Psychopharmacology Principles

3

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3.1 Background

This chapter aims to cover general principles of geriatric psychopharmacology as they may apply to the on-call primary care clinician or psychiatrist. This chapter limits the "clinical encounter" to telephone calls where a face-to-face mental status examination of the patient and access to complete medical records is not possible. Please refer to Chap. 10 for medication treatment of specific psychiatric complaints and Chap. 12 for detailed coverage of chief adverse side effects of psychotropic medications.

3.2 Basic Principles of On-Call Geriatric Psychopharmacology

Table 3.1 summarizes some basic principles of using psychiatric medications in the on-call setting. While this is not comprehensive, the authors distilled some of the basic rules and mental shortcuts based on their collective clinical experience, citing

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Table 3.1 Basic principles of on-call geriatric psychopharmacology (AVOID)

Avoid prescribing medications when possible	Time limit the on-call physician order for a medication, especially for high-risk medications such as benzodiazepines and hypnotics Avoid drug-drug interactions when starting a new medication
Verify medications actually taken	Adjust timing or the dosing of current medications before adding new medications
Optimize current medications and medication dosages	Avoid treating the side effects of one medication with another agent Adjust timing or the dosing of current medications before adding new medications Ensure medications are given a good trial – "start low, go slow, but go all the way" Take advantage of desired side effects such as sedation and weight gain
Identify the most effective mode of medication delivery	In acute agitation, consider appropriate modes of drug administration When indicated, consider checking serum levels of medications for clinical efficacy and medication adherence
Diagnose correctly and determine the target symptoms	Use the diagnosis to guide medication selection and titrate to target dose Determine the underlying etiology of symptoms before starting medications Many symptoms and behaviors can be reversible without required medication

relevant empirical evidence as much as possible. We proposed the following five clinical pearls with the acronym AVOID.

3.2.1 *Avoid* Prescribing a Psychiatric Medication Without Clear Indication Whenever Possible

Pharmacotherapy can be challenging in geriatric patients due to age-related changes in pharmacokinetics and pharmacodynamics and high rates of medical comorbidities, all of which lead to increased risks of polypharmacy, drug-drug interactions, and adverse drug events [1]. Nearly every psychotropic medication is listed in the American Geriatrics Society Beers Criteria, as each class of psychotropic medication has substantial risks of harm in geriatric patients [2]. Coupled with the limitations of the on-call clinical encounter mentioned above and the tenet of the Hippocratic Oath to "first do no harm," on-call clinicians should avoid prescribing new medications for geriatric patients as much as possible. Since the clinical diagnosis becomes ever more elusive without a clinical examination and complete access to medical records, medication indication is more likely to be based on second-hand reports of symptoms rather than on a clear clinical diagnosis. Should a medication be prescribed, it should be initiated for a time-limited course and with a clear monitoring plan to assess for drug-drug

interactions, medication adverse events, and effectiveness. This monitoring plan should also ensure reevaluation of the patient before continuing medication for a longer trial, ideally with an inpatient follow-up the following day or a follow-up outpatient visit within 1–2 weeks.

3.2.2 *Verify* Medications Actually Taken

A complete medication review with information about medications that have actually been taken in the last 24–72 h is imperative. Regardless of setting, patients often do not take all their medications exactly as they have been prescribed and instructed. Missed doses can results from patients with cognitive impairment forgetting to take their medications, hospitalized patients being too busy getting a medical procedure at the time medications are due, or nursing home patients being already drowsy at the time of medication administration. Before adding a new medication, first review with the nursing staff, caregivers, and patients the current medication administration. Consider adjusting the timing or the dosing of the current medications to help address reported symptoms.

3.2.3 *Optimize* Current Medications and Dosages

3.2.3.1 Reduce Medications Before Adding a Medication

In the USA, 50 % of Medicare beneficiaries take five or more medications and polypharmacy is a well-known problem in geriatric patients [3]. It is especially important to review recently added medications to determine if any new symptoms are due to a medication adverse event. Avoid treating the side effects of one medication with another medication. Instead, consider decreasing dose to reduce side effects or find a better-tolerated alternative.

3.2.3.2 Ensure Medications Are Given a Good Trial

While the adage of "start low and go slow" is time tested and wise guidance, clinicians must also avoid starting too low and going too slow and ensure they "go all the way." Medications such as benzodiazepines can exhibit a J-curve phenomenon where low doses can be associated with a paradoxical disinhibition or agitation, and higher doses can produce the necessary sedation to manage acute agitation and physical aggression [4]. While risk factors for benzodiazepines-related paradoxical reaction remain poorly understood [5], we know from clinical experience that patients with occult alcohol use disorder are at high risk since they have developed tolerance for alcohol (through activity on the GABA receptors), and therefore smaller doses of benzodiazepines are more likely to cause disinhibition (similar to having an "alcohol buzz").

Another common geriatric psychiatry prescribing adage is to utilize the potential benefit of medication side effects. For example, the sedation and weight gain side effects of mirtazapine are frequently used to treat insomnia and weight loss.

Nevertheless, low doses of multiple concomitant medications without achieving target dose range contribute to problematic polypharmacy. Similarly, "slow" titration of some medications that are needed to produce the clinical effects during the on-call settings will lead to undertreatment. The consequence of undertreatment of acute agitation and physical aggression could potentially result in physical injury to the patient, staff, and caregivers.

3.2.4 *I*dentify the Most Effective Mode of Medication Delivery

Once a medication is prescribed, it is important to ensure that the patient receives the desired dose. Often there can be delays in the drug actually being delivered to the patient due to insurance coverage, drug availability, or delay in drug administration (which can be common in long-term care settings). In truly emergent situations, such as acute agitation, it is rare that oral pill or tablet administration will be accepted by the patient; thus, alternative modes of delivery should be considered. Medication injection, liquid, orally dissolving tablets, crushed medications with food or beverage, and topical formulations are potential alternatives. When in doubt, consider checking serum levels of antidepressants or antipsychotics, and when indicated, check serum levels of valproic acid, lithium, or carbamazepine [6]. Although drug levels may not necessarily correlate with clinical efficacy, getting the serum drug level can be helpful in monitoring medication adherence.

3.2.5 *D*iagnose Correctly and Determine the Target Symptoms

Use the diagnosis to guide medication selection and titrate to target dose. Many geriatric patients have cognitive impairment and are unable to fully express their needs or feelings. Various "unmet" needs such as environmental changes, unfamiliar caregiver, sitting in a soiled diaper, or uncontrolled pain can cause agitation. It is important to ask about these factors and determine the underlying etiology of symptoms before starting psychopharmacotherapy. Many of these symptoms and behaviors can be reversed without requiring medication [7].

3.3 Age-Related Changes in Pharmacokinetics and Pharmacodynamics

3.3.1 Pharmacokinetics

In general terms, pharmacokinetics refers to "effects of the body on drugs." This includes medication *absorption*, *metabolism*, *distribution*, *and excretion*. With aging comes reduced medication absorption due to reduced gastric emptying and intestinal

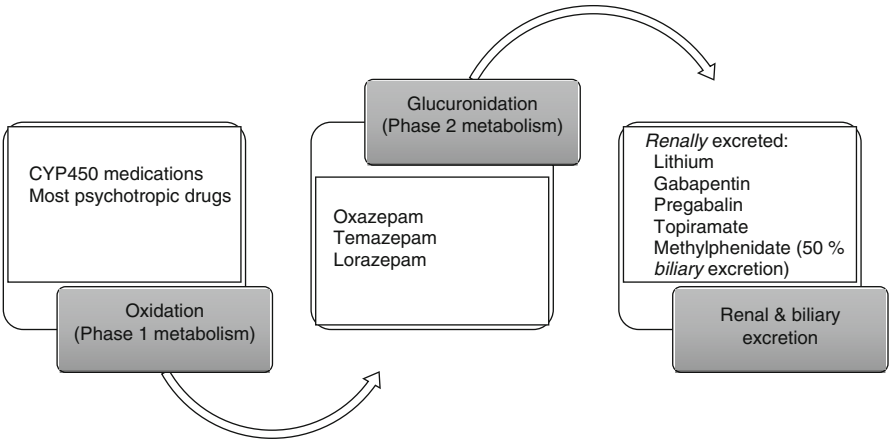

Fig. 3.1 Pathways of drug metabolism and excretion [8–11]

motility and reduced gastric acidity (especially for those taking proton pump inhibitors). Inhibitors of P-glycoprotein in the intestinal wall (e.g., garlic and grapefruit juice and common psychiatric medications such as amitriptyline, fluoxetine, paroxetine, haloperidol, and risperidone) can lead to increased absorption and high serum levels for P-glycoprotein substrates (e.g., amitriptyline, citalopram, paroxetine, venlafaxine, quetiapine) [8]. Overall, reduced absorption due to aging is thought to reduce the time to achieve serum drug levels but not necessarily the magnitude of the levels [9].

Most psychotropic drugs are metabolized by the liver (via phase 1 oxidation and phase 2 glucuronidation) and excreted through the bile or unchanged through the kidney. Other drugs are converted to active metabolites that pass through the kidney (e.g., metabolites of risperidone, bupropion, venlafaxine) [8–11] (see Fig. 3.1). Choosing a psychotropic drug that does not require phase 1 biotransformation or only requires glucuronidation (e.g., lorazepam, oxazepam, temazepam) may be considered in patients with liver disease.

While drug metabolism may be reduced in geriatric patients, genetic polymorphism (especially for various cytochrome P450 enzymes) tends to account for more individual differences than aging. Approximately 8 % of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers, whereas the rest are extensive metabolizers (the majority of individuals). CYP2D6 metabolizing capacity should be considered when psychotropics are coadministered with drugs that inhibit CYP2D6 [12, 13].

The volume of drug distribution is increased for lipophilic drugs (e.g., diazepam) since body fat composition may increase by more than 30 % in geriatric patients leading to increased half-life for lipophilic drugs [8]. However, geriatric patients with malnutrition may in fact have reduced body fat composition [9] so that lipophilic drugs may have lower than anticipated half-lives. Lithium and other water-soluble drugs distributed in total body water can be especially

difficult to manage in renal disease or other medical conditions, which can result in rapid hemodynamic changes (e.g., aggressive diuresis, excessive diarrhea, or vomiting) and which could further result in severe drug toxicity. As the total body water volume decreases, a previously therapeutic drug level can become acutely toxic.

Drug excretion is most significantly affected by reduced glomerular filtration rate (GFR), which can progressively decline by nearly 50 % starting from age 30 to 80 years. Medical comorbidities, such as congestive heart failure and chronic renal disease, are more common in the geriatric patients and further contribute to the effect of an already reduced GFR, which influence the excretion of water-soluble drugs and the metabolites of certain drugs [8, 9].

3.3.2 Pharmacodynamics

Pharmacodynamics refers to "effects of the drug on the body." In general, aging leads to reduced neurotransmitter receptor activity in the brain, and this necessitates lowering of the target doses for most medications. Some important age-related changes include decreased baroreceptor responsivity (leading to increased risk of orthostatic hypotension from alpha antagonists), decreased D_2 receptor density (leading to increased sensitivity to parkinsonism), decreased cholinergic activity (resulting in increased response to anticholinergic agents), increased sensitivity of GABA-aminergic system (leading to increased sensitivity to benzodiazepines), and decreased serotonin reuptake receptor binding and attenuated concentrations in 5-HT_1A and 5-HT_2A receptor density (leading to mood dysregulation and anxiety). Geriatric patients may only need 30–50 % of the serum concentration of benzodiazepines to achieve the same effect compared to younger patients [14]. As for antipsychotics, a recent positron emission tomography study in geriatric patients with schizophrenia confirms previous clinical adage that the dopamine D_2 and D_3 receptor occupancy for optimum antipsychotic effect should be lowered to 50–60 % rather than 65–80 % for younger patients [15]. While less is known about antidepressant receptor physiology, lower target doses are recommended as higher doses are more likely to cause adverse events such as altered heart rate, increased risk of bleeding, and cardiovascular risks such as QT_C prolongation (e.g., citalopram and TCAs). Figure 3.2 summarizes the common age-related and non-age-related pharmacokinetics and pharmacodynamics in the geriatric population [13–15].

3.4 Common On-Call Medications

On-call clinicians will often receive calls about depression, anxiety, agitation, confusion, or insomnia. Table 3.2 lists the most commonly prescribed medications in geriatric patients by drug class for the most common psychiatric presentations that

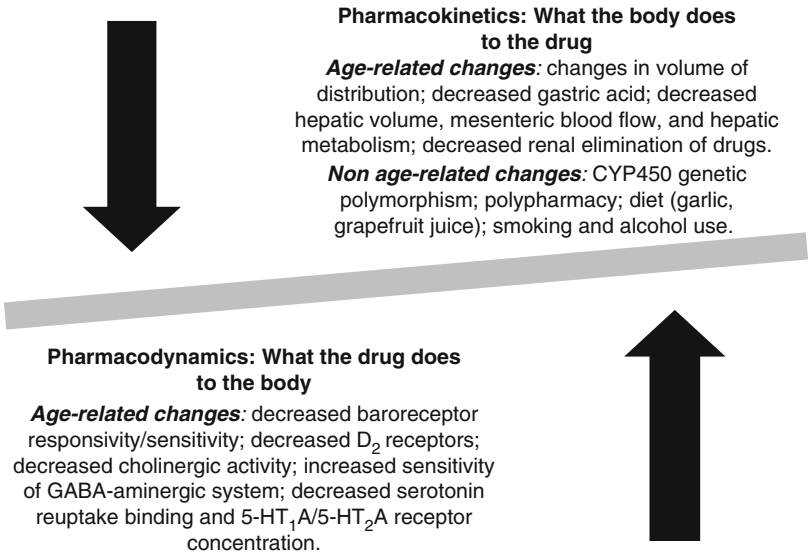

Fig. 3.2 Pharmacokinetics and pharmacodynamics in geriatric patients [13–15]

clinicians are likely to be addressing in the on-call setting [10, 11]. We also list other medications that clinicians may encounter. Although clinicians may not start all these medications while on call, they should be mindful of the adverse effects and possible need to reduce the dosage or discontinue some of these medications. We present below some strategies and interventions for common on-call psychiatric presentations.

3.4.1 Depression and Anxiety

Depression and anxiety should rarely be treated by starting a new medication without an initial face-to-face diagnostic assessment. However, since patients may develop side effects, it is not uncommon to make dose adjustments or switch to a different antidepressant over the phone with proper informed consent. As for anxiety disorders, the most common call is for acute anxiety or panic attack where the caregiver or nursing staff requests a benzodiazepine (such as lorazepam). Most of these calls should be managed by giving specific instructions to the caller to use behavioral interventions (e.g., deep breathing techniques). The use of benzodiazepines in the geriatric patients should be limited due to the many risks (e.g., falls, hip fracture, motor vehicle accidents, cognitive impairment) [16–19], but when absolutely necessary, the preference should be for short-acting agents and agents that avoid first-pass metabolism in the liver and thus have no active metabolites, e.g., oxazepam, temazepam, and lorazepam (also known as OTL for "outside the liver") (see Fig. 3.1).

Table 3.2 Common on-call medications in geriatric psychiatry [10, 11]

Medication (starting dose/day)[a]	Dose adjustments	Side effects and other considerations
Antidepressants		
Citalopram (10 mg) [escitalopram (5 mg)]	Renal impairment: no adjustment necessary Hepatic impairment: citalopram max dose 20 mg/day	SIADH/hyponatremia, risk of bleeding, risk of falls, anorexia Akathisia, headache, agitation, GI complaints, diarrhea, constipation, sexual side effects QTc prolongation warning by the US FDA and Health Canada: risk at dose >40 mg/day, max 20 mg/day in patients over 60 Escitalopram is an enantiomer of citalopram and is twice as potent as citalopram
Sertraline (25 mg)	Renal impairment: no adjustment necessary Hepatic impairment: lower or less frequent dosing	SIADH/hyponatremia, risk of bleeding, risk of falls, anorexia Akathisia, headache, agitation, GI complaints, diarrhea, constipation, sexual side effects
Venlafaxine (37.5 mg XR)	Mild to moderate renal impairment: 25–50 % dose reduction Hemodialysis: 50 % dose reduction Hepatic impairment: 50 % dose reduction	Dose-related increase in BP, nausea, constipation, sexual side effects Useful for pain May need to start at 12.5–25 mg IR for frail elderly SIADH/hyponatremia, risk of bleeding, risk of falls
Duloxetine (30 mg)	Renal impairment: avoid use Hepatic impairment: avoid use	Dry mouth, nausea, constipation, sexual side effects, diarrhea Useful for neuropathic pain, fibromyalgia SIADH/hyponatremia, risk of bleeding
Mirtazapine (7.5–15 mg) [ODT]	Renal impairment: clearance reduced, increase dose slowly Hepatic impairment: clearance reduced, increase dose slowly	Sedation, weight gain, constipation, mild anticholinergic effects Decreased WBC More sedating when used at lowest doses (<15 mg)
Bupropion (37.5–50 mg)	Renal impairment: consider reducing frequency and/or dose Hepatic impairment: consider reducing frequency and/or dose	Dry mouth, agitation, constipation Can lower seizure threshold No data to support use in anxiety disorders

Mood stabilizers		
Lithium (150–300 mg qhs) [liquid]	Severe renal impairment: relative contraindication	Tremor, benign leukocytosis, hypothyroidism, hyperparathyroidism, interstitial nephropathy, diabetes insipidus, neurotoxicity (with overdose/toxicity), cardiac conduction abnormalities, GI upset, acne Pretreatment and monitoring studies: Ca, renal panel, CBC, TSH, eGFR, serum lithium level, ECG
Valproate (125–250 mg qd-bid-tid) [IV, liquid, sprinkles]	Hepatic impairment: use lower dose, contraindicated in severe liver disease Avoid in hyperammonemia, pancreatitis, thrombocytopenia/leukopenia, pregnancy	Headache, tremor, dizziness, ataxia, nausea, vomiting, diarrhea, constipation, reduced appetite, weight gain, somnolence, thrombocytopenia, hepatotoxicity, pancreatitis, hyponatremia, suicidal behavior and ideation, hyperammonemia Pretreatment and monitoring studies: CBC, liver enzymes, serum valproate level Check for serum hyperammonemia if altered mental status (and consider urea cycle enzyme deficiency as cause of hyperammonemia)
Lamotrigine (12.5–25 mg qd-bid)	Hepatic impairment: reduce target dose	Dizziness, sedation, ataxia, confusion, headaches, nausea, vomiting, diarrhea, blurred vision, Stevens-Johnson syndrome Increased risk of suicidal ideation and behavior Start at 12.5 mg when used with valproate to avoid increased risk of skin rash
Antipsychotics	Class-wide side effects: sedation, anticholinergic symptoms, orthostatic hypotension, extrapyramidal symptoms (EPS), akathisia, QTc prolongation, metabolic side effects, acute kidney injury, cognitive decline, cerebrovascular adverse events, and death in patients with neurocognitive disorders. Prominent side effects for specific medications noted below	

(continued)

Table 3.2 (continued)

Medication (starting dose/day)[a]	Dose adjustments	Side effects and other considerations
Haloperidol (0.25–0.5 mg bid) [IM, LAI, liquid]	Renal impairment: no adjustment necessary Hepatic impairment: mild to moderate, no adjustment necessary; severe, use is contraindicated Avoid if QTc >500 ms	EPS: rigidity/parkinsonism, akathisia, dyskinesia Increased mortality
Olanzapine (2.5–5 mg) [IM, LAI, ODT]	No adjustment necessary Avoid in diabetes	Anticholinergic, weight gain, hyperglycemia, hypertriglyceridemia
Risperidone (0.25–0.5 mg qd-bid) [IM, LAI, ODT, liquid]	Renal impairment: reduce dose Hepatic impairment: reduce dose	EPS, hyperprolactinemia
Quetiapine (12.5–25 mg)	Hepatic impairment: reduce dose	QTc prolongation, orthostatic hypotension, anticholinergic, weight gain, hyperglycemia, hypertriglyceridemia
Sedatives/hypnotics		
Lorazepam (0.25–0.5 mg qd-bid) [IM, IV, topical gel, liquid]	Renal impairment: mild to moderate, no adjustment necessary; renal failure, use not recommended Hepatic impairment: mild to moderate, no adjustment necessary; hepatic failure, use not recommended	Elderly are prone to CNS depression even after low doses; start very low initial doses, depending on the response of the patient, to avoid oversedation or neurological impairment Paradoxical reactions (including anxiety, agitation, and excitation) can occur
Trazodone (12.5–50 mg qhs)	Hepatic impairment: caution	Orthostasis, QTc prolongation, priapism
Doxepin (3–6 mg qhs)	Hepatic impairment: 3 mg max dose Renal impairment: 3 mg max dose; contraindicated in patients with urinary retention	Anticholinergic side effects in doses >6 mg/day
Melatonin (1–3 mg qhs)	No adjustment necessary	Drowsiness, headache, dizziness, nausea Indicated for use in jet lag, circadian rhythm sleep disorders, delayed phase sleep disorder

Note: [a]Use lower dose for patients aged >75 or those >60 with frailty and multiple medication comorbidities. *IM* (available as intramuscular formulation for acute treatment; dose often needs reduction as intramuscular is more bioavailable than oral), *LAI* (available as long-acting injectable formulation, check prescriber guide for dose conversion), *ODT* (available as oral dissolving/disintegrating tablet)

3.4.2 Acute Agitation and Physical Aggression

The first-line treatment for behavioral disturbance in patients with major neurocognitive disorders (NCDs) (formerly dementia) is non-pharmacological interventions for the unmet needs [7]. However, medication may be required, especially if the agitated or aggressive behavior is escalating, has not responded to non-pharmacological approaches, and may cause physical injury to or put the patient and/or caregivers at risk of imminent harm. Often a medical work-up is limited as the patient will not provide urine or blood samples nor permit physical examination during an acute episode. In such instances a one-time low dose of antipsychotic, preferably second-generation atypical, is usually a reasonable choice. Careful evaluation of the underlying etiology of the agitation, such as unmet needs, should be conducted once the acute crisis has passed and prior to establishing regular use of an antipsychotic. The use of antipsychotics in patients with major NCDs has been associated with increased risk of cerebrovascular adverse events and death [20–22], which led many regulatory agencies to issue black box warnings. Thus, the use of antipsychotics in patients with major NCDs requires close monitoring for adverse events and a time-limited course with attempts at gradual dose reduction when clinically appropriate. It is important to note that risperidone is approved in Canada for "short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer's type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others" [23] and in the UK for up to 6 weeks for the treatment of "persistent aggression due to moderate to severe" major NCD [24]. Antipsychotics do not have such specific approval for the treatment of NCD-related psychosis or aggression in the USA by the Food and Drug Administration.

3.4.3 Delirium

Delirium management starts with a strategy that attempts discontinuation of new medications (e.g., anticholinergic medication) that could contribute to delirium and identifies and treats the underlying medical condition (e.g., acute infection). Non-pharmacological interventions are of the utmost importance and are addressed elsewhere. The treatment of delirium with short-term (<1 week) use of antipsychotic medications is recommended for patients in acute distress and who may pose danger to themselves or others [25]. Patients with history of Parkinson's disease and major NCD with Lewy bodies may be particularly sensitive to high-potency antipsychotics, which often cause worsening of movement disorder and agitation in these patients. Although the strongest evidence supports the use of clozapine for Parkinson's-related psychosis, quetiapine is often the first-line antipsychotic in patients with Parkinson's disease and major NCD with Lewy bodies for psychosis and for delirium due to ease of administration [26]. Clozapine is almost never used in delirium for various reasons including its anticholinergic effects. Finally, delirium and delirium tremens related to benzodiazepine and alcohol withdrawal

necessitate primary treatment with benzodiazepines and adjunctively with antipsychotics and anticonvulsants when needed [27].

3.4.4 Insomnia

Sleep disturbances are common in geriatric patients, especially with Parkinson's disease and NCDs. Benzodiazepines and hypnotics should be avoided for long-term use given all the risks discussed above. Nonetheless, the inability of the patient to sleep can be very stressful for caregivers to patients with major NCDs who may stay awake with the patient at night and thus precipitate a crisis phone call request to their primary care physician for management of insomnia. It is important to encourage patients to stay active during the daytime, decrease or eliminate naps, get adequate sunlight exposure, limit or eliminate alcohol or caffeine, and improve sleep hygiene. (See Sect. 10.2.8.2, *Management* of the patient with insomnia.) For cognitively intact geriatric patients, referral for cognitive behavioral therapy for insomnia should be a first-line treatment option and a long-term solution to the problem of insomnia [28, 29]. When non-pharmacological efforts have failed, medication choices should include the use of sedating antidepressants (e.g., low-dose doxepin, mirtazapine, trazodone), ramelteon, melatonin, or prazosin (specifically for the treatment of posttraumatic stress disorder-associated sleep disturbance). Avoid antihistamines to treat insomnia in the geriatric patients due to their high anticholinergic burden and risk for side effects. Consider treating underlying anxiety when ruminations and worries appear to be causing sleep-onset insomnia.

Case Vignette Mrs. A was an 82-year-old female with history of ischemic stroke, hypertension, depression, anxiety, and major NCD due to Alzheimer's disease, who had become more restless over the previous 2 days. The patient's daughter called the community mobile crisis team at 1:00 AM complaining that Mrs. A had been talking to her deceased parents, was calling out and appeared distraught, and attempted to leave the house. Her regular medications included citalopram 10 mg daily, lorazepam 0.5 mg at noon, atenolol 25 mg daily, aspirin 81 mg daily, and acetaminophen 500 mg as needed for pain. She moved to her daughter's house 3 days previously, after her husband (her primary caregiver) was hospitalized. The daughter suspected that Mrs. A might not have taken her medications that day while the daughter was away at work. You were the on-call clinician and responded to the daughter's call. The daughter was asking for a medication to calm Mrs. A down because she was getting "out of control." Based on the information presented, you concluded that Mrs. A was in a new environment, most likely she was not taking her medications properly and that the daughter (or other caretaker) needed to supervise her. You advised the daughter to try to redirect Mrs. A. You explained to the daughter that giving Mrs. A a dose of the prescribed lorazepam 0.5 mg (already available to the daughter) could help her to relax, but the daughter should watch her closely for falls and other adverse events. You advised the daughter to schedule a visit with

Mrs. A's primary care physician to be seen shortly (within 1 week) for full assessment and medication reconciliation.

Key Points

- The acronym AVOID may be used as a set of clinical pearls to approach geriatric psychopharmacology: *A*void medication when possible; *V*erify medications actually taken; *O*ptimize timing and dosing of active medications; *I*dentify the most optimal delivery method; and *D*iagnose correctly.
- Genetic polymorphism may account more for individual medication metabolism than aging. More specifically, CYP2D6 metabolizing capacity should be considered when psychotropic medications are coadministered with drugs that inhibit CYP2D6.
- In general, aging leads to reduced neurotransmitter receptor activity in the brain, and this leads to lowering of the target doses for most medications.
- The first-line treatment for behavioral disturbance in patients with major NCDs is non-pharmacological interventions. Medication may be required, especially if the aggressive behavior is escalating, has not responded to non-pharmacological interventions, and may cause physical injury to patient and/or caregivers.

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