3 Pharmacological Overview in Geriatrics: Pharmacodynamics, Pharmacokinetics, Laboratory Monitoring

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3.1 Introduction

Medical advances and life-prolonging measures have increased life expectancy for individuals in developed countries, including the United States and Canada. The US Centers for Disease Control and Prevention predicts that by 2030, approximately 20%, or 72 million Americans, will be 65 years or older [1]. As the general population ages, one can expect a substantial increase of aging adults with serious mental disorders [2]. Of patients admitted to inpatient psychiatric facilities and geriatric psychiatric units over the last few decades, a greater number have been medically complicated due to co-morbid medical diagnoses [3]. In addition, data suggests that about 25% of seniors take more than four prescribed drugs. This number of prescriptions correlates with a greater incidence of drug-related complications in advanced age [4, 5]. This increase in pharmacodynamic burden impacts a group already vulnerable to adverse drug reactions.

The controlled environment of the inpatient unit permits medication administration based upon reliable drug delivery and direct observations of outcome. Gradual medication adjustment, in concert with monitoring for target symptoms, adverse effects, laboratory findings, and physical examination, ensures the most efficacious results. The authors have found that after a geriatric patient is hospitalized, careful adjustment and discontinuation of medications is as important as adding new medications (Chap. 17: Medication strategies: Switching, Tapering, Cross-Over, Overmedication, Drug-Drug Interactions, Discontinuation Syndromes). Figure 3.1 provides and overview of the pharmacology issues pertaining to the geriatric inpatient.

3.2 Clinical Vignette

A 78-year-old man was admitted for exacerbation of congestive heart failure (CHF), worsening shortness of breath (SOB), loss of energy, weight gain of 15 pounds, anxiety, depressed mood, reduced level of arousal, limited attention, and cognitive decline.

History included: ischemic cardiomyopathy with an ejection fraction of 30%, hypertension, hyperlipidemia, chronic back pain, and coronary artery disease with a myocardial infarction at age 65. The patient stopped his 40-pack years of tobacco use at age 65. Medications on admission: aspirin 325 mg/day, metoprolol 50 mg twice daily, simvastatin 40 mg/day, lisinopril 20 mg/day, furosemide 40 mg/day, tramadol 50 mg three times per day, sertraline 200 mg/day, bupropion XL 300 mg/day, trazodone 100 mg/day, and alprazolam 0.5 mg nightly as needed for insomnia.

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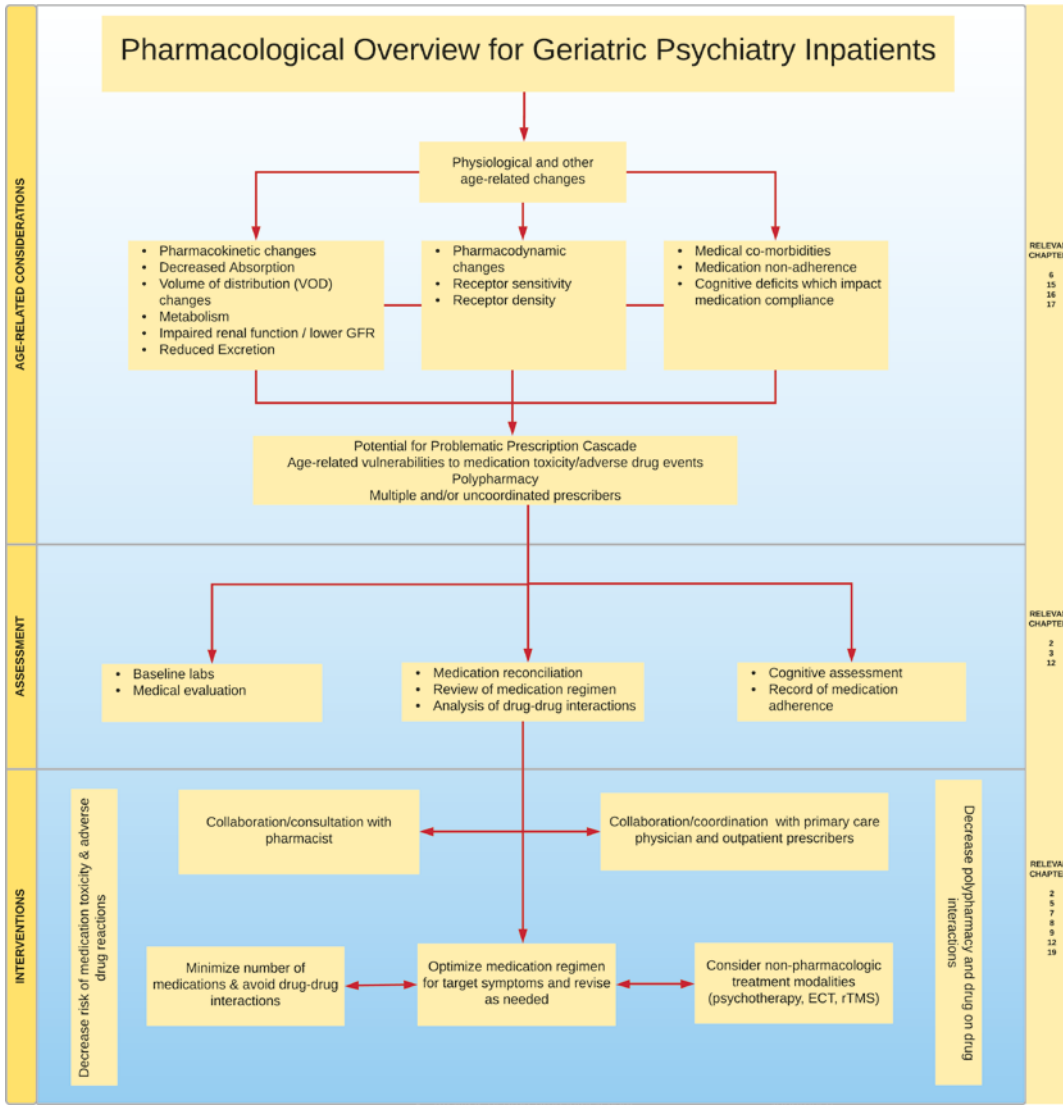

Fig. 3.1 Overview of pharmacology for the geriatric inpatient

The patient was widowed 12 months prior to admission, lived alone, and his children took him to medical appointments. He was behind in paying bills and often did not refill prescriptions. His family believed that he did not understand his medication schedule. Patient was eating adequately, but children had concerns regarding nutrition and follow-up for medical conditions. There was no history of suicidal attempts, but 1 week prior to admission the patient reported that he wished he was dead (Chap. 8: Suicide).

The dose of sertraline at 200 mg/day had been started by the primary care physician 4 months before admission. The depressive symptoms did not improve, and 300 mg/day of bupropion XL was added. Trazodone 50 mg at bedtime for insomnia was started 2 months prior to admission. The patient often awakened with orthopnea and felt anxious, even though his propranolol dose mitigated peripheral symptoms of anxiety. Alprazolam 0.5 mg at bedtime as needed was added 1 month prior to admission for anxiety.

It was not clear how often the patient used the alprazolam.

In the emergency department (ED), a disagreement arose among providers as to whether the patient would be admitted to inpatient psychiatry or internal medicine. The patient's dysphoric mood and suicidal ideation tipped the balance toward admission to the inpatient psychiatric unit with cardiology consultation.

Discussion The effectiveness of the patient's outpatient medication regimen, as well as his compliance, were in doubt. There was no practical way to assess his psychiatric symptoms, medication regimen, or to develop a treatment plan outside of a controlled setting. It was difficult to differentiate depressive symptoms from apathy, lethargy due to heart failure, anxiety, and/or sedation due to medications.

The first focus was a thorough review of the medication regimen and its impact on medical and psychiatric symptoms. A risk of serotonin syndrome, due to serotonin-active medications including sertraline, bupropion, tramadol, and trazodone, was discussed. The inpatient team discontinued bupropion, which had been started for symptoms of apparent intractable depression. The depressive symptoms overlapped with his low energy due to CHF exacerbation. The noradrenergic stimulation of bupropion had worked antagonistically with metoprolol and may have contributed to progression of heart failure. This medication combination and orthopnea contributed to insomnia, which had prompted a prescription for trazodone and alprazolam.

The internal medicine and cardiology teams continued cardiac medications. Intravenous furosemide was started on hospital day 1 to facilitate diuresis since the absorption of PO furosemide was not optimal due to hepatic congestion and gastrointestinal edema. Blood pressure, creatinine, daily weights, and intake/output were monitored. Over the next 5 days of diuresis, the patient lost 5 pounds, and furosemide was converted to PO dosing. Orthopnea became less frequent at night, and anxiety symptoms diminished slightly. Uninterrupted sleep became more frequent.

Concurrent with the aforementioned interventions, trazodone was continued on an as-needed basis for sleep at a dose of 25–50 mg at bedtime. Instead of the maximum dose, sertraline was restarted at 50 mg daily to minimize the risk for serotonin syndrome. The risk of a selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome was considered, but deemed unlikely due to the relatively short-term duration of treatment with an SSRI. Over the next 5 days following admission, tramadol was tapered to a nighttime dose of 50 mg to minimize daytime sedation; the prior daytime dose had interfered with the level of arousal. Acetaminophen was added on an as-needed basis for pain.

Alprazolam was continued for the first 4 days, at a reduced dose of 0.5 mg per night. It was suspected that the patient had been taking alprazolam intermittently, often 3 or 4 times a night, and none on some nights. Over the next 5 days, alprazolam was tapered to 0.25 mg, then discontinued. By hospital day 10, the patient became more anxious at bedtime, and he began to express intense suicidal thoughts. A nighttime sitter was provided.

The inpatient team hypothesized that inconsistent outpatient medication adherence contributed to worsening CHF and depressive symptoms. Increase in congestive heart failure resulted in hepatic congestion, gastrointestinal edema, and acute kidney failure, which affected absorption, metabolism, and renal elimination of various medications. An outpatient prescribing cascade had contributed to worsening psychiatric symptoms after the addition of medications for depressive symptoms, insomnia, and anxiety.

After 10 days in the hospital, patient's level of arousal improved and he was more attentive and able to participate in a full neurocognitive assessment (Chap. 2: Neuropsychological Testing). Deficits in executive functioning were found, but no other evidence supported a major neurocognitive disorder (MNCD). This helped clarify that the contribution of depression to his cognitive decline

was minimal. His cognition had been impacted by medication effect and heart failure.

The patient's anxiety symptoms became less intense along with stabilization of heart failure. The patient no longer alluded to suicidal ideation. He was discharged to a skilled nursing facility which managed his medications. His family felt that he was more accessible and he could participate in group meetings. His heart failure continued to progress, however, and he passed away quietly within 2 years of discharge.

3.3 Pharmacokinetic Changes with Aging

Pharmacokinetics is defined as the processing of a drug or "what the body does to a drug": absorption, metabolism, distribution, and excretion [6]. With age, changes in the physiology of major organ functions affect the body's ability to process drugs. Pharmacokinetic changes are summarized in Table 3.1.

3.3.1 Absorption

Absorption is defined as the movement of a drug from outside the body into the bloodstream and tissues. Since most drugs are prescribed as oral formulations, the rate of drug absorption is influenced by factors that affect gastrointestinal (GI) motility, pH, and various other factors (e.g., expression of epithelial transporters). The rate of absorption of oral drugs is decreased in geriatric adults due to a decreased rate of gastric emptying, decreased intestinal motility, and reduced gastric acidity. In addition, many aging adults are prescribed medications that affect GI motility and pH, such as proton pump inhibitors, opiates, or pro-kinetic agents. Nutritional status may

Table 3.1 Pharmacokinetic changes with aging

Pharmacokinetic process	Changes with aging	Implications	Interventions
Absorption	Delayed gastric emptying Delayed intestinal motility Reduced gastric acidity (especially with proton pump inhibitors)	Reduced medication absorption Longer time to reach steady state or effective serum drug levels	Longer interval before titrating medication—more time between dose changes Different formulations may promote better absorption (e.g., IM or SL)
Distribution	Lipophilic drugs: increased volume of distribution Hydrophilic: decreased volume of distribution	Lipophilic: longer time to reach steady state and slower rate of elimination; longer elimination half-life. Hydrophilic drugs: lower dose required to reach effective therapeutic levels	Lipophilic drugs: longer interval before increasing dose Close monitoring of fluid status in patients sensitive to fluid shifts (e.g., on diuretics, vomiting, diarrhea)
Metabolism	Slower metabolism Decreased cellular metabolic activity	Increased parent drug/metabolite ratio Potential accumulation of unmetabolized drugs	Slower titration of medications to avoid accumulation Consider administration of metabolite Consider administration of drugs that do not require phase I metabolism
Excretion	Decreased GFR with age	Longer elimination half-life of renally excreted drugs	Start medications at lower dose, longer titration period, monitor medication levels closely; monitor serum creatinine

Note: *GFR* glomerular filtration rate, *IM* intramuscular, *SL* sublingual

also affect the rate of absorption of medications (e.g., the rate of absorption may be decreased in malnourished patients with lower expression of intestinal transporters) [7].

Delayed gastric absorption increases the time it takes to achieve serum steady-state levels even though the effective serum levels may not be significantly different [8]. There is a longer lag time to achieve effective serum levels before the need to increase medication doses. Alternate formulations may be considered, if there is poor absorption of oral medications and immediate efficacy is needed (e.g., intramuscular or sublingual formulations) (Chap. 13: Involuntary Interventions). Certain medications need to be administered with food (e.g., ziprasidone, lurasidone) to promote absorption.

3.3.2 Distribution

During aging, the percentage of body water decreases while body fat composition increases. Older adults have an average of 30% more body fat compared to younger adults [9]. As a result, the volume of distribution (VOD) of lipophilic drugs increases with age; while the VOD of hydrophilic drugs decreases. Consequently, the time it takes for lipophilic drugs to reach steady-state levels increases, as does the time it takes to *eliminate* them.

Malnourishment is a factor to consider when estimating distribution rates: the malnourished patient may have reduced fat composition, wherein lipophilic drugs reach steady-state, and are eliminated faster than anticipated. Nutritional status also affects the distribution of protein-bound drugs. Levels of free (active) drugs may be elevated disproportionately to the protein-bound (inactive) drug in patients with protein malnutrition or hypoalbuminemia, affecting its distribution between the aqueous and protein-bound environment [10]. As an example, the effective serum level of valproic acid may appear abnormally low in patients with hypoalbuminemia, as laboratory values represent only the protein-bound fraction of the drug [11]. Providers must specifically request *free* valproic acid levels if albumin levels are low.

Given the decreased VOD for hydrophilic drugs, lower doses are needed to reach therapeutic drug levels in older adults. In geriatrics, a *dose reduction* is usually needed for hydrophilic drugs. The decreased aqueous VOD in seniors makes them more sensitive to dehydration and rapid fluid shifts (e.g., aggressive diuresis, severe diarrhea, vomiting, with drug entry into third spaces such as ascites and pleural effusions). Normal therapeutic levels can quickly reach toxic concentrations in these conditions. Drugs such as lithium need to be used with extreme caution and monitored closely. In the inpatient medical setting, a patient's volume status may change from day to day, especially in those on parenteral fluids, and on medications such as diuretics. Close monitoring is warranted, especially in patients with renal and hepatic disease(s).

3.3.3 Metabolism

Once absorbed into the bloodstream, medications are metabolized by the liver through phase I oxidation via cytochrome P450 enzymes, and phase II glucuronidation to make them more soluble and more amenable to renal excretion (see Fig. 3.2). While most drugs require phase I biotransformation before phase II can occur, some drugs bypass phase I directly, and move to phase II modification. Genetic polymorphisms affect the expression of genes encoding for cytochrome P450 enzymes that may influence the rate of metabolism of different drugs. Genetics may play a role: about 8% of Caucasians are poor metabolizers of CYP2D6 substrates compared with the general population [12]. Cytochrome P450 enzymes can also be induced or inhibited by a variety of drugs. Any drug's half-life and concentration should be considered when co-administered with medications that are potential metabolic inducers or inhibitors. This is a concern in seniors who are prescribed a variety of medications.

Cellular metabolic activity is reduced with aging [13]. Hepatic insufficiency reduces cellular metabolism further, leading to decreased drug

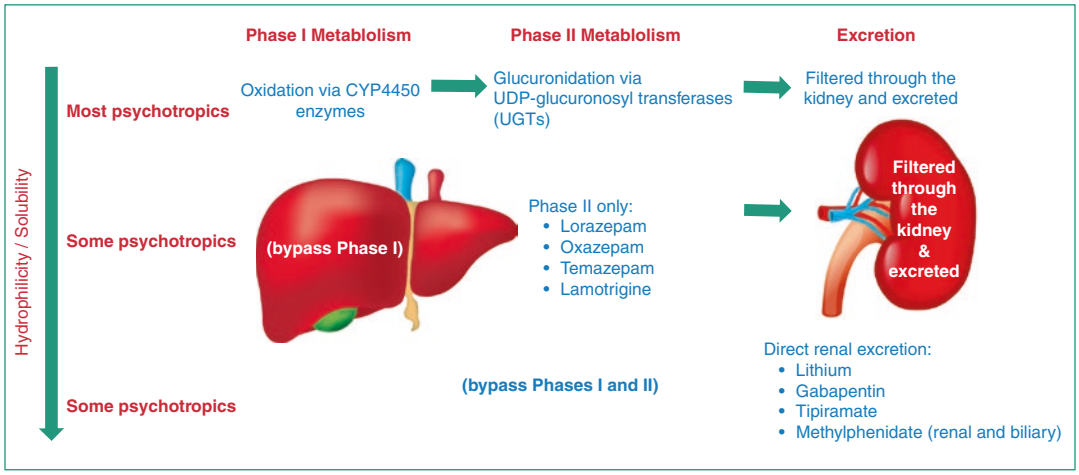

Fig. 3.2 Process of metabolism and excretion of drugs

metabolism, accumulation of unmetabolized drugs, and adverse drug reactions (Chap. 17: Medication Strategies).

In the geriatric patient, administration of a metabolite of the parent drug, if available, or a medication that bypasses phase I metabolism, can be useful. The metabolites of some drugs have bioactive properties and can be equipotent to the parent compound. For example, both the parent compound and metabolites of risperidone (paliperidone), bupropion (hydroxybupropion), and venlafaxine (desvenlafaxine) are highly active at their respective target receptor sites [14, 15] and amenable to renal clearance. Medications such as benzodiazepines, lorazepam, oxazepam, and temazepam, that do not require phase I biotransformation, are recommended for use in patients with liver disease.

3.3.4 Elimination

Drug excretion is most significantly determined by the glomerular filtration rate (GFR), which declines with aging for a variety of reasons. Microscopic, macroscopic, and functional changes in the kidney impair its ability to withstand and recover from injury, increasing the susceptibility of geriatric patients to acute and chronic kidney disease [16]. Even in healthy individuals, GFR can decline by up to 50% between the age of 30 and 80 years [14] and a GFR of 30–60 ml/min, equivalent to stage 3 kidney disease, has been observed in 15–30% of individuals aged 65 and older [17]. Some nephrotoxic drugs further impair renal function (e.g., NSAIDS) and further reduce GFR (e.g., Angiotensin-converting enzyme (ACE) inhibitors). The rate of excretion of hydrophilic drugs and metabolites is significantly decreased with aging, increasing the risk of toxic accumulation of these drugs.

3.4 Pharmacodynamic Changes in Aging

Pharmacodynamics is defined as the effects of a drug on the body or "what the drug does to the body" via targeted action on specific cellular receptors. Table 3.2 summarizes age-related pharmacodynamic changes that lead to increased sensitivity to medication action as well as their side effects [18, 19]. These include decreased receptor density, decreased receptor binding, and increased or decreased receptor sensitivity to the drug. Neurotransmitter receptor density decreases with age, and the central nervous systems of the geriatric patient becomes more vulnerable to agents that affect neurotransmission (most psychotropic drugs). The same medication doses administered to a geriatric patient may lead to greater effects as compared to a younger patient.

Table 3.2 Pharmacodynamic changes and increased sensitivity and side effects to medication

Age-related physiologic changes	Consequences
Decreased baroreceptor responsiveness and decreased sensitivity of the adrenergic system to adrenergic agonists and antagonists	Variable and less predictable responses to adrenergic agonists and antagonists leading to increased risks of both orthostatic hypotension and hypertension
Decreased dopamine-2 receptor density	Increased risk of parkinsonism and extrapyramidal symptoms in response to antipsychotics
Decreased cholinergic activity	Increased sensitivity to anticholinergic side effects of medications
Increased sensitivity of the GABA-ergic system	Increased risk of adverse effects from benzodiazepines (e.g., falls, imbalance, memory loss, sedation)
Decreased serotonin reuptake receptor binding and density of 5-HT1A and 5-HT2A receptors	Increased mood dysregulation and anxiety

Data derived from [14] and [15]

As a result of the pharmacodynamic changes, lower initial starting doses and target doses are often adequate to achieve the same therapeutic effect in older adults. In geriatric patients, increased sensitivity of the GABA-ergic system to benzodiazepines may only need to achieve 30–50% of serum levels to achieve the same therapeutic effect compared to younger patients [20]. Similarly, lower target doses of antipsychotics are recommended: only 50–60% receptor occupancy is required for optimum effects in older patients with schizophrenia, compared with the 65–80% occupancy recommended for younger patients [21]. Lower target doses of antidepressants have been recommended to avoid adverse drug reactions such as falls, bleeding, and cardiovascular events [19] (Chap. 7: Acute Medical Events). Given the overall decreased cholinergic activity with aging, older adults are sensitive to anticholinergic medications [22]. Geriatric patients are vulnerable to delirium from anticholinergic effects, or side effects of many psychotropic drugs (Chap. 12: Delirium). It is best to minimize the use of anticholinergic medications in this population when possible.

3.5 Categories of Psychotropic Medications

Tables 3.3, 3.4, and 3.5 offer prescribing recommendations and dose adjustments to moderate side effects of psychotropic medications in the geriatric patient [6, 23].

3.5.1 Antidepressants

After sedative-hypnotics, antidepressants are the most commonly prescribed class of psychiatric medications. Patients who are admitted to an inpatient geriatric psychiatry unit may already be on a medication regimen that includes an antidepressant for treatment of depressive or anxiety disorders. The outpatient doses need to be scrutinized to make sure they are compatible in the geriatric patient. Often, lower starting doses and a lower target dose are required in the geriatric patient due to pharmacokinetic and pharmacodynamics factors. High or maximum dosing of antidepressants requires attention to potential side effects and drug-drug interactions when evaluating the patient. If antidepressants are not tolerable, non-pharmacological interventions should be considered (Chap. 16: Neuromodulation Interventions: ECT, rTMS, and Novel Treatments; Chap. 18: Psychotherapies and Non-pharmacological Interventions).

Selective-serotonin reuptake inhibitors (SSRIs) are generally well tolerated in the geriatric patient, but certain SSRIs are high inhibitors of cytochrome P450 enzymes and have a higher risk of inducing drug-drug interactions (e.g., fluvoxamine, fluoxetine, paroxetine). Paroxetine is not recommended based on the Beers criteria, due to high anticholinergic burden, sedation, and orthostatic hypotension [24]. Low inhibitors include citalopram, escitalopram, and sertraline. Citalopram carries a risk for prolonging QTc measures and should be used with caution in

Table 3.3 Antidepressants

Medication	Dose adjustments needed		Anti-cholinergic side effects	Risk of drug-drug interaction	Risk of falls	Effects in geriatric patients
	Renal impairment	Hepatic impairment				
Antidepressants[a]						
Sertraline	No	↓ dose and frequency	*Low*	*Low.* Substrate of 2C19, 3A4. Weak inhibitor of 2D6.	Yes	↑ risk hyponatremia, bleeding
Citalopram	No	Yes	*Low*	*Low.* Substrate of 2C19, 3A4. Weak inhibitor of 2C19, 2D6.	Yes	↑ risk hyponatremia, bleeding ↑ risk prolonged QTc
Escitalopram	No	↓ max dose	*Low*	*Low.* Substrate of 2C19, 3A4. Weak inhibitor of 2D6.	Yes	↑ risk hyponatremia, bleeding Lower risk of prolonged QTc compared to citalopram
Fluoxetine	No	↓ dose and frequency	*Low*	*High.* Substrate of 2D6. Strong inhibitor of 2C19, 2D6. Weak inhibitor of 2C9.	Yes	↑ risk hyponatremia, bleeding
Paroxetine	No[b]	No[b]	High	*High.* Substrate of 2D6. Strong inhibitor of 2D6.	Yes	↑ risk hyponatremia, bleeding
Fluvoxamine	No[b]	No[b]	Low	*High.* Substrate of 2D6. Strong inhibitor of 1A2, 2C19. Weak inhibitor of 3A4.	Yes	↑ risk hyponatremia, bleeding
Venlafaxine	Yes	Yes	Low	*Low.* Substrate of 2D6, 3A4.	Yes	Dose-dependent risk of HTN and tachycardia ↑ risk hyponatremia, bleeding
Duloxetine	Avoid	Avoid	Low to Mod	*Mod.* Substrate of 1A2, 2D6. Moderate inhibitor of 2D6.	Yes	↑ risk hyponatremia, bleeding, useful for neuropathic pain and fibromyalgia
Bupropion	↓ dose and frequency	↓ dose and frequency	Low	*High.* Substrate of 2B6. Strong inhibitor of 2D6.	N/A	Lowers seizure threshold (avoid in seizure disorder), potential for precipitating psychosis
Mirtazapine	↓ dose and frequency	↓ dose and frequency	Low to Mod	Low. Substrate of 1A2, 3A4.	Yes	Sedation (at low doses), weight gain, constipation, leukopenia (rare)

[a]Serotonergic side effects: GI upset, decreased libido, erectile dysfunction, increased risk of bleeding, hyponatremia/syndrome of inappropriate anti-diuretic hormone (SIADH)
[b]Decrease dose of immediate release or extended release formulation in renal and hepatic impairment

Table 3.4 Antipsychotics

Medication	Dose adjustment needed		Anti-cholinergic side effects	Risk of drug-drug interaction	Risk of falls	Effects in geriatric patients
Antipsychotics[a, b]						
Haloperidol[c, f]	No	Mild to moderate: No Severe: contraindicated	Low	*Low.* Substrate of 1A2, 2D6, 3A4.	Yes[c]	↑ EPS ↑ QTc (avoid if QTc >500 ms)
Olanzapine[b, c, e, f]	No	No	High	*Low.* Substrate of 1A2.	Yes[c]	↑ metabolic syndrome (avoid in diabetes mellitus)
Risperidone[b, f], Paliperidone[f]	↓dose	↓dose	Low	*Low.* Substrate of 2D6, 3A4.	Yes[c]	↑EPS Hyperprolactinemia
Ziprasidone	No	No	Low	*Low.*	Yes[c]	↑ QTc (avoid if QTc >500 ms) Take with food for optimal absorption
Quetiapine	No	No[d]	High	*Low.* Substrate of 3A4.	Yes[c]	↑ metabolic syndrome, sedation
Clozapine[b, e]	Not defined	Not defined	High	*Low.* Substrate of 1A2, 3A4.	Yes[c]	↑ orthostatic hypotension, metabolic syndrome, sedation, lowers seizure threshold
Aripiprazole[b, c, e, f]	No	No	Low	*Low.* Substrate of 2D6, 3A4.	Yes[c]	↑ akathisia
Lurasidone	Yes	Yes	Low	*Low.* Substrate of 3A4.	Yes[c]	Take with food for optimal absorption
Asenapine[b, e]	No	No, but contraindicated in severe liver failure	Low	*Low.* Substrate of 1A2. Weak inhibitor of 2D6.	Yes[c]	↑ QTc (avoid if QTc >500 ms)

[a]Use lower doses for patients aged > 75 or those > 60 with frailty or multiple medical co-morbidities
[b]Class-wide side effects: extrapyramidal symptoms, akathisia, anticholinergic symptoms, sedation, orthostatic hypotension, metabolic side effects, cognitive decline
[c]Antipsychotics increase the risk of falls as a general medication category; increased parkinsonism and sedation side effects may contribute to fall risk
[d]Decrease dose of immediate release or extended release formulation in renal and hepatic impairment
[e]Available in sublingual formulation
[f]Available in long-acting injectable formulation

those with cardiac disease. Older adults are also more susceptible to hyponatremia, gastrointestinal or other bleeding, and falls with the use of serotonergic antidepressants [25].

Serotonin/norepinephrine reuptake inhibitors (SNRIs) carry an increased risk of hypertension and tachycardia due to noradrenergic stimulation and should be used with caution in older adults.

Table 3.5 Mood stabilizers

Medication	Dose adjustment needed		Anti-cholinergic side effects	Risk of drug-drug interaction	Risk of falls	Effects in geriatric patients
Mood stabilizers						
Lithium	Yes. Relative contraindication with renal impairment.	Not defined	*Low*	*Low.* Not metabolized by CPY450. High risk of toxic levels with NSAIDs, diuretics, ACE inhibitors, and other nephrotoxic drugs	Low	↑ hypothyroidism, diabetes insipidus, tremor, benign leukocytosis. Laboratory: BMP, complete blood count (CBC), GFR, thyroid stimulating hormone (TSH), free T4, lithium level, ECG
Valproic acid	No	Yes[a] ↓dose	*Low*	*Mod.* Substrate of UGT1A4. Weak inhibitor of 2C9 and UGT2B7.	Low	Tremor, ataxia, nausea, vomiting, weight gain, thrombocytopenia, pancreatitis, hyponatremia, hyperammonemia Laboratory: CBC, LAEs, valproic acid level, check ammonia if altered mental status occurs
Lamotrigine[b]	Yes	Yes ↓dose	Low	UGT1A4 substrate (increased half-life) when combined with valproic acid)	Low	↑ risk Stevens-Johnson Syndrome

BMP basic metabolic panel, *GFR* glomerular filtration rate, LAEs liver-associated enzymes
[a]Contraindicated in severe liver disease; avoid in pancreatitis, hyperammonemia, thrombocytopenia
[b]UGT1A4 Glucuronosyltransferase

Venlafaxine is often avoided in older adults as it was found to be less well tolerated and less safe; but not more effective than sertraline in a randomized controlled trial with frail geriatric patients [26]. Duloxetine is a commonly prescribed drug in geriatric patients as it has FDA indications for neuropathic pain and fibromyalgia, in addition to depression and anxiety. It has low inhibitory activity on cytochrome P450 enzymes but its levels may be increased when combined with CYP1A2 and 2D6 inhibitors. A small study showed that at a low dose, duloxetine had comparable safety profiles between older and younger adults despite being eliminated at a slower rate [27].

Even though it is generally well tolerated, bupropion, which is a norepinephrine and dopamine reuptake inhibitor (NDRI), may cause or worsen psychotic symptoms due to its dopaminergic activity. Bupropion carries increased risks of seizures and falls [28, 29] and should be used with caution in older adults, a population with a high prevalence of seizures.

The Beers criteria recommends avoiding tricyclic antidepressants that have a high anticholinergic burden as well as known cardiotoxic properties [24]. Oral formulations of monoamine oxidase inhibitors should be avoided due to the risk of hypertensive crises in combination with tyramine-rich foods. Selegiline transdermal patch in small doses does not require a restricted diet as the drug bypasses the liver, but more research is needed to determine its safety in the geriatric population with major depressive disorder [30].

3.5.2 Antipsychotics

The decreased density of dopamine receptors in older adults may contribute to greater sensitivity to extrapyramidal side effects (EPS) of antipsychotic treatment. This negatively affects patients who have been treated chronically with antipsychotics, and patients who develop a co-morbid movement disorder such as Parkinson disease, or

mild or major neurocognitive disorder (MNCD) with Lewy bodies.

Patients on long-term antipsychotic medications who develop these side effects may need a dose reduction to decrease or eliminate EPS. Dose reduction may often be preferable to treatment of these symptoms with anticholinergic agents such as benztropine, due to risk of delirium. Gradual dose reduction of the antipsychotic should be tried in order to avoid rebound psychosis, maintain the safety and functional stability of the patient, while addressing movement dysfunction.

Atypical antipsychotics (second generation antipsychotics; SGA) have been linked with an increased risk of falls as a result of orthostatic hypotension due to adrenergic receptor antagonism. One study showed a modest increase in the 90-day risk of falls and fractures in geriatric patients with a new prescription of an atypical antipsychotic (specifically quetiapine, olanzapine, and risperidone) [31]. Another recent study re-visited the question but failed to find significant results, likely due to a different approach in statistical analysis [32]. To prevent side-effect-related falls in the geriatric patient, include slow titration of medications, in small increments, and monitor orthostatic vital signs.

A black box warning in the US has been mandated by the FDA for all antipsychotics, highlighting the risk of cerebrovascular events, and mortality for treatment of acute agitation in patients with major neurocognitive disorders (Chap. 6: Major Neurocognitive Disorder with Behavioral Disturbance). It is unclear if this risk exists for geriatric patients who have been taking antipsychotics on a long-term basis (e.g., in those with schizophrenia). Metabolic risks are more relevant in patients taking antipsychotics chronically.

The Beers criteria recommends avoiding the use of typical and atypical antipsychotics in the geriatric population except for the treatment of schizophrenia, bipolar disorder, or short-term use as an antiemetic during chemotherapy [24] (Chap. 12: Delirium; Chap. 5: Legal Aspects for Informed Consent Issues).

Medication absorption is reduced in aging adults, especially in those with poor nutritional status, and alternative formulations of antipsychotic drugs may need to be considered (Table 3.4). Sublingual formulations improve administration. There is evidence of long-term stability of individuals with schizophrenia with long-acting injectable formulations of antipsychotics [33], though specific pharmacokinetic profiles in the geriatric population have not been studied. In emergencies, intramuscular formulations of antipsychotics may need to be administered, though lower doses are recommended in the geriatric patient (Chap. 13: Involuntary Treatment).

3.5.3 Mood Stabilizers

The hepatic and renal functioning of an aging patient on mood stabilizers deserves attention. Given that GFR is decreased in older adults, treatment with lithium should start at a lower dose, titrated at a slower rate, while monitoring lithium levels (e.g., with every dose change, and monthly thereafter) to prevent toxicity. Patients should avoid nephrotoxic drugs, for example, non-steroidal anti-inflammatory drugs, ACE inhibitors, diuretics, and angiotensin-receptor blockers. If these medications are unavoidable, consider stabilizing the patient on valproic acid or an atypical antipsychotic.

Case studies have reported valproic acid-induced extra-pyramidal symptoms and cognitive impairment that is reversible with discontinuation of the drug [34–36], though the mechanism has not been characterized. Valproic acid is also linked to hyperammonemia and hyperkalemia [37–39], potentially causing delirium. Monitoring of serum chemistries, liver function, complete blood counts, ammonia, and valproic acid levels is warranted. As previously discussed in the pharmacodynamics section, levels of *free* valproic acid should be obtained in those with low albumin levels to avoid being misled by abnormally low protein-bound valproic acid measures [11].

Carbamazepine is an autoinducer of CYP3A4 and can increase or decrease the half-lives of many drugs through drug-drug interactions. Carbamazepine should be avoided in the geriatric patient. If a patient with mania has both hepatic

and renal impairment that precludes treatment with lithium or valproic acid, low doses of an atypical (second-generation) antipsychotic should be considered.

3.5.4 Benzodiazepines

Benzodiazepines carry a significant risk of harm for the geriatric patient. Side effects of benzodiazepines include cognitive impairment, falls, and increased mortality. The Beers criteria recommends avoidance of benzodiazepines in the geriatric patient, reserving the use of some long-acting benzodiazepines (e.g., clonazepam, diazepam, chlordiazepoxide), only for brief periods, in the treatment of seizure disorders, alcohol withdrawal, benzodiazepine withdrawal, or pre-procedural anesthesia [24].

In the inpatient geriatric setting, benzodiazepine use should be short-term, at the lowest possible dose, and in acute situations, wherein the patient is not responding to high or maximum doses of antipsychotics or mood stabilizers. In patients with a long-term history of benzodiazepine use or benzodiazepine dependence, taper the medications over a course of time that corresponds with the period of dependence (Chap. 10: Alcohol and Substance Use Disorders in the Geriatric Psychiatry Inpatient).

3.6 Problematic Situations: Polypharmacy, Non-compliance, and the Prescribing Cascade

Polypharmacy is defined as the use of multiple medications from different medication classes for multiple indications. The problem is significant: over half of Medicare patients in the US take five or more medications [40]. Geriatric patients are more likely to be prescribed a greater number of medications due to multiple co-morbid and chronic medical disorders, as well as multiple prescribers. Medication adherence is poor or intermittent, risking medication toxicity. Causes of poor adherence include difficulty in tracking medication refills, doses, scheduling of multiple drugs, and cognitive deficits.

Prescribing cascade: Common elements of problematic, though common, *prescribing cascade* include [41]:

- An increased medication dosage to target symptoms, rather than assessing medication adherence, or absorption issues.
- A new medication for a new symptom that may actually be due to a side effect of another medication.
- A benzodiazepine for insomnia, causing cognitive impairment, which is then treated with a cholinesterase inhibitor, such as donepezil.
- An anticholinergic agent, which may cause overflow incontinence from urinary retention, as well as worsen cognitive function.

Collaboration with a pharmacist can improve the efficiency, accuracy, and safety of the medication reconciliation process. A study of an inpatient geriatric unit, newly staffed with a geriatric pharmacologist, identified 20% of patients had medical conditions with no medications prescribed, 15% of patients had actual and potential adverse drug reactions, 8% of patients had medications prescribed without any indications, and 5% had medications therapeutic duplication of medications [42]. Consultation with a colleague helps ensure that psychiatric and medical target symptoms are addressed with as few medications as possible.

Recommended practices: (1) Determine a specific indication (or target symptom) prior to starting a new medication. The target symptoms should ideally be measurable objectively such as amount of food consumed or hours slept. (2) Evaluate if the condition or target symptom can be treated by optimizing a medication already prescribed. (3) Determine if a symptom is due to a medication side effect. Reduce unnecessary medication whenever possible. (4) Prescribe a medication that can address more than one symptom while minimizing the risk of polypharmacy (Chap. 17: Medication Strategies for Switching, Tapering and Cross-Tapering Medications).

3.6.1 Laboratory and Imaging Work-Up

If possible, obtain a basic medical work-up prior to or at the time of admission to an inpatient unit. Physical examination and laboratory testing include a basic metabolic panel, liver function tests, complete blood count, thyroid stimulating hormone including free Thyroxin (T4) levels, urinary analysis, urinary toxicology, and an electrocardiogram. A computed tomography (CT) scan of the head is indicated for unexplained, new neurological findings, or altered mental status (Chap. 1: Essential Medical Work-up to Rule Out Medical Conditions).

Medications that need blood level monitoring require steady-state levels at initiation, change in dose, and addition or removal of another drug. Patients on medications that affect the liver, kidney, or thyroid functions should have these parameters monitored as well. Use cognitive screening assessments (MoCA or CAM) at admission, regularly if hospitalization is longer than 7 days, and at the time of discharge to determine if cognitive issues are chronic, new, and/or whether further work-up is warranted (Chap. 6: MNCD and Chap. 12: Delirium).

Optimum care of geriatric psychiatric patients may require more laboratory studies and extra vigilance to prevent medication-induced adverse events. In one study, geriatric patients who were staying on an inpatient geriatric psychiatry unit received complete medical work-ups, structured cognitive assessments, aging-sensitive aftercare, monitoring of psychopharmacological side effects, and blood levels of medications at a significantly higher rate compared to comparable patients on a general psychiatry unit [43].

3.7 Summary

The contribution of each of many variables to a medication-related problem is difficult to parse in the outpatient setting, prompting an inpatient unit admission. Medication reconciliation, as well as vigilance for potential side effects and drug-drug interactions, can facilitate the goal of decreasing polypharmacy. Pharmacokinetic and pharmacodynamic changes make the geriatric patient especially vulnerable to adverse drug reactions, and complicate the psychiatric/medical symptom presentation. The decrease in VOD, metabolism, renal excretion, and receptor densities can also impact the potential efficacy of medications. Principles of parsimonious prescribing, coupled with close monitoring in a controlled inpatient setting, can help identify adverse medication effects, as well as the effects of accompanying medical co-morbidities. At best, the inpatient setting can lead to a discharge plan with an improved medication regimen that will foster rational prescribing practices in the outpatient setting.

Take-Away

- Seek to reduce the number of medications.
- Search for one medication with two desired effects, rather than two medications.
- Avoid treatment of adverse effects by adding another medication; consider reduction of dose first.
- If the regimen includes multiple medications, consider the effect of medications on cognition and on psychiatric symptoms.
- Avoid starting a new medication when the patient is taking multiple different medications.
- Titration of medications should be slow, increasing or decreasing doses gradually, in tiny increments.
- Consider the patient's frailty, weight, intake, and hydration.
- Err on the side of under-dosing.
- Perform medication reconciliation in collaboration with the patient, family, caregiver, outpatient clinician(s), and pharmacist.
- Antidepressants, antipsychotics, and benzodiazepines increase the risk of falls.
- Benzodiazepines are not recommended in geriatric patients.

3.8 Prescribing Principle: CARES

C A R E S

Check
- baseline laboratory tests: chemistry, liver function, complete blood count, thyroid function test, electrocardiogram
- medication regimen and adherence
- cognitive function: baseline and ongoing

Avoid
- drug-drug interactions
- benzodiazepines and anti-cholinergic drugs
- polypharmacy

Rule-out
- worsening of medical conditions and medication side effects as cause of symptoms

Eliminate
- unnecessary medications

Start Low and Go **S**low
- Start medications at a lower dose and titrate slowly

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