Pharmacotherapy: Safe Prescribing and Adverse Drug Events

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5.1 Background

5.1.1 General Principles of Pharmacotherapy in Old Age

As a consequence of multimorbidity, older adults carry a high burden of polypharmacy, with increased risk of adverse drug events (ADEs) and potentially avoidable emergency department and hospital admissions. Altered pharmacokinetics and pharmacodynamics result from age-related changes in body composition and organ-system function and frequently necessitate dose modification or avoidance of certain medications. Diet is often unrecognized as an important factor in drug absorption, metabolism, and efficacy. Dietary supplements also can interact with medications, contributing to the risk of adverse drug reactions.

The severity and frequency of adverse side effects, together with altered pharmacokinetics and pharmacodynamics, render many drugs potentially inappropriate for older patients. Tools like the Beers criteria and the STOPP/START criteria have been developed to assist clinicians in recognizing and minimizing the use of these *potentially inappropriate medications (PIMs)*.

Certain types of medications are associated with a high risk of adverse effects in the geriatric population. Anticholinergic medications cross the blood-brain barrier to varying degrees, potentially impairing cognition and precipitating delirium, in addition to adverse peripheral side effects such as constipation, dry mouth, and urinary retention. Many medications from a variety of classes possess anticholinergic properties and when used concurrently can produce a significant anticholinergic burden.

Most psychotropic medications have been associated with an increased fall risk. Many atypical antipsychotics affect glucose metabolism and may cause weight gain, and therefore must be used cautiously or avoided in patients with obesity, diabetes mellitus, and the metabolic syndrome. A number of psychotropic medications, chief among them the selective serotonin reuptake inhibitors (SSRIs) and the selective norepinephrine reuptake inhibitors (SNRIs), may induce the syndrome of inappropriate antidiuretic hormone secretion (SIADH), causing hyponatremia that can become severe enough to cause delirium, coma, and death. Lithium has a low therapeutic index in older patients. Reduced kidney function affects the dosing of lithium, and it can affect renal tubular function, causing impaired water retention and diabetes insipidus. Moreover, the reduced thirst response in older individuals and the common use of diuretics can lead to dehydration and lithium toxicity. Lithium commonly affects thyroid function, most often causing hypothyroidism but rarely causing hyperthyroidism, and also is associated with hyperparathyroidism.

Although rare, neuroleptic malignant syndrome and serotonin syndrome represent potentially life-threatening conditions and have a spectrum of symptoms culminating in rhabdomyolysis, hyperthermia, and brain injury and death. Familiarity with these conditions permits early recognition and management. Typical and atypical antipsychotics, also referred to as first-, second-, and third-generation antipsychotics, as well as some SSRIs may prolong the corrected QT interval (QTc), increasing the risk of potentially fatal ventricular tachycardia. A number of medications, ranging from macrolide antibiotics to amiodarone, can increase the QTc and should be used cautiously in combination with each other and with QTc-prolonging psychotropics. SSRIs reduce serotonin levels in platelets, inhibiting aggregation and increasing bleeding risk. This is of especial concern in older patients because of the prevalence of anticoagulant and platelet-inhibiting drugs used for heart and vascular disease.

5.1.2 Epidemiology of Polypharmacy and Adverse Drug Events

Polypharmacy conventionally is defined as five or more prescription medications, based on epidemiological evidence that the threshold of five or more drugs independently predicts incident falls, disability, frailty, and mortality [1]. Among older adults aged 70 years and older, roughly 60% take seven or more drugs and over 10% take at least ten drugs [2]. Polypharmacy also contributes to potentially serious drug-drug interactions and adverse drug events (ADEs) [3, 4], which account for 6–12% of hospital admissions among older adults [5, 6]. The prevalence of polypharmacy increases with age in parallel with the increased prevalence of multimorbidity, compounded by the indication for multiple medications as standard of care for a variety of chronic conditions, such as heart failure with reduced ejection fraction and diabetes mellitus. In all age groups except the very young, polypharmacy has increased over time, with the largest rise among adults over the age of 69 [7].

Central nervous system (CNS) polypharmacy has been defined as concurrent use of three or more CNS-acting medication classes. A recent study examined 1062 office visits from the US National Ambulatory Medical Care Survey that documented CNS polypharmacy during the years 2004 to 2013. After adjustment for age, sex, race, and ethnicity, the study found a significant 10% reduction in the use of benzodiazepines between 2004 and 2011, as well as a dramatic 55% reduction in the use of tricyclic antidepressants. Although there were no temporal changes in the use of either selective serotonin reuptake inhibitors or non-benzodiazepine, benzodiazepine receptor agonist sleep aids, there was a significant 24% rise in opioid use during this time period [8]. Older adults in their last year of life have experienced a substantial increase in extreme polypharmacy (≥10 medications), and in the final month of life, this polypharmacy not infrequently includes drugs intended to prevent future illness (e.g., statins), whose continuation seems questionable. In the last month of life, psychoactive medications were prescribed to 51% of patients [9].

Table 5.1 Examples of age-related changes in pharmacodynamics

Drug	Pharmacodynamic effect	Age-related change
Furosemide	Peak diuretic response	↓
Morphine	Analgesic effect	↑
Verapamil	Acute antihypertensive effect	↑
Scopolamine	Cognitive function	↓
Temazepam	Postural sway	↑
Diazepam	Sedation, postural sway	↑
Warfarin	Anticoagulant effect	↑

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In the USA, there has been a nearly linear increase over time in the number of specialty physician referrals made by primary care providers [10], resulting in an increase in the number of potential prescribers for an individual patient. Many specialists are unable to keep up with current prescribing standards in other specialties, thus prescribing medications for the illness they are treating that may have significant drug-drug interactions or that pose a threat for ADEs due to age-related changes in pharmacokinetics (i.e., drug metabolism) and pharmacodynamics (i.e., drug action).

Pharmacokinetic alterations of drugs attributed to organ-system aging are reviewed in ▶ Chap. 1, ▶ Sect. 1.10, and in ◘ Table 1.2, Summary of age-related changes that affect the pharmacokinetics of drugs. Pharmacodynamic changes occur as a result of age-related alterations at the organ-system or cellular level that affect the action of the drug, and commonly alter the timing, peak effect, or magnitude of the drug's intended action or side effects. ◘ Table 5.1 provides examples of pharmacodynamic changes with aging [11].

Specialists may also prescribe a drug without having an accurate knowledge of the patient's other medications or medical conditions, a phenomenon known as "silo prescribing." The dosing guidelines developed by pharmaceutical companies and approved by the US Food and Drug Administration, Health Canada, the Therapeutic Goods Administration of Australia, and other national regulatory agencies are largely based on standard adult dosing without factoring in clinically significant differences in the pharmacokinetics and pharmacodynamics of medications in older patients. Unless a medication has specific geriatric dosing guidelines, a good rule of thumb is to select a dose below the standard starting dose for adults. Because the lower starting dose may not be effective in some patients, timely follow-up is required to be able to titrate the dose upward as needed to achieve the desired clinical outcome. ◘ Table 5.2 gives examples of prescribing behavior that can result in adverse drug events.

5.1.3 Prescription Complexity

Polypharmacy contributes to the complexity of medication regimens but is not the only determinant. Older adults commonly must cope with changing medications and doses, when and how to take a medication (e.g., with food, before bedtime), and remembering to take medications with multiple daily doses or infrequent dosing (e.g., once weekly). Evidence is accumulating that the *complexity* of the patient's medication regimen, not just polypharmacy and their multimorbidity, predicts both hospitalization and hospital readmissions (◘ Fig. 5.1) [12].

Teaching Points

Polypharmacy involves the simultaneous prescription of ≥ 5 medications, increases with age and multimorbidity, and has been associated with an increased risk of drug-drug interactions, adverse drug events, hospitalization, and mortality. Pharmacokinetics of medications often changes in old age as a result of declining renal function and alterations in hepatic metabolism, necessitating changes in dosing. For some medications, the action of the drug (pharmacodynamics) changes, causing alterations in the onset, peak effect, or magnitude of action, as well as an increase in severity and frequency of adverse reactions, even after adjusting for changes in pharmacokinetics. The complexity of drug regimens can lead to medication nonadherence and also predicts hospitalization independent of the number of drugs.

5.1.4 Drug-Food/Nutrient Interactions

A food-drug interaction may be a physical or chemical reaction that occurs between a medication being taken for therapeutic effect and components of the patient's diet, including nutritional and dietary supplements. From a chemical standpoint, this interaction can be synergistic, competitive, or antagonistic in nature. The nature of the interaction may alter the effectiveness of the drug and thus impact the systemic medical and/or psychiatric status of the patient. Alternately, the interaction may affect absorption of the nutrients/food being ingested, thereby affecting the nutritional status of the patient. Like most drug-drug interactions, food-drug interactions may be pharmacokinetic or pharmacodynamic in nature.

Absorption

Orally administered drugs are particularly susceptible to a reduction in bioavailability due to the presence of food at either of their primary absorptive sites, the stomach and the lumen of small intestinal tract. For some drugs this decreased absorption is minimal; however, for medications such as alendronate and other bisphosphonate drugs, administration with food may reduce absorption by as much as 85%

Table 5.2 Examples of prescribing behavior that can result in adverse drug events or failure to achieve the desired results

Type	Examples
"Silo prescribing": prescribing by specialists who are not up-to-date in the management of diseases outside their specialty and/or without awareness of potential contraindications and drug-drug interactions (see PIMs below)	Oxybutynin prescribed by gynecologist for urinary urgency in patient with mild cognitive impairment Doxazosin prescribed by urologist for urinary hesitancy in patient with orthostatic lightheadedness Paroxetine prescribed by psychiatrist for depression in patient with glaucoma
Contributing to medication regimens that are overly complex, increasing the risk of nonadherence and ADEs (see text for discussion)	Excessive polypharmacy Multiple daily dosing when a single sustained-release option is available Difficult or confusing dosing schedules (e.g., fasting, once weekly with water only, do not lie down afterward for 30 minutes)
Increasing dose(s) of medication or adding additional medication when not effective, without assessing possibility of and reasons for medication nonadherence	Unrecognized cognitive impairment Neglect by a caregiver charged with dispensing medications Misunderstanding medication regimen and rationale for medications due to medical illiteracy, low educational level, or language barrier Unrecognized cultural beliefs regarding use and purpose of medications
Medication prescribed to treat unrecognized side effect of another medication	Haloperidol for new hallucinations in patient begun on ropinirole for restless leg syndrome Donepezil for "early dementia" in patient routinely taking amitriptyline, lorazepam, and hydrocodone/acetaminophen (paracetamol) Meclizine prescribed for "dizziness" in patient taking high-dose gabapentin
Using standard "adult" doses without accounting for altered drug metabolism and effects due to age-related physiologic changes	A given dose of fluoxetine may have higher serum levels and delayed elimination in older patients, especially women Age-related increase in sedation and postural sway with benzodiazepines, leading to increased risk of falls/fractures Prescription of morphine to geriatric patients due to age-related reduction in renal function (reduced clearance of drug)
Prescribing without awareness of pharmacologically active over-the-counter drugs and supplements	Patient started on warfarin for prevention of thromboembolism in chronic atrial fibrillation who develops excess bleeding despite therapeutic INR because also taking supplemental fish oil capsules, increasing bleeding risk
Use of potentially inappropriate medications (PIMs) (see text for discussion)	Bupropion to treat depression in a patient with history of seizures First-generation antihistamine (e.g., diphenhydramine) in older patient with allergic rhinitis Calcium channel blocker (e.g., amlodipine) for hypertension in older patient with constipation Amitriptyline for depression or neuropathic pain

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[13]. The absorption of iron can also be significantly reduced by the concurrent consumption of coffee or tea [14]. Some medications, on the other hand, require food for optimal absorption, e.g., lurasidone, a newer atypical antipsychotic, which needs at least 350 calories of food for efficient absorption [15]. Apart from absorption, gastric emptying time may also be affected by the administration of food; meals with a high-fat or high-fiber content may cause a reduction in gastric emptying time. Dietary fiber, in particular, is known to affect the absorption of digoxin and amitriptyline, leading to lowered serum levels of these drugs [16]. Laxatives, which are commonly used by older patients, may accelerate gastrointestinal transit time and hence reduce absorption by shortening contact with the small bowel mucosa, affecting, for example, the absorption of antipsychotics.

Chelation reactions are usually mediated by divalent and trivalent cations (e.g., iron, calcium, magnesium, zinc, aluminum [aluminum]), which bind the drug and hinder absorption. Chelation is a major potential source of drug interactions between food/nutritional supplements and susceptible medications (e.g., tetracycline, ciprofloxacin). For example, even the small amount of calcium in the milk added to coffee or tea can markedly reduce the absorption of tetracycline [17]. Alteration of gastric pH due to the use of chronic acid suppression therapy may result in alteration in the levels of drugs, such as ketoconazole, which are most efficiently absorbed in an acidic environment; conversely, there may be an increase in ketoconazole bioavailability in response to drinking an acidic beverage such as a cola [18]. Calcium carbonate, the principal form of dietary calcium, requires dissociation in an acidic environment for absorption in the duodenum and jejunum. Proton pump inhibitors (PPIs) reduce calcium absorption and in as little as 1 year may promote the development of osteoporotic fractures [19, 20]. They also reduce the absorption of vitamin B_{12}, increasing the risk of peripheral neuropathy and cognitive decline.

Fig. 5.1 Factors contributing to the complexity of medication regimens

Data are emerging showing a relationship between PPI use and an increased risk of major neurocognitive disorder due to Alzheimer disease. The plausibility of this association has been demonstrated in rodent models, in which PPIs enhance the production of beta amyloid and alter its degradation by microglia, leading to higher levels of beta amyloid in the brain [19].

Metabolism of Drugs

The metabolism of medications may be also affected by food. Grapefruit has been found to be a potent inhibitor of hepatic CYP3A4, which is necessary for the metabolism of several drugs. The consumption of grapefruit or grapefruit juice can lead to increased levels of carbamazepine, triazolam, buspirone, and lurasidone, all of which rely heavily on CYP3A4 for their metabolism. Grapefruit juice, when consumed at the same time as the ingestion of the statin drugs simvastatin and atorvastatin, increases the levels of those drugs by 260%, compared with water, and by 90% if consumed 12 hours later [21]. This can lead to toxic levels of the statin and to rhabdomyolysis. Drug administration may also be harmful to levels of vitamins. Both phenobarbital and phenytoin may increase the metabolism of vitamin D, vitamin K, and folic acid. Some foods may be harmful especially when ingested in large quantities; for example, foods high in tyramine (e.g., aged cheeses, cured meats, soy sauce), in a person concurrently taking a monoamine oxidase inhibitor (e.g., tranylcypromine) may lead to a hypertensive crisis, characterized by increased heart rate, flushing, and headache.

Distribution of Drugs

Highly protein-bound drugs (e.g., phenytoin, warfarin) may be displaced in a person who has a poor nutritional status and a reduction in serum albumin. Displacement reactions may impact the volume of distribution and the plasma half-lives of these medications.

Altered Effect

Caffeine contained in food or beverages concurrently taken with methylphenidate may further increase the excitatory side effects of this medication. Large amounts of caffeine may also reduce the effects of anxiolytics and mood stabilizers. Ethanol acts as a stomach irritant and may augment gastric mucosal injury from salicylates or nonsteroidal anti-inflammatory drugs. It also adds to the CNS depressant effects of sedating psychotropics like benzodiazepines and sedating antihistamines like diphenhydramine. It is well known that vitamin-K-containing foods, such as spinach, interfere with the action of the anticoagulant warfarin.

Nutritional Status

Medications may affect the nutritional status of patients by reducing food intake due to side effects, including decreases in appetite, constipation, nausea, diarrhea, taste disturbances, and dryness of the mouth. Medications should be carefully assessed for any such negative effects and, where possible, dose reductions, alternate drugs, and nondrug measures offered to treat the target symptoms. Atypical antipsychotics and the antidepressant, mirtazapine, may also lead to significant weight gain, and glucose monitoring is essential, as well as a dietician referral to decrease the risk of obesity and subsequent systemic metabolic derangements, additional medications, and morbidity.

5.1.5 Dietary Supplements and Drug-Supplement Interactions

Dietary supplements are not subject to the regulations imposed by national drug safety organizations like the US Food and Drug Administration, and their contents and potency often are unknown. Based on the 2002 US Food and Drug Administration Health and Diet Survey, over 75% of adults over the age of 54 used a dietary supplement; of these individuals, 84% took a multivitamin or multimineral supplement, 81% took a single-ingredient vitamin or mineral (e.g., calcium), and 34% reported use of herbs, botanicals, or other dietary supplements [22]. The high prevalence of supplement use has been associated with adverse drug reactions. Based on extrapolation from representative surveillance data from 63 US emergency departments from 2004 to 2013, an estimated 23,005 (95% CI 18,611–27,398) emergency department visits annually could be attributed to adverse events related to dietary supplements; approximately 12% of these visits were made by persons age 65 and older [23]. Older patients have a high prevalence of multimorbidity and polypharmacy, leading to the potential for supplement-drug interactions.

Table 5.3 Examples of interactions between dietary supplements and psychoactive medication

Supplement	Drug/drug class	Adverse drug event
St. John's Wort	Tricyclic antidepressants Benzodiazepines SSRIs	Potential decrease in tricyclic levels 25–50% reduction in levels Increased drowsiness, serotonin syndrome
Ginseng	Monoamine oxidase inhibitors	Reported manic-like symptoms, tremulousness, headache
Ginkgo biloba	Trazodone	Report of coma

Data extracted from Gardiner et al. [25]

A number of herbs and herbal supplements may interact with warfarin. For example, St. John's wort (*Hypericum perforatum*) increases warfarin clearance and reduces its plasma concentration. Conversely, chamomile tea, consumed by patients for its purported calming, anxiolytic, and gastric-soothing effects, inhibits the metabolism of warfarin by CYP1A2, CYP3A4, and CYP2C9, potentially increasing the risk of bleeding [24]. Case reports link fish oil and cranberry juice with an elevated international normalized ratio (INR) in patients taking warfarin. St. John's wort potentially decreases digoxin levels and decreases bioavailability of verapamil and may lower plasma blood levels of statins [25]. Table 5.3 summarizes the potential interactions of three common supplements with psychoactive medications [25].

Teaching Points

Diet and individual foods and beverages can affect the absorption, metabolism, distribution, and effectiveness of medications with potential short-term and long-term adverse consequences. Similarly, dietary supplements, consumed by 75% of US adults, can interact with individual drugs and have been associated with emergency department visits for adverse reactions, both from the supplement and because of drug-supplement interactions.

5.1.6 Potentially Inappropriate Medications (PIMs)

Polypharmacy and ADEs may result from the prescription of medications that are inappropriate for older adults by virtue of an unfavorable risk to benefit ratio that results from age-associated alterations in drug metabolism or increased vulnerability to potential side effects, especially if safer alternatives are available. PIMs have been associated with a 43% increased risk of ADEs [26]. Among 518 patients aged 65 and older admitted to an Australian tertiary care center, 55% were taking one or more PIMs, and 27% were taking two or more. Sixty-one percent were discharged on at least one PIM. In 5.6% of cases, a PIM was found to potentially cause or contribute to the reason for admission [27]. Among 400 Brazilian outpatients aged 60 and older, nearly 30% experienced the iatrogenic "trifecta" of polypharmacy *plus* potential drug-drug interactions *plus* ≥ one PIM [9]. Evidence is accumulating that PIMs lead to overall greater use of healthcare services, especially hospitalization, and add to healthcare costs [28].

Identifying PIMs

Researchers have developed tools to recognize PIMs because clinicians cannot possibly know all the harmful side effects and interactions of even commonly prescribed medications. The two most widely used PIM tools are the Beers criteria [29] and the STOPP/START criteria (*S*creening *T*ool of *O*lder Persons *P*otentially Inappropriate *P*rescriptions/*S*creening *T*ool to *A*lert Doctors to the *R*ight *T*reatment) [30]. Updated in 2015 by a thirteen-member expert panel to reflect new drugs and the evolution of knowledge regarding drug-drug interactions and adverse side effects in older adults, the Beers criteria offer the advantage of rating both the quality of supporting evidence and the strength of their recommendations. New for the 2015 update are lists of select drugs which should be avoided or whose dose should be adjusted based on renal function, as well as select drug-drug interactions known potentially to be harmful in older adults.

The Beers criteria are oriented to drugs used in the USA and Canada. The STOPP/START criteria, developed in Ireland, focus on the European pharmacopoeia. Comparisons of the performance of the two PIM tools suggest that STOPP/START is more sensitive than Beers criteria. Among a sample of 1329 Irish primary care patients with a mean age of 75, 346 PIMs were found by the STOPP/START criteria, compared to 243 by the Beers criteria [31]. Although the STOPP/START do not rate the strength of the supporting evidence or make prescribing recommendations, they have been shown to be superior to the Beers criteria in identifying PIMs that lead to ADEs [32, 33]. In a meta-analysis of outcomes associated with application of the STOPP/START criteria, Hill-Taylor et al. found that the criteria can reduce PIM prescriptions in both the hospital and community environments [32]. Individual studies have shown a significant benefit of the STOPP/START criteria in reducing falls, primary care visits, and average drug cost [33]. Some clinicians may disagree with the recommendations in the Beers criteria, such as the categorical recommendation against the use of typical and atypical antipsychotics as treatment for the behavioral problems of major neurocognitive disorders. PIMs ultimately are decision support tools to inform the clinician of potential harm that must be balanced against potential benefit from a medication for an individual patient. Clinicians should integrate at least one PIM decision support tool into their prescribing practice for older patients. The Beers criteria can be downloaded as a pocket card or as part of the iGeriatrics Mobile App for Apple™ or Android™ [34].

Teaching Points

Potentially inappropriate medications (PIMs) are drugs associated with an unacceptably high risk of adverse drug events in older adults, often when safer alternatives exist. The use of these drugs offers a low benefit to side effect ratio and should be avoided or minimized except when a safer alternative is unavailable or contraindicated for a given patient. Tools have been developed using literature searches and expert opinion to identify PIMs, of which the two most commonly used are the Beers criteria and the STOPP/START criteria, developed for the North American and European pharmacopoeias, respectively. The Beers criteria can be found on convenient smartphone applications.

5.1.7 Medications of Special Concern for Older Adults

Anticholinergic Medications

To varying degrees, anticholinergic drugs cross the blood-brain barrier and bind to muscarinic and histamine receptors, causing sedation and, in older adults, impairing cognition and precipitating delirium. First-generation antihistamines such as diphenhydramine have a well-known association with delirium. In addition to adverse side effects in the central nervous system (CNS), anticholinergic drugs contribute to dry eyes, dry mouth, precipitation or exacerbation of narrow-angle glaucoma, constipation, urinary retention, and tachycardia, all in a dose-dependent manner. Some of these side effects have been therapeutic targets. For example, the antimuscarinic drug, oxybutynin, is used to treat urinary urgency and incontinence. Strongly anticholinergic medications are considered PIMs, but many commonly prescribed drugs have mild anticholinergic properties which go unrecognized by clinicians and which, taken together, can produce a substantial anticholinergic burden. A number of scales have been developed that calculate the total anticholinergic burden of a patient's prescriptions. The two most commonly used, the Anticholinergic Cognitive Burden Scale (ACB) and the Anticholinergic Risk Scale (ARS), used a combination of literature review and expert opinion to rank the anticholinergic activity of a drug from 0 (none) to 3 (severe). The results for individual drugs are then summed. In a community-based study of adults aged 65 and older (mean age, 77 years), nearly half were prescribed medications with an ACB score of ≥ 3 and roughly 20% were receiving medications with an ACB score of ≥ 5. Higher ACB scores were associated with the number of prescription and over-the-counter medications, as well as with the number of chronic illnesses [35]. The prevalence of anticholinergic burden in this study may have been skewed because patients were referred for a pharmacy evaluation by a senior services program. In a large population-based French study of adults over the age of 75, 10% received at least one prescription with a high anticholinergic burden. In the nursing home population, the prevalence of high anticholinergic burden rose to 24% [36]. Studies using the ACB have shown a significant association between total anticholinergic burden and cognitive impairment [37].

The long-term, cumulative exposure to anticholinergic drugs has been linked to the development of major neurocognitive disorders, including Alzheimer disease [38, 39]. The cognitive side effects of anticholinergic drugs should raise caution about the growing pharmaceutical interest in antimuscarinic agents as potential treatments for refractory mood disorders [40]. In older adults, anticholinergic drugs also have been associated with an increased risk of community-acquired pneumonia and traumatic fractures [41]. ◘ Table 5.4 lists commonly prescribed medications with moderate to high anticholinergic burden, together with safer alternatives [42–45]. ◘ Table 5.5 shows common medications by class whose mild to moderate anticholinergic activity often goes unrecognized, but which can contribute to significant anticholinergic side effects when simultaneously prescribed with other anticholinergic medication [42–45].

Teaching Points

Anticholinergic drugs cross the blood-brain barrier to varying degrees, causing sedation and potentially impairing cognition in older adults that can result in frank delirium. These medications also cause a variety of peripheral manifestations ranging from dry mouth to constipation in a dose-dependent fashion. Many common medications have mild anticholinergic properties which, when added together, can produce a cumulative anticholinergic burden that can be clinically significant.

Psychotropics and Fall Risk

Approximately one-third of adults 65 and older fall annually, and a substantial proportion of these falls result in traumatic fractures. Psychotropic medications play a significant role in adding to fall risk in the older population. Bloch et al. conducted a meta-analysis of 71 studies with data on psychotropic drug use and falls in adults aged 60 years and older. The authors defined a psychotropic drug as any drug that affected the CNS, but focused their review on antidepressants, benzodiazepines, sedative-hypnotics, narcotics, and antipsychotics. ◘ Table 5.6 summarizes their key findings, showing that psychotropic medication increases the risk of any fall between 29% and 44%, while increasing the risk of traumatic falls like ground-level hip fracture between 81% and 276% [46].

The majority of studies that have examined the association between the SSRI class of antidepressants and falls have found a significant association, but the single-randomized controlled trial found in a comprehensive, systematic review of falls and SSRIs was underpowered with 142 subjects and did not find a statistically significant association (OR 1.56, 95% CI 0.63–3.83) [47]. Although the consistency of

Table 5.4 Examples of anticholinergic medications

Medication class	Medication name	Anticholinergic activity[a]	Examples of safer alternatives
Antipsychotic			
Atypical	Olanzapine	H	Aripiprazole
	Quetiapine	M	
	Risperidone	M	
	Ziprasidone	M	
Typical	Haloperidol	M	
	Trifluoperazine	H	
	Chlorpromazine	H	
Antidepressant			
SSRI	Paroxetine	M	Citalopram, escitalopram
Tricyclic	Amitriptyline	H	
	Nortriptyline	H	
Antidiarrheal			
	Loperamide	M	
Antiemetic			
	Prochlorperazine	H	Ondansetron[b]
H2 blocker antacids			
	Ranitidine	M[c]	Proton pump inhibitors, H2 blocker: famotidine
	Cimetidine	M	
All first-generation antihistamines			
	Diphenhydramine[d]	H	Second-generation ("nonsedating") antihistamines: cetirizine, loratadine
	Chlorpheniramine	H	
	Clemastine	H	
	Hydroxyzine	H	
Anti-vertigo antihistamines			
	Meclizine	H	
	Dramamine	H	
Bladder antispasmodics			
	Trospium	H	Mirabegron (beta 3 agonist)
	Oxybutynin	H	Darifenacin, solifenacin[e, b]
	Tolterodine	H	
Antiparkinson disease medication			
	Benztropine	H	
	Amantadine	M	

Data extracted from Refs. [42–45]
[a]*M* moderate, *H* high
[b]May cause QTc prolongation
[c]Considered low risk by one anticholinergic scale, but has consistently been associated with delirium in older adults
[d]Diphenhydramine is also found in over-the-counter (nonprescription) sleep aids
[e]M3 selective, not associated with cognitive impairment, may cause constipation and dry mouth

Table 5.5 Drugs with often unrecognized anticholinergic activity that can add to the total anticholinergic burden

Psychiatric drugs	Cardiac drugs	Diuretics	Miscellaneous
Benzodiazepines	*Antiarrhythmics*	Furosemide	*Analgesics*
Alprazolam	Atenolol	Triamterene	Codeine
Diazepam	Metoprolol	Chlorthalidone	Morphine[a]
Clorazepate	Digoxin		*Anticoagulants*
Antidepressants	Quinidine[b]		Warfarin
Bupropion	*Antihypertensives*		Dipyridamole
Fluvoxamine	Captopril		*Anti-glaucoma*
Trazodone	Hydralazine		Timolol maleate
Antipsychotics	*Antianginal*		*Anti-inflammatory*
Haloperidol	Isosorbide		Hydrocortisone
			Anti-gout
			Colchicine
			Bronchodilator
			Theophylline[b]

Data extracted from Refs. [42–45]
[a]Not recommended in older adults due to decreased renal clearance
[b]Rarely prescribed due to high potential for toxicity and drug interactions [3–6]

Table 5.6 Pooled odds ratios (OR) and 95% confidence intervals (95% CI) for falls and traumatic falls in adults aged 60 and older

	Antidepressants OR (95% CI)	Benzodiazepines OR (95% CI)	Antipsychotics OR (95% CI)	Sedative-hypnotics OR (95% CI)
No. of studies	41	20	20	33
Any falls	1.44 (1.31–1.59)	1.31 (1.16–1.47)	1.29 (1.11–1.50)	1.40 (1.24–1.58)
Traumatic falls	2.12 (1.80–2.48)	2.24 (1.60–3.13)	2.76 (2.06–3.68)	1.81 (1.56–2.10)

Data extracted from Bloch et al. [46]

association between SSRIs and falls has been strong, observational and retrospective studies may be confounded by indication bias [47, 48]; i.e., most patients receive antidepressants for depression, and there is evidence that the depression *itself* may influence fall risk by contributing to disability [49]. To add to the complexity of understanding the association between antidepressants and falls, fall risk depends in part on having previously experienced a serious fall. In an analysis of 2948 men and women enrolled in the longitudinal Health, Aging, and Body Composition Study (Health ABC; mean age, 73.6 years), no association was found between any antidepressants and falls in subjects without a history of falls or fall-related fractures, but SSRIs were the only class of antidepressant to be significantly associated with a *recurrent* fall (OR 1.62, 95% CI 1.15–2.28), after adjustment for study site, drugs that increase risk of falls, self-reported depression, Center for Epidemiologic Studies Depression (CES-D) score, pain, sleep problems, anxiety, and comorbid conditions [50].

Teaching Points

At the present time, it remains uncertain how much SSRIs and other antidepressants independently contribute to the risk of falls, but attention should be paid to the additive effect they may have on fall risk. The Beers criteria *strongly* recommend avoidance of three or more CNS-active medications if considering SSRIs, tricyclic antidepressants (TCAs), or benzodiazepines because of an increased risk of falls and fractures; tricyclics, however, fall under the category of anticholinergic medications, which the Beers criteria recommend avoiding [51].

Antipsychotics and Metabolic Syndrome

Patients who are prescribed atypical antipsychotics experience higher rates of obesity, hyperlipidemia, diabetes mellitus, and the full metabolic syndrome[1] than those taking typical antipsychotics or mood stabilizers. Erickson et al. used pharmacy and medical claims data for older patients residing in the western USA to evaluate the association of atypical antipsychotics with an increased odds ratio of having new treatment-dependent diabetes mellitus. Those exposed to atypical antipsychotics had a 32% greater odds ratio of developing treatment-dependent diabetes mellitus compared to individuals not taking these agents [52]. Other pharmacoepidemiologic studies have provided inconsistent results regarding the association of atypical antipsychotics and diabetes mellitus; significant study heterogeneity makes it difficult to systematically review the studies via meta-analysis. At present, the preponderance of evidence suggests that clozapine and particularly olanzapine increase the risk of diabetes mellitus, whereas risperidone and quetiapine do not [53]. However, the use of typical antipsychotics as the frame of reference may be misleading. Lipscombe et al. found that geriatric patients currently receiving a typical antipsychotic had a 2.86 OR of hospitalization for hyperglycemia, compared to a 1.52 OR for current users of an atypical antipsychotic [54]. Significant hyperglycemia can develop in just days [55], especially in patients with obesity or a prior history of diabetes mellitus.

Teaching Points

Atypical antipsychotics have been associated with the development of the metabolic syndrome, and both atypical and typical antipsychotics have been associated with the development of hyperglycemia, which can occur within days of the start of treatment. In the inpatient setting, psychiatrists should monitor the fasting blood glucose after starting an antipsychotic, especially if the patient has risk factors for diabetes mellitus, such as a history of hyperglycemia, obesity, or other elements of the metabolic syndrome. A logical approach for older outpatients newly started on an antipsychotic is to obtain a fasting blood glucose after 1 week and 1 month and to ask the patient or informant about symptoms of hyperglycemia, such as polydipsia, polyuria, and new fatigue. The patient also should be monitored for weight gain.

1 The metabolic syndrome is defined as meeting at least 3 of the 5 criteria: abdominal obesity, hypertriglyceridemia, low high-density-lipoprotein cholesterol, hypertension, and a fasting blood glucose >100 mg/dL (5.55 mmol/L).

Psychotropic Medication and Hyponatremia

Definition of Hyponatremia

Hyponatremia is defined as a serum sodium concentration of < 135 mEq/L (135 mmol/L). Symptomatic hyponatremia is determined by its severity and the rate of decline; if insidious or chronic, some patients remain asymptomatic with a sodium below 120, although 120 or below generally is considered a critical value. Mild hyponatremia can present with nonspecific fatigue, headache, nausea, and muscle cramps, but as the sodium drops, the rate of flow of water into neurons and glia increases as a result of the widening concentration gradient, causing cerebral edema. A rapid lowering of the serum sodium into the 120 seconds (mEq/L/mmol/L), or a serum sodium of ≤ 120 mEq/L (120 mmol/L), may precipitate neuropsychiatric symptoms such as delirium, lethargy, restlessness, and abnormalities of gait and may result in seizures, coma, and ultimately death due to brain swelling. Hyponatremic seizures represent a medical emergency and require transfer to the emergency department or medical intensive care unit.

Clinically significant hyponatremia can be caused by net salt excretion by the kidney, as occurs from diuretics; by volume depletion with avid water retention from physiologically elevated antidiuretic hormone (ADH; also called vasopressin) and/or free water replacement without adequate replacement of salt; by net water retention due to physiologically elevated ADH as seen in cirrhosis and heart failure; from water intoxication during purposeful, rapid consumption of excessive amounts of water; and by *inappropriate* elevation of ADH, known as the syndrome of inappropriate antidiuretic hormone (SIADH). SIADH most commonly results from the action of medications on the CNS; many offending drugs are psychotropics.

Hyponatremia Associated with Psychotropic Medication

Data showing an association between antidepressants and hyponatremia in older adults have been gleaned through observational and case-control studies, leaving the results vulnerable to bias. With these limitations in mind, studies suggest that the greatest risk of hyponatremia occurs with SSRIs and selective norepinephrine reuptake inhibitors (SNRIs), with lower risks for tricyclic antidepressants (TCAs) and the remaining classes of antidepressants. Coupland et al. analyzed a large regional database of 40,516 patients 65 and older to evaluate the relative odds ratio of hyponatremia among different classes of antidepressants and adjusted for age, sex, depression severity and duration, use of medications known to affect serum sodium, and comorbid conditions. Compared to not taking antidepressants, patients prescribed SSRIs were significantly more likely to develop hyponatremia (OR 1.52, 95% CI 1.33–1.75); the respective ORs for TCAs and all other antidepressants considered together did not achieve statistical significance [56]. Using serum sodium level < 130 mEq/L

(< 130 mmol/L) as the cutoff, the incidence of hyponatremia with SSRIs has been reported between 0.06% and 2.6%, compared to 0.08–4% for SNRIs and 0.01–0.33% for TCAs [57]. The wide range reflects the heterogeneity of the studies. Among older adults using SSRIs and SNRIs (the highest-risk antidepressants; TCAs should not be a first-line antidepressant in the geriatric population), the risk of hyponatremia rises with age and sex, concurrent use of other agents that may affect serum sodium, and comorbidities that affect water handling by the body [57] (Fig. 5.2). Age likely is a proxy for age-associated decline in renal function and concomitant reduction in the ability to excrete free water.

The phenothiazine and butyrophenone classes of antipsychotics have infrequently been associated with SIADH. The anticholinergic effect of phenothiazines and the resulting dry mouth may also lead to increased fluid intake, augmenting the sodium-lowering effect of any inappropriate ADH secretion [58, 59].

Diagnosis and Management of SIADH

In the presence of symptomatic hyponatremia, urine and serum electrolytes and urine and serum osmolality should be obtained *statim*. In the absence of neuroendocrine or renal dysfunction, hyponatremia should lead to net urinary excretion of free water, but in SIADH, the urine osmolality is inappropriately high. Diuretics cause hyponatremia by salt and free water excretion, usually resulting in low urine osmolality. Severe mental status changes related to very low sodium, and particularly hyponatremic seizures, represent a medical emergency. The sodium should be rapidly increased by 4–6 mEq/L (mmol/L) but not more than 9 mEq/L (mmol/L) over 24 hours and 18 mEq/L (mmol/L) over 48 hours with the goal of raising the sodium to > 125 mEq/L (mmol/L). Initially, this rise can be achieved by intravenous 3% saline, given as a bolus of 100 ml over 1 hour. Hypertonic saline should only be administered under close medical supervision on a medical inpatient unit or in the emergency department. In severe cases (e.g., seizures, coma), a rate of rise faster than the above parameters leads to overly rapid shifts in fluid and electrolytes within the CNS and may cause myelinolysis. Mildly symptomatic hyponatremia, consisting of lethargy or mild confusion, should be treated by aggressive fluid restriction of 800 to 1000 ml of fluids per 24 hours. Normal saline (0.9% sodium chloride solution) should *not* be used to raise serum sodium. In SIADH, sodium handling by the kidney remains normal. Consequently, the excess salt is excreted, but the remaining free water is absorbed, potentially worsening the hyponatremia. Asymptomatic hyponatremia between 125 and 135 mEq/L (mmol/L) can be treated with a slightly more liberal fluid restriction of 1500 ml/24 hours. In SIADH, physiologic handling of sodium is not affected in the

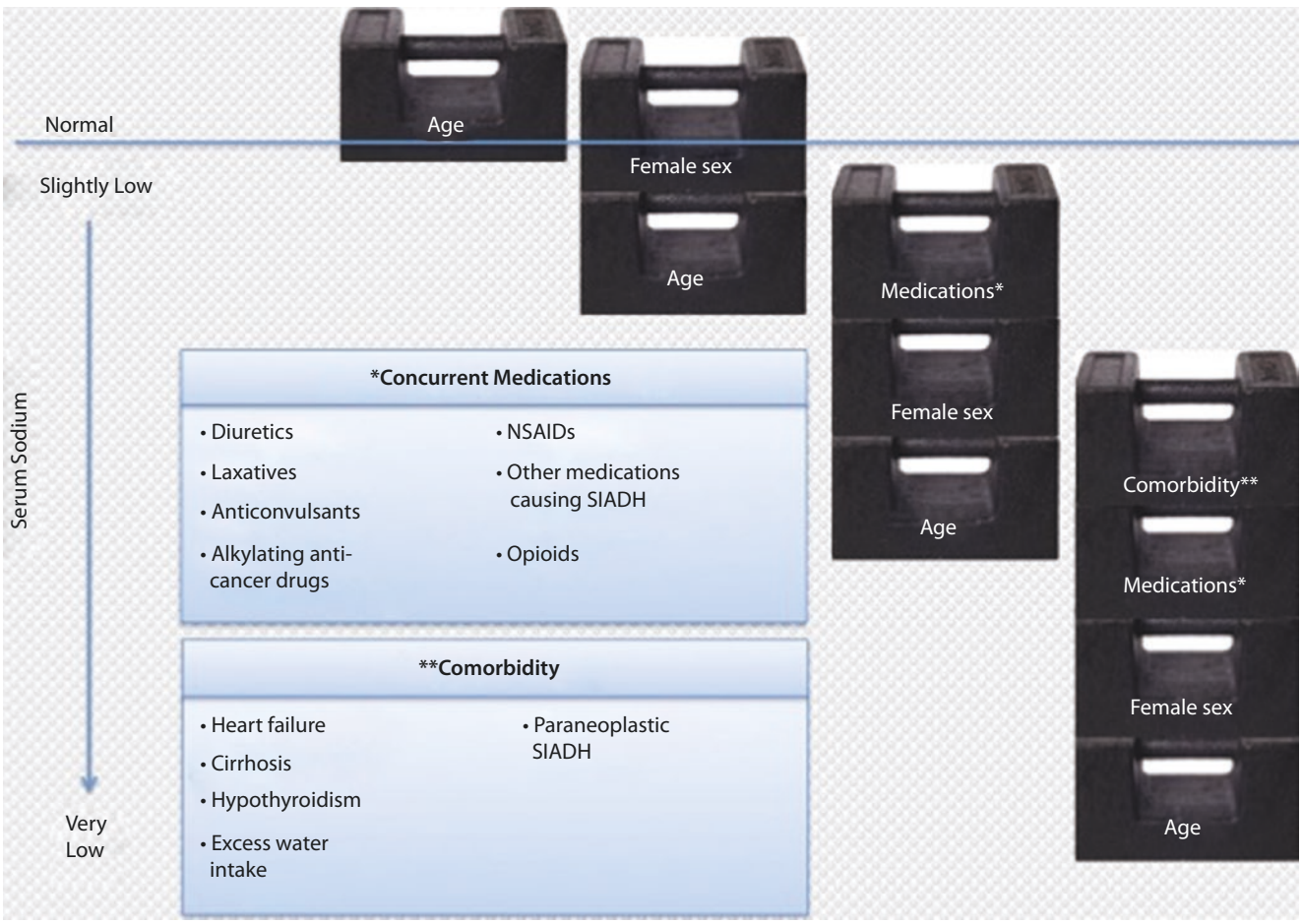

Fig. 5.2 Risk factors for hyponatremia in the older patient

presence of healthy kidneys. However, when there is underlying salt wasting (i.e., inappropriate sodium excretion causing an inappropriately high urinary sodium for the degree of hyponatremia, as might happen with chronic use of loop diuretics), salt tablets can be added to the fluid restriction. Patients susceptible to heart failure or with cirrhosis generally should not receive salt tablets, and hypertonic saline should be administered cautiously while monitoring for signs and symptoms of fluid overload.

Teaching Points

A number of classes of psychotropic medications, particularly SSRIs and SNRIs, can cause SIADH, leading to potentially serious hyponatremia that may be compounded by the concurrent administration of other sodium-lowering drugs, as well as heart failure and cirrhosis, which stimulate the kidney to retain salt and water. Delirium and seizures in conjunction with hyponatremia constitute a medical emergency requiring prompt treatment. Asymptomatic and mildly symptomatic hyponatremia can be managed by fluid restriction. More severe cases may require the addition of 3% (hypertonic) saline to bring the serum sodium to ≥ 125 mEq/L (mmol/L).

The Adverse Effects of Lithium in Older Patients

Despite its well-known potential toxicity, lithium remains a first-line mood stabilizer treatment for bipolar disorder, as well as an augmentation agent for treatment-resistant unipolar depression. Elevated levels and long-term use of lithium can lead to chronic kidney disease, polyuria, and nephrogenic diabetes insipidus with difficulty concentrating urine.

Lithium concentrates in the thyroid gland and inhibits its release of thyroid hormone, thereby increasing the risk of development of a goiter and hypothyroidism. Lithium enters the CNS and concentrates in both the hypothalamus and the pituitary gland, resulting in exaggerated release of thyroid stimulating hormone. In spite of the suppressive effect of lithium on thyroid hormone release, it infrequently can induce hyperthyroidism, possibly by directly damaging follicular cells, causing the release of stored thyroid hormone [60].

Rarely, lithium has been associated with hyperparathyroidism, although the exact mechanism remains unclear. Lithium appears to act on the calcium-sensing receptor, raising the level of serum calcium necessary to turn off the secretion of parathyroid hormone. It is also possible that in some cases lithium unmasks a previously subclinical hyperparathyroid state [61].

Acute lithium toxicity can lead to fever, altered mental status, and coma; cognitive changes have a good prognosis with recovery in 6–12 months, at least in younger patients. Irreversible loss of cerebellar Purkinje cells can result from acute or subacute toxicity, leading to cerebellar symptoms, including intention tremor, ataxic gait, and dysarthria. In chronic lithium use, cerebellar injury can develop with therapeutic lithium levels [62].

Age-associated physiologic changes increase the risk of lithium toxicity. Decreasing muscle mass and reduced production of creatinine can mask age-associated declines in the glomerular filtration rate. Healthy younger adults can compensate for the polyuria from nephrogenic diabetes insipidus by increasing their fluid intake, but the thirst response is blunted in older adults, predisposing them to a net loss in intravascular volume that may result in prerenal azotemia (elevated blood urea nitrogen to creatinine ratio) and dehydration, with a resulting increase in the serum lithium concentration and a upward spiraling risk of lithium toxicity. The signs and symptoms of lithium toxicity can be mistaken for age-associated conditions and the side effects of other medications. Dry mouth from dehydration can be mistakenly attributed to anticholinergic medication or sicca syndrome, a slight tremor or unstable gait to Parkinson disease or peripheral neuropathy.

Common comorbid conditions among older adults or their treatment increase the risk of lithium toxicity; intravascular volume depletion from the polyuria of uncontrolled diabetes mellitus or from the use of loop diuretics predispose to lithium toxicity. Nonsteroidal anti-inflammatory drugs for pain can impair renal function, increasing the risk of lithium toxicity. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for hypertension or heart failure may reduce kidney perfusion and the glomerular filtration rate, causing lithium levels to rise. Delirium resulting from lithium toxicity or from hypernatremia from unrecognized nephrogenic diabetes insipidus may be attributed to comorbid bipolar disorder, psychotic disorder, major depressive disorder, or another cause, rather than to the side effects of lithium. Chronic use of loop diuretics (e.g., furosemide, bumetanide, torsemide) and ACE inhibitors each has been associated with a ≥ 60% relative risk increase of hospitalization for lithium toxicity in older adults. The risk is highest during the first month of use [63], underscoring the need to closely follow lithium levels each time an agent that may affect hydration status or renal function is prescribed.

Teaching Points

Both chronic use of lithium and acute lithium toxicity can impair the water-retaining effect of ADH on the renal tubule, leading to nephrogenic diabetes insipidus, and can lead to acute and chronic cerebellar dysfunction causing disabling dysarthria, tremor, and ataxic gait, contributing to fall risk. Chronic administration of lithium can induce hypothyroidism and (less commonly) hyperthyroidism and has also been linked to hyperparathyroidism. In older patients, these risks of lithium toxicity are magnified due to the age-associated decline in renal function,

Teaching Point (Continued)
comorbid conditions that lead to the use of medications that further compromise kidney function or predispose to dehydration, and other age-associated conditions. It therefore is critical that lithium levels be closely monitored in older patients and, whenever possible, that lithium be administered at the lowest effective dose. If possible, alternatives to lithium should be sought.

5.1.8 Adverse Reactions Meriting Special Consideration

Neuroleptic Malignant Syndrome and Serotonin Syndrome: Recognition and Management

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are potentially life-threatening adverse drug reactions that belong to a group of dysautonomias whose symptoms overlap, making differentiation often difficult. NMS is considered an idiosyncratic reaction to dopamine blocking agents (most commonly antipsychotic medication) that may appear unpredictably during the course of treatment. Changes in antipsychotic agent, high doses, the rapidity and magnitude of upward titration, and co-administration of a mood stabilizer such as lithium increase the risk for NMS [64]. In contrast, SS represents direct dose-dependent toxicity from serotonergic agonists. Both syndromes can present with hypertension, tachycardia, hyperthermia (> 40 °C), autonomic dysfunction, mental status changes, and increased motor tone. To further complicate differentiation, not all features of either syndrome need be present for a clinical diagnosis. Figure 5.3 shows the overall similarities and differences between NMS and SS. Due to similarities in presentation [65], differentiating the two requires a careful review of medication exposure (including over-the-counter and "street" drugs) and examination for key differentiating features.

An important differentiating exam finding is hyperreflexia progressing to clonus in SS compared to typically decreased reflexes in NMS. In the psychiatric patient, the co-administration of both an antipsychotic and a serotonergic antidepressant has become commonplace, being used in cases of refractory depressive disorders (with or without psychotic features), psychotic disorders with concurrent depressive symptoms, and severe agitation and emotional dysregulation in major neurocognitive disorders. The combination of an antipsychotic (typical [phenothiazine derivative, butyrophenone] or atypical) with a SSRI or SNRI increases the risk of SS and should be made cautiously in the older adult, using the lowest possible effective dose of each drug. Other commonly used medications in the geriatric population have serotonergic properties, and given the prevalence of polypharmacy in older adults, the psychiatrist should carefully review the patient's medication list for these serotonergic drugs before starting an antipsychotic, SSRI, or SNRI (Table 5.7). Because clinicians may understandably be reluctant to stop all serotonergic drugs indefinitely when they are providing substantial benefit to the patient, it is helpful to determine the onset of serotonin toxicity in relation to the initiation or dose increase of a serotonergic agent in order to identify the immediate precipitant of the toxicity. However, this association should not be considered definitive, and in cases of moderate-severe SS, all serotonergic agents should be held, even if this places the patient at risk for serotonin withdrawal.

Neuroleptic Malignant Syndrome

NMS appears to be caused by the depletion of dopamine in the CNS or by the blockade of dopamine type 2 (D_2) receptors. Central dopaminergic blockade has been posited as the best possible explanation; antipsychotic drugs block dopamine receptors in multiple regions of the CNS, including the basal ganglia, hypothalamus, corpus striatum, and spinal areas. All antipsychotics, not just high-affinity D_2 receptor drugs like haloperidol and risperidone, have been implicated in NMS, including clozapine, quetiapine, aripiprazole, and olanzapine. High doses and a faster rate of upward titration increase the risk of NMS. More than half of reported cases have involved the co-administration of two or more psychotropics [64], but it is unclear whether this association represents potentiation or simply reflects the severity of the underlying psychiatric illness. Of note, the abrupt withdrawal of dopaminergic drugs in patients with Parkinson disease has been linked to NMS or at least to a NMS-like syndrome.

Serotonin Syndrome

There are no reliable data on the incidence of SS because of its rarity coupled with lack of recognition of milder cases. However, the widespread use of SSRI and SNRI antidepressants, together with the expanding pharmacopoeia of medications that either are serotonin agonists or that interfere with the metabolism of SSRIs, SNRIs, or MAO inhibitors, suggests that the incidence is likely to rise. Approximately 40% of cases of SS arise from a single agent [66], with the rest resulting from increased CNS serotonin levels due to the administration of multiple serotonin agonists. Table 5.7 lists medications that can increase brain serotonin levels. Many older patients receive opioids for chronic pain plus a SSRI or SNRI, either for a concurrent depressive disorder or as an adjunctive analgesic to reduce the daily opioid dose. This practice can place the patient at risk for SS. Non-phenanthrene opioids should be avoided or discontinued whenever possible in patients receiving a serotonergic psychotropic medication; non-phenanthrene opioids include tramadol, methadone, propoxyphene, meperidine, and fentanyl. The phenanthrene opioids, such as hydrocodone, morphine, and codeine, can be used safely with serotonin antidepressants [67]. Serotonergic pain

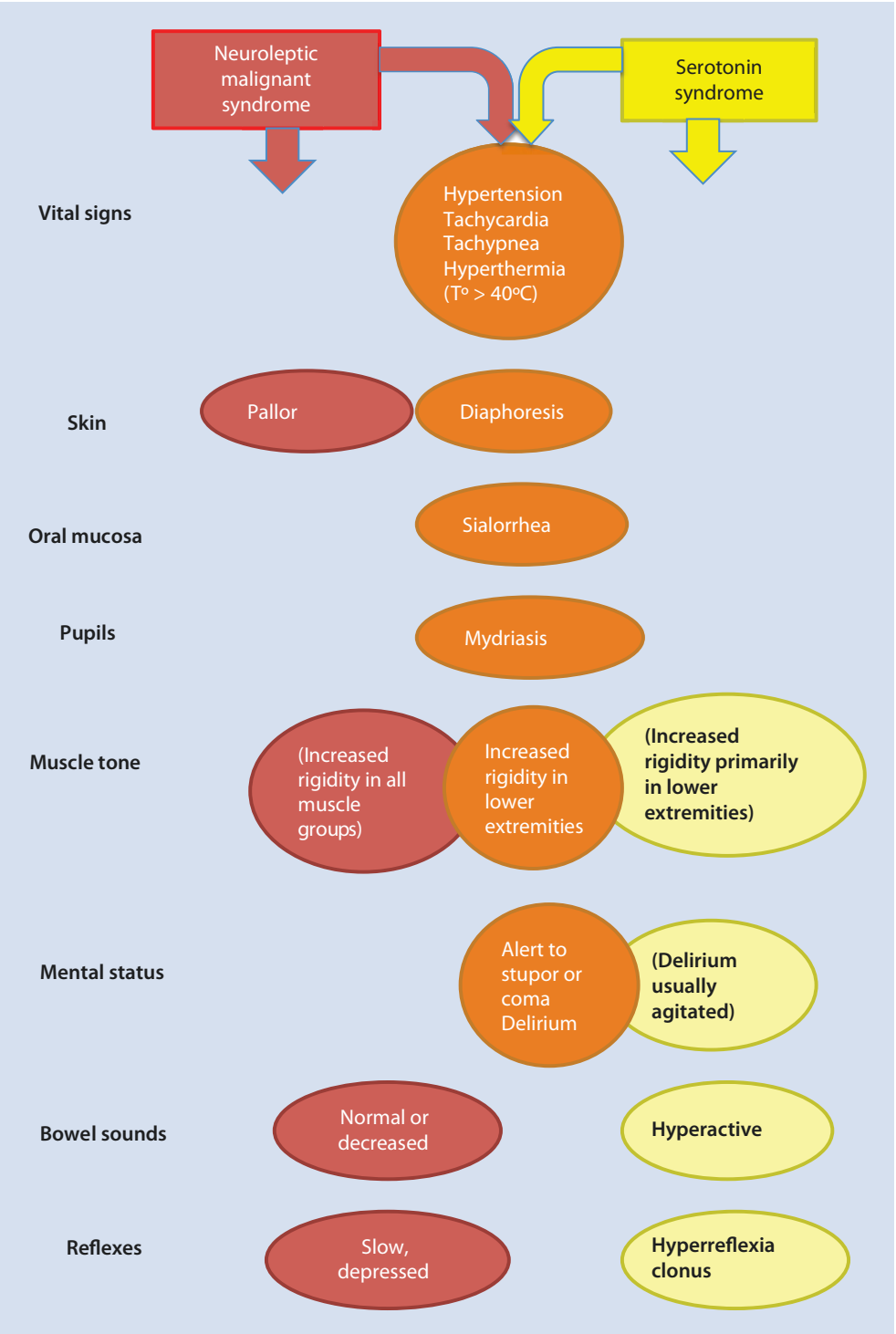

Fig. 5.3 Similarities and differences between neuroleptic malignant syndrome and serotonin syndrome

medications by themselves have been associated with SS, especially tramadol [66].

Dextromethorphan (a cough suppressant found in many over-the-counter cold remedies) also can precipitate SS. The macrolide antibiotic erythromycin (but not the second-generation macrolide, azithromycin) inhibits the metabolism of SSRIs, as can the anticonvulsant carbamazepine. Because the oxazolidinone class of antibiotics (linezolid, tedizolid phosphate) are weak MAO-B inhibitors, they have the potential to induce SS in patients receiving a serotonin-enhancing antidepressant [68].

SS can present insidiously across a continuum of severity with only one or a few of the characteristics. Mild, subacute cases can be missed, the symptoms being attributed to common morbidities in older adults (e.g., hypertension, infection) or to the comorbid psychiatric disorder in the case of akathisia and anxiety disorder. In more severe cases, tremor can be suppressed by hypertonicity (Fig. 5.4) [69].

Table 5.7 Drugs that can precipitate serotonin syndrome

Drug Class	Drugs
Antidepressants	SSRIs
	SNRIs
	Trazodone
	Tricyclic antidepressants
	MAOIs
	St. John's Wort *(Hypericum perforatum)*
Anxiolytics	Buspirone
Mood stabilizers	Lithium
	Valproic acid
	Carbamazepine
Amphetamines and derivatives	Dextroamphetamine
	Methylphenidate
	Sibutramine (Meridia; withdrawn in USA)
	3,4-methylenedioxymethamphetamine (ecstasy)
	Methamphetamine
Analgesics	Fentanyl
	Meperidine
	Tramadol
Muscle relaxants	Cyclobenzaprine
Antiemetics	Ondansetron
	Metoclopramide
Antimigraine drugs	Triptans
	Ergot alkaloids
Miscellaneous	Cocaine
	Linezolid
	Tedizolid
	5-Hydroxytryptophan
	Tryptophan

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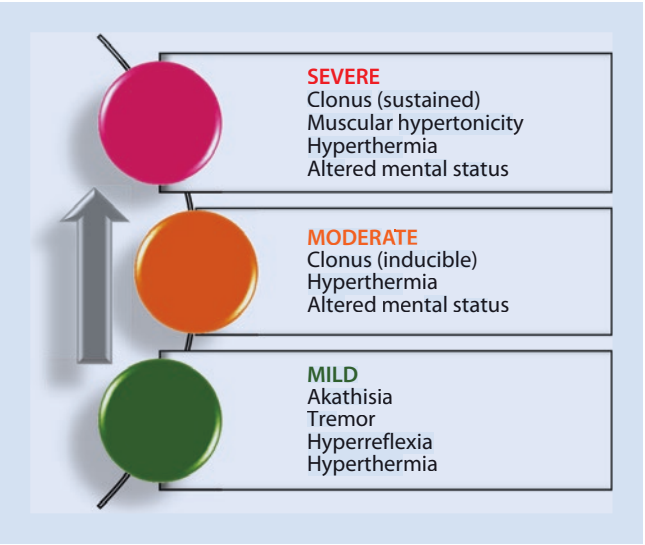

Fig. 5.4 The spectrum of signs and symptoms in serotonin syndrome

Management of Neuroleptic Malignant Syndrome and Serotonin Syndrome

NMS and severe cases of SS are medical emergencies requiring close medical and nursing management and should be transferred to the emergency department or to the intensive care unit. Care for NMS is largely supportive and begins with the discontinuation of the antipsychotic. Although NMS is idiosyncratic with an unpredictable occurrence, patients who have had it are vulnerable to a recurrence if rechallenged with an antipsychotic; the rate of recurrence upon later rechallenge may be as high as 30–50% [64]. Thus, simply reducing the dose of antipsychotic is not recommended as part of the initial treatment, placing clinicians in the dilemma of placing their patient at risk of another episode of NMS or eliminating a mainstay of pharmacological management of psychotic disorders. As all antipsychotics have been linked to NMS, switching agents also do not necessarily reduce risk of recurrence, although subsequent prescribing of antipsychotics for patients upon recovery from NMS should favor lower D_2 blocking agents (e.g., quetiapine, clozapine) to mitigate the risk of recurrent NMS. Bromocriptine and amantadine are dopamine agonists that have been used to counteract the D_2 blockade in NMS, but bromocriptine increases the risk of SS and may worsen psychotic symptoms. Amantadine may cause delirium in older patients. Intermediate-acting benzodiazepines may be necessary to control severe agitation, despite the risk of exacerbating or prolonging delirium.

For SS, the first step in treatment is eliminating the offending drugs or at least minimizing the doses; the lower the serotonergic burden, the faster the recovery. Even when the precipitating agent appears to have been identified (e.g., SS after tramadol started for chronic pain in a patient taking duloxetine for depression and diabetic neuropathy), both agents should be stopped or reduced to hasten recovery, despite the risk of serotonin withdrawal. Cyproheptadine, a serotonin ($5\text{-}HT_{2A}$) and histamine (H1) antagonist used to treat the symptoms of carcinoid syndrome, has been shown in case reports to mitigate the symptoms of SS, provided the patient is able to take per os. Positron emission tomography scans have demonstrated that cyproheptadine 4 mg and 6 mg every 8 hours can block 85% and 95%, respectively, of $5\text{-}HT_{2A}$ receptors in the prefrontal cortex [70]. While it has the potential to prophylactically protect against SS in patients in whom multiple serotonergic agents are essential [70], there are no randomized trials to verify its efficacy, and its anticholinergic properties render it problematic for older patients.

In both NMS and SS, vital signs should be monitored frequently. Severe hyperthermia (> 40 °C) can induce seizures and irreversible brain damage and requires aggressive external cooling with ice packed around the patient or a cooling blanket. Severe muscle rigidity induced by involuntary isotonic muscle contractions is found in both conditions, but can be especially severe in NMS. The tonic muscle contractions lead to rhabdomyolysis, which, in turn, can precipitate acute renal failure because of the renal tubular toxicity of the myoglobin released into the circulation by damaged muscle. Muscle relaxants therefore are needed when muscle rigidity is present. Dantrolene is more effective than benzodiazepines and is associated with a relatively lower risk of inducing delirium. Serum electrolytes and a complete blood count should be obtained in all patients and serially monitored. A creatine kinase level (CK) should be monitored. CK >1000 U/L (16.7 μkat/L) reflects muscle injury severe enough to induce renal tubular injury. During rhabdomyolysis, intravascular volume depletion exacerbates the renal tubular injury. While the CK remains > 1000 U/L (16.7 μkat/L), intravenous fluids should be infused at a rate of 150–200 ml/hour to generate a urine output > 100 cc an hour to dilute and wash out the myoglobin. In older patients, this infusion rate can lead to significant volume overload and heart failure and therefore may require the concurrent use of diuretics. In severe rhabdomyolysis, alkalinization of the urine can reduce the binding of myoglobin to the renal tubules and reduce the risk of renal failure.

Teaching Points

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are rare but potentially life-threatening reactions to antipsychotics and serotonergic drugs, respectively. In milder cases, the symptoms can be mistaken for other age- and disease-associated conditions unless considered in the differential diagnosis. NMS is idiopathic and not exposure dependent; rechallenge with any antipsychotic in the future exposes the patient to a 30–50% risk of recurrence. SS, in contrast, is dependent on the total serotonergic burden. Medications from a variety of classes of drugs have serotonergic activity that, when combined with known serotonin agonists like SSRIs and SNRIs, can precipitate serotonin syndrome. For both conditions, treatment is supportive after discontinuation of the offending medications.

QTc Prolongation and Risk of Ventricular Arrhythmias

The corrected QT interval (QTc) lengthens with age, so that drugs that prolong this interval can cause a dangerously long QTc interval that predisposes the patient to potentially life-threatening ventricular tachycardia that begins as *torsades de pointes* (TdP), named for the apparent "pivoting" of the tachycardia around the baseline and also characterized by variations in the amplitude of the QRS complex (Fig. 5.5). The threshold

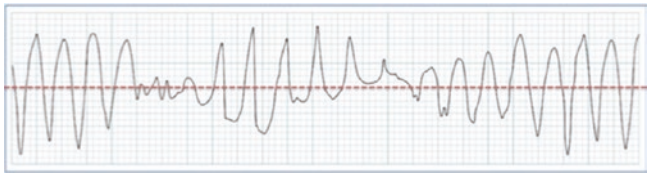

Fig. 5.5 Torsades de pointes arrhythmia

of QTc that should raise concern about TdP risk is > 450 milliseconds in men and > 470 milliseconds in women. In addition to congenital QTc syndrome, a prolonged QTc can be seen in bradycardia and with electrolyte abnormalities (hypocalcemia, hypokalemia, and hypomagnesemia). Both hypokalemia and hypomagnesemia can result from the chronic use of loop diuretics and thus can be seen in patients with heart failure; heart failure with reduced ejection fraction (HFrEF) independently increases the risk of ventricular tachycardia.

Although case reports suggest an association between QTc prolongation and phenothiazines, haloperidol and its cousin, droperidol, and the second-generation antipsychotics (risperidone, quetiapine, ziprasidone, and clozapine), epidemiologic evidence has not shown a consistent, predictable class effect of these drugs. The actual incidence of TdP-associated sudden death is very low [71]. Of the atypical antipsychotics, olanzapine and aripiprazole have the least effect on QTc. Fluoxetine and citalopram have been linked to QTc prolongation, with citalopram doing so in a dose-dependent manner, leading to a recommendation that 20 mg of citalopram be the maximum safe dose in older patients. Although escitalopram has not been clearly linked to QTc prolongation, the fact that it is the s-enantiomer of citalopram lead Health Canada to advise caution when used in older patients [72]. Sertraline and paroxetine are associated with a lower degree of risk. Among older-generation antidepressants, tricyclics as a class can cause TdP when taken in overdose, but their relationship to QTc prolongation at therapeutic levels remains unclear [73].

A number of common medications are known to prolong the QTc and independently increase the risk of TdP and sudden death and are therefore relatively contraindicated for co-administration with QTc-prolonging psychotropic medication. Of importance are the macrolide antibiotics (erythromycin, clarithromycin, and azithromycin), multiple antiarrhythmic medications (amiodarone, dronedarone, sotalol, procainamide, quinidine, disopyramide), chloroquine (an antimalarial commonly used as an immunomodulator), the antihistamine astemizole, the commonly employed antiemetic ondansetron, and methadone. There are case reports of the cholinesterase inhibitors, donepezil and galantamine, causing QTc prolongation, but the association is not definitive. However, citalopram is commonly prescribed for depression or the management of dementia-associated agitation in patients with major neurocognitive disorders who are taking a cholinesterase inhibitor, so awareness of the association is important.

General guidelines for prescribing a QTC-prolonging medication are provided in Fig. 5.6.

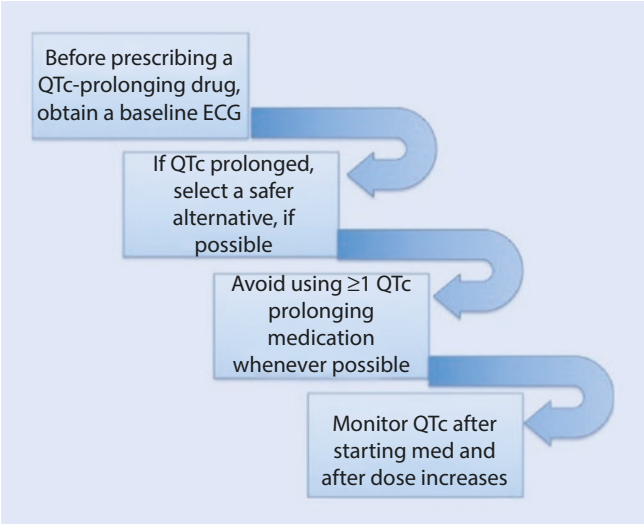

Fig. 5.6 Guidelines for prescribing drugs that prolong the QTc

Teaching Points

All classes of antipsychotics and some SSRI antidepressants have been linked to prolongation of the corrected electrocardiographic QT interval (QTc), which in turn has been associated with an increased risk of torsades de pointes, ventricular tachycardia, and sudden death. Among the antipsychotics, aripiprazole and olanzapine are believed to have the least relative effect on the QTc, and among the SSRI antidepressants, sertraline and paroxetine appear to have a lower relative risk of QTc prolongation. Because of citalopram's dose-dependent effect on the QTc, the maximum recommended daily dose in older adults is 20 mg. Multiple commonly prescribed medications affect the QTc, necessitating a careful medication reconciliation before prescribing a QTc prolonging drug. Whenever possible, only one QTc-prolonging drug should be prescribed at one time.

Selective Serotonin Reuptake Inhibitors and Risk of Bleeding

Serotonin reuptake inhibitors can reduce platelet serotonin by up to 90%, potentially compromising hemostasis by inhibiting an important mediator of platelet aggregation [65]. SSRIs have been associated with an increased risk of gastrointestinal bleeding [74] and add to the risk associated with concomitant use of aspirin and nonsteroidal anti-inflammatory drugs. SSRIs have also been associated with an increased risk of stroke from subarachnoid hemorrhage [75]. SSRIs therefore should be prescribed cautiously in patients taking an anticoagulant or antiplatelet agent for comorbid conditions such as deep venous thrombophlebitis, atrial fibrillation, carotid artery disease, and coronary heart disease.

Teaching Point

The inhibition of serotonin by SSRIs affects platelet aggregation and potentially increases bleeding risk. Care must be exercised when considering a SSRI (and presumably also a SNRI) in patients with a history of gastrointestinal bleeding, intracranial hemorrhage, or taking other platelet inhibitors or an anticoagulant.

5.2 Case Studies

The following case-based studies reflect issues of polypharmacy in older adults and the specific adverse drug events that need to be actively considered when prescribing psychotropic medications, as well as the communication among prescribing clinicians and the active use of pharmacy profiling that are recommended to facilitate safe medication prescribing and monitoring.

5.2.1 Case 1

Case 1 History

Ms. G., a 67-year-old woman, was brought to the emergency department by paramedics after a shop owner called the police about a woman in a wheelchair who was acting strangely. When found, she was seated in her wheelchair outside in the cold rain and disoriented, agitated, and incoherent. In the emergency department her initial vital signs were blood pressure 136/101 mm Hg, heart rate 121 beats/minutes and regular, respiratory rate 20 breaths/minutes, and O_2 saturation 98% on room air. Her temperature was 37.2 °C (98.9 ° F). Because of her agitation, she was given haloperidol 5 mg IV x 1, followed later by midazolam, 0.5 mg IV, and lorazepam 2 mg IV, which made her somnolent but arousable. Her past medical history, per the electronic medical record (EMR), was notable for a history of chronic obstructive pulmonary disease, epilepsy, osteoarthritis, a "psychiatric illness" believed to be bipolar disorder, hypertension, and severe osteoarthritis, which led her to rely on a wheelchair. However, her last EMR entry was 14 months earlier. Per her records, she lived in an apartment with a roommate. She had a 25+ pack-year smoking history and a history of ethanol abuse. Her outpatient medications were listed as clonazepam 0.5 mg twice daily, amlodipine 10 mg daily, losartan 100 mg daily, and citalopram 20 mg daily. Because of altered mental status, computerized tomography of the head was obtained and was negative except for mild periventricular white matter changes. After stabilization in the emergency department with placement of an intravenous line delivering 5% dextrose in normal saline at 125 ml/hour, she was admitted to the medical service.

On examination, she was a chronically ill-appearing, lethargic, disheveled woman appearing older than her listed age. She was flushed throughout her body. She was febrile to 38.2 °C, blood pressure 107/43 mm Hg, heart rate 125 beats/minutes and regular, respiratory rate 28 breaths/minutes, and

O_2 saturation 98% on room age. Her oral mucus membranes were dry, heart exam revealed regular rate and rhythm, and her lungs were clear to auscultation. On neurological examination, she had diffusely increased muscle tone, greater in the lower extremities. When she held her arms out straight, there was a fine hand tremor. Her biceps and ankle reflexes were 3+ with 16-beat clonus of the right ankle and sustained clonus of the left ankle when flexed abruptly. She had 20° flexion contractures of both knees, and there was marked involuntary resistance to further flexion. On mental status examination, she was arousable only with deep sternal rub and would follow one-step commands only for a few seconds before drifting off to sleep. She could not provide a coherent history.

Her alcohol level was 44 mg/dL (9.52 mmol/L). Her complete blood count was notable for a hemoglobin of 9.7 g/dL (97 g/L); her white cell count was within normal limits. Her blood urea nitrogen was low at 6 mg/dL (2.14 mmol/L), and her creatinine was 0.6 mg/dL (53 µmol/L). Her urinalysis was a dirty specimen with lots of squamous epithelial cells and many bacteria per high-power field; urine dipstick was 1+ nitrite positive and heme positive without red cells. Urine was sent for culture and sensitivity. A gas chromatography toxicology screen returned 12 hours after admission, positive for citalopram and methamphetamines.

The following morning, the patient was more arousable, although still delirious based on the Confusion Assessment Method. Her temperature was 38.5 °C (101.3 °F) and blood pressure 162/94 mm Hg. Her muscle tone remained increased, especially in the lower extremities, but was improved from the night before. Because of her fever and "dirty" urine, she was empirically given 1 g of ceftriaxone for a presumptive urinary tract infection.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. Was the management of her agitation appropriate?

? Question 2. What is her presumptive diagnosis and what is the appropriate management going forward?

Case 1 Answers

Case 1 Answer 1 (Question 1—Was the management of her agitation appropriate?)

The patient's was reportedly uncooperative, yelling, and resisting care in the emergency department. She was given a "cocktail" consisting first of haloperidol, followed by a short- and then intermediate-acting benzodiazepine. Based on her examination findings of increased tone, tremor, borderline hyperreflexia, and clonus, serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) should have come to mind. Her core temperature was within normal limits, but she had been outside in the cold rain and might have been expected to be relatively hypothermic. Her blood pressure was low, but she was also volume depleted. SS was suggested by the prescription of citalopram, a serotonergic antidepressant. She had a history of psychiatric illness and had not been seen at the medical center for over a year. Presence of an antipsychotic could not be excluded without a toxicology screen. Since NMS could not be ruled out as the cause of her neurological and motor findings, it was inappropriate to empirically administer haloperidol. Although benzodiazepines could exacerbate her confusion and confound monitoring of her mental status, they were appropriate tranquilizers in this setting. Moreover, they act as mild muscle relaxants and could help mitigate her increased motor tone, although likely were not given for that reason. Benzodiazepines, however, are second-line muscle relaxants after dantrolene. One further clue that this was SS and not NMS was her reflexes. She showed 3+ reflexes at the ankles, which is brisk but not abnormal. In older adults the ankle reflexes are commonly diminished, so 3+ can be considered borderline hyperreflexic. Hyperreflexia helps distinguish SS from NMS, in which the reflexes typically are suppressed. However, on early presentation this distinction should not have been considered definitive and haloperidol ideally should not have been administered in the emergency department.

Case 1 (Continued)

After the presumptive diagnosis of serotonin syndrome made in the morning after admission, a creatine kinase (CK) level returned at 3660 U/L. The infusion rate of the normal saline was increased to 200 ml/hour to increase her urine output to approximately 150 ml/hour. She was monitored every 4 hours for signs and symptoms of fluid overload, and after 16 hours of forced diuresis, she became dyspneic and was found to have an increased respiratory rate to 36 breaths/minutes, jugular venous distention, and crackles 1/3 up her posterior lung fields. A single dose of intravenous furosemide 40 mg was administered with improvement in her symptoms. Her urine culture at 24 hours showed no growth. Her creatinine had doubled from 0.6 mg/dL (53 µmol/L) to 1.2 mg/dL (106 µmol/L).

On hospital day 3, she was more alert, conversant, and cooperative, but remained disoriented to time and place. Her clonus was reduced to 4 beats, her motor tone was minimally increased, her ankle reflexes were 1+, and her tremor had disappeared. Normal saline was continued, but the rate was reduced to 100 cc/hour when her CK level dropped to 1820 U/L. By hospital day 4, her CK dropped below 1000 U/L and the IV infusion was stopped. Her serum creatinine remained stable at 1.2 mg/dL (106 µmol/L). A psychiatric consultation found that she had decisional capacity, with a Mini Mental State Exam score of 28/30, missing only the day of the week and the day's date. They confirmed that she had been taking citalopram 10 mg daily as an outpatient and recommended restarting the SSRI before she developed withdrawal symptoms. Although the medical team strongly recommended discharge to a skilled nursing facility for rehabilitation, she insisted on being discharged back to her

apartment. The team asked the social worker to report her to Adult Protective Services for possible self-neglect. She was discharged home on hospital day 5 with a creatinine trending downward at 0.9 mg/dL (89 μmol/L).

Case 1 Answer 2 (Question 2—What is her presumptive diagnosis and what is the appropriate management going forward?)

The constellation of signs and symptoms plus her toxicology screen confirm the diagnosis of moderately severe serotonin syndrome. The formal diagnosis was not made until early in the second hospital day due to the delay in obtaining the results of the toxicology screen. However, the presence of severe muscle rigidity and heme positivity without hematuria should have raised immediate concern for rhabdomyolysis. A creatine kinase level should have been obtained much earlier and muscle relaxants started empirically. Cyproheptadine, a serotonin (5-HT_{2A}) and histamine (H1) antagonist, would have been the preferred choice, although as an antihistamine, it has anticholinergic side effects that could have contributed to Ms. G.'s delirium. Dantrolene could have been used for the muscle spasms, which carries a lower delirium risk than diazepam, which, for muscle relaxation, would have required doses that would have significantly sedated her and clouded evaluation of her mental status. The patient's fever easily could have been caused by the rhabdomyolysis. Her initial IV fluid rate should have been higher, given her volume depletion and need to prevent renal tubular toxicity by myoglobin.

Case 1 Analysis This case illustrates that serotonin syndrome can easily be missed, with the symptoms in Ms. G. masked by agitation and limited cooperation, resulting in her motor findings initially being overlooked. Her initial agitation was attributed to her underlying psychiatric illness and later to her use of amphetamines, although agitation is a key component of serotonin syndrome (Fig. 5.4). Even when her motor findings were noted, the team failed to suspect rhabdomyolysis until the following morning, at which time appropriately aggressive forced diuresis was initiated. However, by that time myoglobin-induced acute kidney injury already had taken place. Cyproheptadine arguably should have been given, although her motor rigidity and rhabdomyolysis improved without it. Her serotonin syndrome likely was precipitated by recreational methamphetamine use, adding to the serotonergic agonism of her SSRI (Table 5.7).

5.2.2 Case 2

Case 2 History

Ms. A. was a 72-year-old woman with a history of left non-small cell lung carcinoma with brain metastasis. She had received combination therapy with chemotherapy and cranial radiation and was clinically stable without apparent tumor recurrence. She was a former heavy smoker, now abstinent for 10 years. Medical history also included coronary artery disease with congestive heart failure, hypertension, hyperlipidemia, hyperthyroidism, and recurrent urinary tract infections. Shortly after diagnosis of the CNS metastatic spread of lung cancer, she developed major depressive disorder and was treated with citalopram, 20 mg per day. Before starting citalopram, her serum sodium level was 130 mEq/L (mmol/L) (normal, 135–145 mEq/L [mmol/L]); pretreatment MoCA was 27 out of 30, and Hamilton Depression Inventory score was 20, consistent with a diagnosis of major depressive disorder. She had sleep and appetite disturbances and mild difficulties with concentration, but had no evidence of psychotic symptoms or suicidal ideation.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What surveillance is indicated for mild hyponatremia (without delirium) in a patient on SSRI treatment?

Question 2. What can explain the presentation of delirium and hyponatremia in this patient?

Question 3. What medication options are considered for depression in a patient who has recovered from SSRI-associated SIADH?

Case 2 Answers

Case 2 Answer 1 (Question 1—What surveillance is indicated for mild hyponatremia (without delirium) in a patient on SSRI treatment?)

Continuing periodic monitoring of her electrolyte panel and cognitive status is indicated in the context of depression management. Within 1 month of starting citalopram, Ms. A. developed cognitive impairment with reduced level of consciousness and was acutely unable to accomplish activities of daily living. Due to acute mental status changes in a cancer patient, she was admitted to the hospital for comprehensive evaluation. Magnetic resonance imaging of her brain showed decreased size of the heretofore documented metastatic lesions, without evidence of edema. She had mild cortical atrophy and white matter disease but no evidence of stroke or any other acute CNS process. Serum sodium was 121 mEq/L(mmol/L); the rest of the renal panel was normal. Serum osmolality was 268 mOsm/kg, urine osmolality was 472 mOsm/kg, and urine sodium was 131 mEq/L (mmol/L). Liver-associated enzymes were normal, as were TSH, B_{12}, calcium, and vitamin D levels.

A psychiatric consultation-liaison service examination revealed mild somnolence (RASS −1; drowsy on approach with prompt full arousal to speech with sustained eye contact), blunted and perplexedly dysphoric affect, no suicidal/homicidal ideations, and no psychosis. Thought processes

were mildly perseverative with some tangentially. MoCA score was 18 out of 30, with deficits in recall memory, orientation, and concentration most prominently noted. The rest of the psychiatric consultation was unremarkable.

Case 2 Answer 2 (Question 2—What can explain the presentation of delirium and hyponatremia in this patient?)

Ms. A. was diagnosed with delirium due to SIADH/hyponatremia, attributable to citalopram, with additional risk factors of lung cancer and CNS metastatic disease. Citalopram was immediately discontinued, and electrolyte levels and volume status were monitored daily. Her level of consciousness and cognitive function gradually improved, with normal level of consciousness (RASS 0; alert, calm) and improved MoCA (score of 25, with residual deficits in recall and concentration) within 6 days. She was discharged on hospital day 7, with a serum sodium level of 130 mEq/L (mmol/L) and renormalized serum and urine osmolality. Her mood continued to be mildly depressed, and she was prescribed mirtazapine 7.5 mg po qhs with a plan for monitoring of renal panels every 2 weeks for 3 months for surveillance for possible recurrence of SIADH.

Case 2 Answer 3 (Question 3—What medication options are considered for depression in a patient who has recovered from SSRI-associated SIADH?)

Most antidepressants have been at least anecdotally associated with SIADH, though the risk appears most dramatic for SSRI and SNRIs. Based on the current state of the literature, these classes of antidepressants are likely best avoided in these patients, with other antidepressants used, but with continued vigilance for recurrence of SIADH.

Case 2 Analysis The syndrome of inappropriate antidiuretic hormone (SIADH) is associated with systemic demographic and illness factors (e.g., increased age, malignancy, pulmonary disease, brain lesions) and medications (e.g., thiazide diuretics, vincristine, cyclophosphamide). Many classes of psychotropic medications have been associated with SIADH (e.g., SSRIs, SNRIs, mirtazapine, carbamazepine, antipsychotics, tricyclic antidepressants, monoamine oxidase inhibitors). With sufficiently low serum sodium, patients may develop delirium as the presenting syndrome. Clinical evaluation reveals hyponatremia, normal blood urea nitrogen and creatinine levels, a normal volume status, decreased serum osmolality, and increased urine osmolality. If sodium levels are 120–134 mEq/L (mmol/L), reversal of the provocative stimulus, fluid restriction, and monitoring of electrolyte and fluid status may be adequate to reverse hyponatremia. More severe hyponatremia may require cautious administration of hypertonic saline, with or without a loop diuretic to remove excess salt and water. Excessively rapid correction of severe hyponatremia may result in central pontine myelinolysis.

In this patient's case, the SSRI-associated SIADH risk was potentiated by lung cancer with CNS metastatic disease. The precipitous drop in sodium level shortly after SSRI initiation and a similarly brisk return toward eunatremia after SSRI discontinuation correlated with onset and later resolution of her delirium. For continued antidepressant treatment, choice of a non-SSRI antidepressant (in this case mirtazapine or bupropion) may minimize risk of SIADH recurrence, but continued vigilance (especially during the first 3 months of the new treatment) is needed for surveillance. At any time during antidepressant treatment, a presentation of delirium mandates immediate assessment of serum sodium, serum and urine osmolalities, assessment of fluid status, and search for other possible causes of SIADH.

5.3 Key Points: Pharmacotherapy, Safe Prescribing and Adverse Drug Events

- Age-related changes in drug metabolism and action increase the vulnerability of older patients to adverse drug reactions.
- Polypharmacy, arising from age-associated multimorbidity, adds to the risk of adverse drug events (ADEs), as does the prescription of potentially inappropriate medications (PIMs).
- Often overlooked are important interactions between drugs and over-the-counter supplements and food-drug interactions.
- Older adults are particularly vulnerable to complications from anticholinergic drugs, which span numerous classes of medication and include numerous psychotropic medications.
- Lithium continues to be prescribed to older adults but is associated with an increased risk of toxicity because of age-related changes.
- Falls and fall risk increase with age and have also been associated with psychoactive drugs, especially antidepressants.
- Other adverse reactions to which older patients are more susceptible include QTc prolongation and risk of ventricular tachycardia, hyponatremia from drugs inducing the syndrome of inappropriate antidiuretic hormone (SIADH), and bleeding from serotonergic drugs.
- Neuroleptic malignant syndrome and serotonin syndrome, although rare, are life-threatening conditions that can easily be missed in their early stages because the symptoms mimic other conditions commonly seen in older patients.
- Tables 5.8 and 5.9 provide a summary of the common adverse drug events by class and the key points to remember regarding psychotropic medications for the older adults.

Table 5.8 Summary of common adverse drug events by class of psychotropic medication

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
Antipsychotics	Phenothiazines	EPS/parkinsonism	Parkinson disease and other parkinsonian disorders (e.g., Lewy body disease)	Avoid antipsychotics with higher D_2 receptor potency to minimize risk of drug-induced parkinsonism (D_2 receptor potency: risperidone > olanzapine > quetiapine)
		Anticholinergic effects	(See conditions listed for anticholinergic effects of tricyclics)	Concomitant use of other anticholinergic drugs
	Haloperidol	Orthostatic hypotension	Parkinsonian disorders	High incidence of autonomic dysfunction in Parkinson disease
			Known orthostatic hypotension	Caution in patients on antihypertensives
	Atypical antipsychotics		Pre-existing orthostatic hypotension	Orthostatic hypotension affects ~1/3 of patients ≥ age 75
		Seizures		May lower seizure threshold
		Excess sedation		May contribute to falls and fall-related injuries
		QTc prolongation	Known QTc prolongation, history of ventricular tachycardia	Use with caution with SSRIs and SNRIs, especially citalopram, as well as with macrolide antibiotics, cardiac medications like amiodarone
		Falls and fall-related injury	History of falls	Use caution when using concurrently with antidepressants, benzodiazepines, anticonvulsants, which increase fall risk
		Glucose intolerance and weight gain	Diabetes mellitus	Concurrent use of mirtazapine may exacerbate weight gain
			Obesity	
Antidepressants	Tricyclics (e.g., amitriptyline)	Anticholinergic side effects	Glaucoma	May precipitate acute, vision-threatening rise in intraocular pressure in narrow-angle glaucoma
			Delirium	Use cautiously with other anticholinergic medications (see Table 5.4)
			Benign prostatic hypertrophy	May precipitate urinary retention
		Increased fall risk	History of falls	
	SSRIs, SNRIs	SIADH	History of hyponatremia	Concurrent use of sodium-lowering medications (e.g., diuretics) or drugs also associated with SIADH (e.g., opioids)
		Increased risk of bleeding	Recent history of intracranial hemorrhage	Avoid or use with caution in patients taking anticoagulant or patients taking platelet inhibitor (e.g., aspirin)
			Recurrent gastrointestinal bleeding	
		Serotonin syndrome		Use with caution with other serotonergic agents
		QTc prolongation	Known QTc prolongation, history of ventricular tachycardia	Use with caution with SSRIs and SNRIs, especially citalopram, as well as with macrolide antibiotics, cardiac medications like amiodarone.

(continued)

Table 5.8 (continued)

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
	Paroxetine, fluoxetine (SSRIs)	Drug-drug interactions		Prolonged half-lives (especially fluoxetine). May interact with drugs metabolized by CYP450 pathway
	Bupropion	Lowers seizure threshold	Active seizure disorder	Use with caution with other drugs which may lower seizure threshold. Concomitant use of SSRI or SNRI increases risk of serotonin syndrome
			Recent intracranial injury or stroke	Period of increased seizure risk
Anxiolytics	Benzodiaz-epines	Sedation	Unsteady gait	Cumulative effect with other CNS depressants
		Increased fall risk	History of falls	
		Cognitive impair-ment	Pre-existing cognitive impairment	
		Delirium	Advanced age	
		Drug dependence	Known benzodiazepine dependence/abuse; known alcohol depen-dence/abuse	Shorter-acting benzodiazepines (e.g., alprazolam) have higher risk of drug dependence
Sedative-hypnotics	Non-benzodiaz-epine, benzodiazepine receptor-binding drugs	Daytime sedation Increased fall risk	Unsteady gait History of falls	Cumulative effect with other CNS depressants
	Zolpidem			
	Temazepam			
	Flurazepam			
	Estazolam			
	Eszopiclone			
	Triazolam			
Mood stabilizers	Carbamazepine	Sedation	Unsteady gait	Narrow therapeutic index; levels may be increased by CYP3A4 inhibitors
		Fatigue	History of falls	Use with caution with other drugs that may lower serum sodium (e.g., SSRIs, diuretics)
		Ataxia		
		Increased fall risk		
		Blurred vision		
		Hyponatremia (SIADH) Hepatotoxicity Blood dyscrasias	History of hyponatremia Liver disease Anemia, neutropenia	
	Valproic acid	Hepatotoxicity	Liver disease	Cumulative effect with other CNS depressants
		Hyperammonemia	Urea cycle enzyme deficiency	

Table 5.8 (continued)

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
		Pancreatitis	History of pancreatitis	
Cognitive enhancers	Cholinesterase inhibitors			
	Donepezil Rivastigmine Galantamine	Gastrointestinal intolerance (anorexia, nausea, diarrhea)		If symptoms resolve after lowering dose or stopping, may not return if rechallenge with same drug or different drug from same class
		Vivid dreams		
		Fatigue		
		Bradycardia (heart rate < 60)		Exaggerates neurocardiogenic dysautonomia seen in Alzheimer disease
		Syncope		Avoid or use with caution when taking drugs which slow heart rate or affect cardiac conduction (beta blockers, digoxin, verapamil)

Adapted from Hirsch et al. [11]

Table 5.9 Summary of teaching points on Adverse Drug Events (ADEs)

Keys to safe prescribing for the older patient
Safe prescribing of psychotropic medication to older patients is especially challenging because of the prevalence of age-associated changes in pharmacokinetics and pharmacodynamics and polypharmacy caused by multimorbidity, increasing the risk of ADEs
All clinicians should be familiar with at least one tool to identify potentially inappropriate medications in the older patient, which are associated with an excessive risk of adverse reactions compared to benefits when safer alternatives exist
All older patients seen in psychiatric consultation require a careful review of their medications and assessment of the risk for drug interactions and side effects before prescribing
Medication review should include over-the-counter medications and unregulated supplements, which can have significant interactions with prescribed drugs
The patient's diet is important and may affect drug absorption, kinetics, and the risk of ADEs
In older adults, adverse events not only can be life-threatening (torsades de pointes, neuroleptic malignant syndrome, and serotonin syndrome), but can lead to injuries, functional impairment, disability, impaired quality of life, and premature mortality (falls and syncope)
Safe prescribing equals prudent prescribing

5.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following antipsychotics has the highest risk of diabetes mellitus?

A. Olanzapine
B. Haloperidol
C. Quetiapine
D. Aripiprazole
E. Risperidone

Answer: A

Whereas all atypical antipsychotics have been associated with the development of the metabolic syndrome, both typical and atypical antipsychotics have been associated with the development of hyperglycemia. Among the given options, olanzapine is associated with the highest risk of diabetes mellitus (statement A) (see ▶ section Antipsychotics and Metabolic Syndrome for further details).

MCQ 2. Which of the following antipsychotics has the highest degree of anticholinergic effect and thus would be problematic in delirium?

A. Clozapine
B. Haloperidol
C. Risperidone
D. Olanzapine
E. Aripiprazole

Answer: A

It is difficult to predict the likelihood of anticholinergic side effects occurring with various doses of antipsychotics. However, the atypical antipsychotics clozapine and olanzapine have significant affinity for the muscarinic receptors, while haloperidol, risperidone, and aripiprazole do not. Therapeutic doses of clozapine, and to a lesser extent olanzapine, are associated with clinically relevant anticholinergic activity; therefore, the correct answer is A.

MCQ 3. Which of the following mood stabilizers used for bipolar disorder has a risk of hyperammonemia, which may present as delirium?

A. Lithium
B. Carbamazepine
C. Oxcarbazepine
D. Olanzapine
E. Valproate

Answer: E

Although cases of carbamazepine and olanzapine-induced hyperammonemia have been reported [76, 77], oxcarbazepine did not show significant effects on the increase in blood ammonia level. Lithium is known to cause renal, not hepatic dysfunction. However, the use of valproate frequently results in hyperammonemia and delirium. Valproate-induced hyperammonemic encephalopathy and delirium may even occur in patients with normal liver function, despite normal doses and serum levels of valproate. Therefore, statement E is correct.

MCQ 4. Which of the following SSRIs is most likely to induce problematic drug-drug interaction?

A. Sertraline
B. Escitalopram
C. Citalopram
D. Fluoxetine

Answer: D

Of the SSRIs, fluoxetine is generally not recommended for treatment in older adults because of its long half-life, prolonged side effects, and drug-drug interactions. Although not included as an answer option, paroxetine is also generally not recommended in older adults as it has the greatest anticholinergic effect of all the SSRIs, similar to that of some tricyclics (desipramine and nortriptyline). The SSRIs considered to have the best safety profile in older adults are sertraline, escitalopram, and citalopram, which have the lowest potential for drug-drug interactions based on their cytochrome P450 interactions, whereas fluoxetine, paroxetine, and fluvoxamine have higher risks of drug-drug interactions. Therefore, statement D is the correct answer.

MCQ 5. What mechanism is causative of the orthostatic hypotension seen with quetiapine?

A. Dopamine-4 blockade
B. Dopamine-2 blockade
C. Histamine-1 blockade
D. Alpha-2 agonism
E. Alpha-1 blockade

Answer: E

Quetiapine has affinity for D_2, 5-HT_{1A}, 5-HT_{2A}, H1, and alpha-1 receptors. Alpha-1 antagonism can cause orthostatic hypotension (statement E). Quetiapine is a strong antagonist at histamine H1 receptors, which is linked to sedative effects and weight gain, not orthostatic hypotension. The other mechanistic options (dopaminergic, alpha-2 agonistic) do not cause orthostatic hypotension.

MCQ 6. Which of the following is a common metabolic complication of lithium?

A. Hyperthyroidism
B. Hypothyroidism
C. Hyperparathyroidism
D. Hypoparathyroidism
E. Glucose dysregulation

Answer: B

Chronic administration of lithium can commonly induce hypothyroidism and less commonly hyperthyroidism. Lithium use has also been linked to hyperparathyroidism, but not hypoparathyroidism. Lithium therapy has not been associated with glucose dysregulation. Therefore, the correct answer is B.

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