boyer and Shannon (2005)	
Moderate	Worsening neuromuscular symptoms such as opsoclonus (uncontrolled eye movements—rapid, involuntary, unpredictable, conjugate, and fast), agitation, hypertension, hyperthermia (>40 °C/104 °F), delirium, hyperactive bowel sounds and diarrhea, nausea, and vomiting	
Severe	Severe neuromuscular excitation: Rigidity, respiratory failure, tonic-clonic seizures, altered cognition and arousal (manifested as coma or delirium), autonomic dysfunction with severe hyperthermia (>40 °C, >104 °F), and blood pressure fluctuation. Without treatment of the rigidity, hyperthermia can lead to rhabdomyolysis (manifest by high CPK), cell damage, myoglobinuria, renal failure, metabolic acidosis, acute respiratory distress syndrome, disseminated intravascular coagulation, and death. In SS, spontaneous/induced clonus and hyperreflexia are both more pronounced in the lower extremities	

Sources: Boyer and Shannon (2005), Dunkley et al. (2003) and Fink and Taylor (2001)

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and hyponatremia. SSRIs, SNRIs, TCAs, and mirtazapine are associated with hyponatremia and SIADH in the geriatric patient. Antidepressant-associated hyponatremia is more likely present when ADs are combined with an antihypertensive agent or more than one hypoglycemic agent (Grover et al. 2018). The prevalence of SIADH among those taking an antidepressant ranges as high as 15–20% depending on the agent and parameters used to define hyponatremia (Greenblatt and Greenblatt 2016). Medication-induced hyponatremia is usually caused by SIADH, confirmed by low serum osmolality and high urine osmolality. Other causes such as psychogenic polydipsia, heart failure, nephrotic syndrome, and acute kidney injury should also be considered.

SSRIs, several other antidepressant categories, and non-antidepressant serotonergic agents may also increase the risk of hyponatremia in geriatric patients. Risk factors for SIADH in response to AD treatment include older age (>85 years), female sex, and low body mass index (Greenblatt and Greenblatt 2016; Leth-Møller et al. 2016). Concomitant diuretic use, baseline low-normal plasma sodium levels, and lung and CNS cancers are also risk factors for SIADH. The geriatric patient has an increased risk of falls, seizures, cognitive deficits, all of which can also be associated with hyponatremia (≤125 mEq/L) (Mendez and Cummings 2003). Antidepressant-induced hyponatremia/SIADH can present with delirium.

The mean time to onset of hyponatremia from SSRIs is 2–4 weeks following initiation (Leth-Møller et al. 2016). Mild cases of hyponatremia can usually be managed with fluid restriction and discontinuation of the provocative medication. Most cases resolve within 2 weeks of stopping the offending medication (Kirby and Ames 2001).

Cardiac complications. Citalopram, and to a lesser degree its enantiomer escitalopram, among all SSRIs, pose a risk of QTc prolongation, in a dose-dependent manner (over 30 mg/day of citalopram or 15 mg/day of escitalopram), which can increase the risk of fatal arrhythmias such as *Torsades de Pointes* (TdP) (Beach et al. 2018). The US FDA issued a black box warning for citalopram and lowered the recommended maximum dose to 20 mg/day for individuals older than 60 years (US Food and Drug Administration 2017). Hepatic impairment, poor CYP2C19 metabolism, or the presence of CYP2C19 inhibitor medications raises the risk. Although 10–20 mg/day of citalopram can induce QTc prolongation, the actual risk of *Torsades de Pointes* (TdP) may not be clinically significant (Beach et al. 2018). Some studies report that citalopram doses >40 mg daily did not demonstrate a greater risk of arrhythmia or mortality compared to doses <20 mg daily (Zivin et al. 2013). Nonetheless, it is still recommended to discontinue citalopram in individuals with EKG evidence of severely long QTc or other evidence of cardiac conduction system disease. The geriatric patient with persistent QTc intervals greater than 500 ms and other relative contraindications (e.g., hypomagnesemia, hypokalemia, recent myocardial infarction, decompensated heart failure) should not receive citalopram. Except for citalopram and escitalopram, patients taking SSRIs had lower rates of cardiac events and dysrhythmias compared to those taking MAOIs, TCAs, and SNRIs (Beach et al. 2018). Trazodone can have adverse cardiovascular effects, including orthostasis, and rarely, extrapyramidal symptoms and syncope at high doses (Mayor et al. 2015).

Falls. Among aging adults, falls constitute the fifth leading cause of death, due to fractures, head trauma, and institutionalization (Van Swearingen and Studenski 2014). Ten to fifteen percent of falls cause major injuries in this population (Lord et al. 2017), especially during an inpatient stay. SSRIs may increase fall risk in the aged with odds ratios of 1.6–1.9 (Lenze et al. 2017), but some authors suggest that an association of increased fall risk with SSRIs does not constitute a cause and effect (Gebara and Lenze 2015). Orthostasis, sedation, or decreased postural control (Kvelde et al. 2015) may contribute to falls, gait instability, agitated confusion, urinary incontinence, and urinary frequency (Murray et al. 2007).

Serotonin/norepinephrine reuptake inhibitors (SNRIs) are included in updated Beers Criteria,

with the recommendation to avoid them in patients with a history of falls or fractures (American Geriatrics Society Beers Criteria Update Expert Panel 2019).

Discontinuation syndrome. Insomnia, nausea, imbalance, sensory disturbances, and hyperarousal can emerge following discontinuation of SSRIs (Harvey and Slabbert 2014). These subtle changes in mood, sleep, and appetite may be mistaken for signs of a depressive disorder relapse and/or an anxiety disorder. Delirium and psychosis associated with discontinuation of antidepressants have been reported. Discontinuation symptoms typically last about a week are often mild and self-limited. This time course can facilitate their differentiation from a recurrence of the original target symptoms of depression or anxiety. Risk factors include use of SNRIs (due to sudden withdrawal of added noradrenergic stimulation) and anti-depressants with shorter half-lives (e.g., fluvoxamine, paroxetine), although there are also case reports of discontinuation syndrome after stopping SSRIs with longer half-lives (Harvey and Slabbert 2014).

Gastrointestinal (GI) bleeding and hemorrhagic stroke (HS). SSRIs are associated with an increased risk of bleeding, especially gastrointestinal bleeding [OR 1.55 (95% CI 1.32–1.81)] (Laporte et al. 2017). This risk increases with the use of nonsteroidal anti-inflammatory drugs and low dose aspirin (Yuan et al. 2006). Furthermore, the use of SSRIs in conjunction with oral anticoagulants (OACs) in older adults can be lethal. Warfarin, the most prescribed OAC globally, shows significant risk of drug–drug interactions with fluoxetine and fluvoxamine (Spina et al. 2020).

Medications which inhibit serotonin and/or noradrenaline reuptake have been shown to increase the risk of HS in patients aged 65 years and older (Shafer et al. 2019). One case-control study of 4059 cases and 40,590 controls found an increased risk of HS in SSRIs (OR 1.39, 95% CI 1.22–1.58), selective serotonin/norepinephrine reuptake inhibitors (SNRIs) (1.69, 1.35–2.11), norepinephrine and specific serotonergic ADs (1.44, 1.22–1.69), and norepinephrine reuptake inhibitors (3.81, 1.54–9.43), compared with tri- and tetracyclic antidepressants. Patients with a high baseline risk of bleeding and depression had the greatest risk.

Sexual side effects. Adverse effects such as decreased libido, anorgasmia, erectile dysfunction, and delayed ejaculation are common reactions to SSRIs and SNRIs with rates ranging from 20 to 70%, though these adverse effects may be under-reported (Serretti and Chiesa 2009). *Chronic* use of serotonergic antidepressants increases the risk of sexual dysfunction. Non-serotonergic and newer antidepressants are less likely to produce these adverse effects. For example, rates of sexual dysfunction reported with bupropion, a noradrenergic and dopaminergic reuptake inhibitor, are comparable to placebo (~15%) and the rates of mirtazapine, an alpha-2-antagonist, are slightly above placebo (~20%). Evidence shows that switching from an SSRI to vortioxetine can lead to improvement in sexual dysfunction although these studies were done by the manufacturer (Jacobsen et al. 2019).

Other adverse effects associated with antidepressants. Duloxetine requires dose adjustments for patients with mild renal failure and is to be avoided in patients with a Glomerular Filtration Rate (GFR) of <30 mL/min and those with hepatic insufficiency. Mirtazapine and bupropion require dose adjustments in patients with renal and hepatic impairment. Bupropion is associated with an increased risk for seizures, although not specific to the aged. It also has a risk of inducing or worsening psychotic symptoms due to its dopaminergic and noradrenergic properties.

Antipsychotics (APs)

Geriatric patients have decreased D2-receptor density and increased risk of adverse effects from dopamine antagonism, necessitating close symptom monitoring and lower AP doses (Tsuboi et al. 2011). APs in aging adults have been associated with worsening cognitive impairment and sedation due to longer treatment durations, baseline cognitive impairment, metabolic adverse effects, and anticholinergic properties of APs

(MacKenzie et al. 2018; Tsuboi et al. 2011; Wolf et al. 2016). Antipsychotics are considered Potentially Inappropriate Medications (PIMs) in major neurocognitive disorders (MNCD) and carry an FDA black box warning due to an increased risk for stroke, cognitive impairment, and mortality in this population (American Geriatrics Society Beers Criteria Update Expert Panel 2019). *Brexpiprazole* has been approved by the US FDA for agitation associated with dementia due to Alzheimer's disease. For further discussion, see Chap. 9 *Psychotic Symptoms and Syndromes*.

Categories of Adverse Effects in APs

Neuroleptic Malignant Syndrome (NMS). This life-threatening, rare syndrome can occur within 72 h after starting a dopamine antagonist, especially a first-generation antipsychotic (FGA) with geriatric patients on high dosages at particular risk. Mood stabilizers (e.g., lithium, carbamazepine), antidepressants (e.g., paroxetine, sertraline, amitriptyline), and antiemetic agents (e.g., metoclopramide) (Tse et al. 2015) have also been implicated.

Symptoms include hyperthermia of >100.4 °F on at least two measurements, along with profuse diaphoresis, tremor, sialorrhea, akinesia, generalized rigidity, dystonia, trismus, myoclonus, dysarthria, dysphagia, hemodynamic instability, and delirium. Laboratory studies include elevated creatine kinase (CK) and potassium from the leakage of these intracellular substances into the bloodstream because of rhabdomyolysis and decreased serum iron. Interventions should include abrupt discontinuation of antipsychotics, emergency stabilization, supportive treatment in a hospital with intravenous fluids to facilitate elimination of CK and protect against kidney injury, and cooling blankets to normalize decrease hyperthermia. Rarely, the use of dopamine agonists such as dantrolene and bromocriptine may be required.

Extrapyramidal Symptoms (EPS). Extrapyramidal symptoms can be divided into early (acute dystonia, akathisia, Parkinsonism) and later-onset (tardive dyskinesia [TD]), and often prompt medication discontinuation (Divac et al. 2014). Dystonic reactions due to APs are characterized by rigidity in a specific muscle group, which can be life threatening when respiratory muscles are involved. Intramuscular diphenhydramine or benztropine for immediate muscle relaxation can ameliorate the rigidity, although anticholinergics raise the risk of delirium in geriatric patients. Akathisia, characterized by motor restlessness, responds to AP dose reduction, treatment with beta-adrenergic blockers, and/or benzodiazepines.

Parkinsonism can emerge a few days to several months after AP initiation. The increased risk of parkinsonian symptoms is due in part to loss of dopamine production with increasing age, which underscores the need for an age-adjusted approach to FGA and second-generation APs (SGAs) for the oldest-old and frail. Switching to SGAs is often recommended because SGAs have a lower risk of EPS compared to FGAs, although the risks are not negligible (Gurevich et al. 2012). The rates of AP-induced parkinsonism are 55% with haloperidol (FGA) and 26% with olanzapine (SGA) (Divac et al. 2014).

TD appears after months or years of AP treatment and is difficult to resolve; anticholinergic drugs are not recommended. There is limited evidence for the efficacy of vitamin supplementation (Soares-Weiser et al. 2018). Switching to an SGA, dose reduction or gradual discontinuation are options. Parsimonious use of APs combined with social interaction can help reduce risk of TD, EPS, and mortality (Ballard et al. 2016).

If EPS emerges, lowering AP doses, switching to an SGA, or a lower potency FGA are recommended over the use of anticholinergic medications such as diphenhydramine and benztropine. Highly anticholinergic APs such as chlorpromazine are not recommended. Clozapine, which is highly anticholinergic, is not commonly used in geriatric patients, but can be of benefit for psychosis in Parkinson's disease or major neurocognitive disorder with Lewy bodies, due to its relatively mild EPS profile (Weintraub and Hurtig 2007). Lower clozapine doses minimize the risk of neutropenia, constipation, and lowering the seizure threshold.