10 Medications and Cognition in Older Adults

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Practicing clinicians cannot escape the irony that elderly patients are more predisposed to medication side effects (e.g., due to reduced renal clearance) and to cognitive disorders (e.g., Alzheimer's disease), and yet this same population is prescribed more medications, some of which may impair cognition. It is therefore incumbent upon the clinician to recognize when cognitive problems might be due to medications or combinations of medications, which medications are the most common offending agents, and how to treat these individuals optimally, by either substituting safer drugs or using non-pharmacological therapies. In addition to adverse motor effects such as impaired fine motor coordination and imbalance, many medications prescribed to elderly patients can produce adverse cognitive effects that impact attention, memory, and executive functions. The scope of this potential problem is immense, with upward of one-third of older adults taking psychotropic medications like antidepressants, anxiolytics, antipsychotics, and sedative-hypnotics [1]. Many more elderly patients are prescribed medications for non-neuropsychiatric conditions that can also negatively affect cognition (e.g., antihistamines).

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Clinical Assessment

History is always key in diagnosing the potential cause of cognitive decline. For example, progressive cognitive decline of insidious onset is typical for Alzheimer's disease, whereas forgetfulness after new treatment for hypertension might be due to beta-blocker use. It should be kept in mind that the addition of a new medication may unmask an underlying incipient cognitive disturbance such as neurodegenerative dementia or borderline cognitive function related to prior cerebrovascular disease. Indeed, preexisting dementia puts patients at 2–3 times the risk for developing delirium [2]. In obtaining a cognitive history, reports from a spouse, adult child, or caregiver are essential since cognitive impairment or behavioral changes may not be apparent to the patient. In this regard, a correlation between the addition of a new medication or change in dose of an existing medication can be important in identifying an offending agent.

Laboratory assessment should be directed at potential effects of medications on metabolism (e.g., hypokalemia related to diuretics or hypoalbuminemia resulting in higher circulating drug levels), serum levels of some medications (e.g., antiepileptic toxicity), or supervening medical conditions that can affect drug clearance or potentiate drug effects (e.g., complete blood counts and urinalysis to diagnose urinary tract infection). One must keep in mind that most

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elderly patients have reduced muscle mass and therefore lower serum creatinine values, so that a value within the normal laboratory range may actually represent impaired renal clearance in these individuals [3]. Consequently, most medications should be started at reduced doses in the elderly population, with upward titration proceeding slowly and cautiously ("start low, go slow").

Medications That Can Affect Cognition

Though many medications have the potential for affecting cognition, there are several classes of medications that are the most common offenders (Table 10.1). Rather than an exhaustive review of any potentially problematic drugs, this section will discuss those medications that the clinician is most likely to encounter in a typical hospital or office practice. In addition, toxic effects associated with drug overdose will not be discussed so that the focus will be on cognitive and behavioral problems that arise during normal prescribing practice. Cognition-enhancing drugs such as those used to treat Alzheimer's disease (e.g., donepezil, memantine) will be covered elsewhere in this volume. One convenient way to approach these various medications is by dividing them into neuropsychiatric drugs (i.e., drugs that are designed to act on the nervous system) and systemic drugs (i.e., drugs that primarily target tissues outside the nervous system).

Neuropsychiatric Drugs

Antidepressants

Depression can produce cognitive impairment, usually as attentional deficits that can resemble memory loss, so-called pseudodementia. It can also worsen cognition in patients with underlying cognitive impairment. Treatment of depression in patients with or without cognitive impairment may therefore have benefits on cognitive functioning in this group [4]. However, positive effects on cognition in the elderly can depend on the choice of antidepressant [5], and certain antidepressants have the potential to worsen cognition.

Tricyclic Antidepressants

As a group, tricyclic antidepressants (TCAs, e.g., amitriptyline, nortriptyline, imipramine, clomipramine, desipramine, doxepin) are effective antidepressants but have anticholinergic effects that can worsen memory functioning in the elderly. Given the cholinergic deficits seen in age-related illnesses such as Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies, it is not surprising that the elderly population may be especially sensitive to the negative cognitive effects of this class of medications [6]. Approximately 5–7% of geriatric inpatients who received a TCA may develop delirium [7, 8]. In a mouse model of memory and learning, the TCAs amitriptyline and imipramine worsened memory and potentiated the effects of the anticholinergic agent scopolamine, whereas the selective serotonin agent fluoxetine had no effect on memory and could reverse scopolamine's negative effects [9].

TCAs have been demonstrated to have negative effects in the elderly on measures of verbal memory [10–13]. In a randomized controlled crossover trial of patients with Alzheimer's disease, subjects receiving clomipramine had both greater acute and lasting improvements in depression compared to placebo but significantly lower cognitive scores [14]. However, low-dose imipramine (25 mg/day) was shown not to worsen memory in patients with Alzheimer's disease with or without depression [15]. In a large population-based study ($N = 1488$ patients), TCA use was not associated in the short or long term with cognitive deficits or memory impairment [16].

The atypical TCA tianeptine has fewer anticholinergic and cardiovascular side effects than older generation TCAs [17]. In a small study of elderly patients with depressive symptoms, tianeptine reduced depression significantly, as well as improved cognition [18]. In a larger trial

Table 10.1 Medications that can affect cognition (see text for discussion)

Medical condition	Drugs that might impair cognition	Safer drug alternatives	Non-pharmacological alternatives
Depression	Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin)	SSRIs (e.g., fluoxetine, paroxetine, sertraline, citalopram, escitalopram) SNRIs (e.g., venlafaxine, duloxetine) Tianeptine	Counseling Psychotherapy Group therapy Cognitive-behavioral therapy
Psychosis, agitation	High-potency antipsychotics (e.g., chlorpromazine, haloperidol)	Atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine) Aripiprazole?	Structured environment Regular daily routines Trained caregiver
Insomnia	Benzodiazepines (e.g., alprazolam, triazolam, temazepam, diazepam, lorazepam) Diphenhydramine	Z-drugs (e.g., zolpidem, zaleplon, eszopiclone) Chloral hydrate Melatonin Ramelteon Suvorexant?	Proper sleep hygiene (i.e., no late-day caffeine, no napping, regular exercise, fixed bed/awakening time) Cognitive-behavioral therapy
Parkinson's disease	Anticholinergics (e.g., trihexyphenidyl)	L-dopa Dopamine agonists (e.g., pramipexole, ropinirole) MAO-B inhibitors (e.g., selegiline, rasagiline) COMT inhibitors (e.g., tolcapone, entacapone)	Exercise Neurorehabilitation Deep brain stimulation
Epilepsy	Phenobarbital Primidone Topiramate	Carbamazepine Valproate Levetiracetam Lamotrigine	Vagus nerve stimulation
Pain	Opiates (e.g., morphine, codeine, oxycodone, hydrocodone)	Acetaminophen NSAIDs Tramadol Topical agents	Biofeedback Physical therapy Acupuncture Chiropractic therapy
Motion sickness, vertigo	Scopolamine	Meclizine[a] Dimenhydrinate[a]	Vestibular exercises
Hypertension	Beta-blockers[b]	Diuretics (e.g., hydrochlorothiazide) ACE inhibitors (e.g., captopril, lisinopril, ramipril) Angiotensin receptor antagonists (e.g., losartan)	Exercise Weight reduction
Urinary urge incontinence	Oxybutynin	M3 selective agents (e.g., tolterodine, trospium, solifenacin, darifenacin) Mirabegron?	Scheduled toileting Fluid restriction Caffeine avoidance

ACE angiotensin-converting enzyme, *COMT* catechol-*O*-methyltransferase, *M3* muscarinic receptor, *MAO-B* monoamine oxidase-B, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant

[a]There are abundant data for scopolamine's amnesic effects but less so for these other two agents listed

[b]Lipophilic beta-blockers such as propranolol or metoprolol are more likely to impair cognition compared to hydrophilic beta-blockers such as atenolol

comparing tianeptine with escitalopram in patients with major depressive disorder, there was greater improvement in multiple measures of cognitive function after controlling for changes in depression in the tianeptine group [19].

Selective Serotonin and Serotonin/Norepinephrine-Reuptake Inhibitors

Selective serotonin-reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, citalopram, escitalopram) and serotonin/norepinephrine-reuptake inhibitors (SNRIs, e.g., venlafaxine, duloxetine, desvenlafaxine) are the most commonly prescribed antidepressants. Fortunately, they do not seem to be associated with the negative cognitive effects seen with TCAs [20]. Escitalopram improved cognition as well as mood in depressed elderly patients with memory impairment [21]. Though sertraline seemed to provide greater cognitive benefits than fluoxetine in elderly patients with depression [5, 22, 23], the efficacy of fluoxetine appears to be comparable to that of paroxetine [24]. Fluoxetine may also provide some benefits for memory in non-depressed patients with mild cognitive impairment [25].

Duloxetine and venlafaxine do not affect histaminergic or cholinergic receptors and have been shown to improve certain cognitive measures in older depressed patients [26–28]. Given their apparent safety in patients susceptible to cognitive impairment and their potential for improving cognition, SSRIs and SNRIs should be considered preferred treatments for depression in older patients. The prescribing physician, though, should be aware of the risk, albeit small, of delirium induced by serotonin agents as part of the serotonin syndrome, which is also characterized by myoclonus, rigidity, hyperreflexia, tremors, and autonomic instability. The risk of this syndrome is increased when monoamine oxidase (MAO) inhibitors (and perhaps triptan migraine medications) are co-administered.

Other Antidepressants

Although selective MAO-B inhibitors are safely used to treat Parkinson's disease (e.g., rasagiline, selegiline), nonselective MAO inhibitors such as phenelzine and tranylcypromine are not routinely used to treat depression nowadays due to their risk in causing hypertensive crisis and lethal interactions with other medications. The norepinephrine-dopamine reuptake inhibitor bupropion is an effective antidepressant, often used in combination with SSRIs, as well as a useful aid for smoking cessation. However, bupropion can increase the risk of seizures and should be used with caution in elderly patients, especially those with Alzheimer's disease, who carry a two- to six-fold risk of seizures compared to age-matched control patients [29].

Antipsychotics

Antipsychotic drugs, or neuroleptics, are dopamine receptor antagonists used in the treatment of hallucinations or delusions that might occur in disorders such as schizophrenia or dementia. They are also used to treat affective diseases (e.g., bipolar disorder), Tourette's syndrome, and nausea. This group of medications carries the risk of extrapyramidal side effects (EPS) including parkinsonism (bradykinesia, rigidity, and tremors), dystonia, akathisia, and tardive dyskinesia. The first-generation "conventional" or "high-potency" antipsychotics (e.g., chlorpromazine, haloperidol) are less selective in their blockade of dopamine receptor subtypes and are associated with a greater risk of EPS. The second-generation "atypical" antipsychotics (e.g., risperidone, olanzapine, quetiapine) preferentially block serotonin 5-HT2A receptors more than dopamine D2 receptors and are believed to have a lower risk of EPS [30].

It should be noted that the use of either conventional or atypical antipsychotics in the elderly may be associated with increased mortality [31] and that the Food and Drug Administration has issued advisories that caution their use in this patient group [32]. The potential magnitude of this problem was highlighted by a recent study of the National Nursing Home Survey, which demonstrated that one quarter of nursing home residents are prescribed antipsychotics, and of these, perhaps 40% are prescribed antipsychotics inappropriately [33]. Though antipsychotics are commonly used in managing behavioral

problems in the elderly, their use cannot be endorsed in most patients. Indeed, many patients with Alzheimer's disease can experience substantial benefits in neuropsychiatric symptoms, as well as cognition and daily functioning, with treatment using approved dementia agents such as donepezil [34], rivastigmine [35], or memantine [36]. Furthermore, though many of the neuroleptics have been shown to improve cognition in patients with schizophrenia (e.g., executive function), there are fewer data on their effects in nonschizophrenic elderly patients.

Conventional Antipsychotics

The older neuroleptics such as chlorpromazine exhibit anticholinergic activity, so one might predict that they would detrimentally affect cognition in older individuals and in particular patients with Alzheimer's disease. The results of studies examining antipsychotic use in elderly demented patients have been mixed, with some studies showing no effect on cognition [37–39] and others demonstrating negative effects on cognition [40–42]. One should interpret these studies with caution, however, since dementia patients with psychotic symptoms or behavioral disturbances have a worse prognosis than patients without these problems and they tend to experience more rapid cognitive decline [43, 44].

Atypical Antipsychotics

The newer generation of antipsychotics seems to confer neuropsychiatric and sometimes cognitive benefits to elderly patients with psychosis, while being associated with fewer EPS [45]. However, the risk of EPS, as well as orthostatic hypotension and sedation, is not negligible, putting this group of patients at risk for falls and bone fractures.

Clozapine is a dibenzodiazepine with perhaps the lowest risk of EPS among neuroleptics. However, it carries a risk of agranulocytosis as high as 1% during the first several months (requiring weekly monitoring of blood counts) and roughly 0.01% after 1 year of use [46]. This agent also possesses anticholinergic activity, which can impair memory function, at least when studied in patients with schizophrenia [47]. Olanzapine has been shown to worsen cognition in patients with Alzheimer's disease, especially those with greater baseline impairment [48].

Compared with haloperidol, quetiapine had a wider range of benefits on psychiatric symptoms in patients with Alzheimer's disease and improved memory and daily functioning without producing significant EPS [49]. Quetiapine also showed neuropsychiatric benefits without cognition deterioration in an open-label pilot study of Alzheimer's patients [50]. Another small, open-label study using risperidone demonstrated improvement in psychosis, agitation, and aggression in patients with dementia without impacting cognition [51].

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study group randomized over 400 patients with Alzheimer's disease and psychosis or agitation to antipsychotic medications (risperidone, olanzapine, or quetiapine) or placebo [52]. When this group examined time to discontinuation as a primary study endpoint, they concluded that adverse effects offset any advantages on neurobehavioral symptoms of antipsychotics compared to placebo [53]. In a subsequent analysis of antipsychotic medication versus placebo, though, the authors indicated that treatment with olanzapine or risperidone (and perhaps quetiapine) improved certain behavioral symptoms but had neither positive nor negative effects on cognition. Similar benefits on behavioral symptoms without cognitive deterioration were seen with these three agents in another smaller study of outpatients with Alzheimer's disease [54]. A recent review of 69 studies in which quetiapine was used in older patients demonstrated that quetiapine worsened cognition, caused more falls, and resulted in higher mortality in patients with signs of parkinsonism [55]. However, these detrimental effects did not occur in patients with dementia. In addition, quetiapine was overall safer when compared to risperidone and olanzapine on measures of falls, stroke, and death.

Aripiprazole is a newer agent used in the treatment of schizophrenia, bipolar disorder, and as an adjunctive to antidepressants for major depression. Several recent placebo-controlled studies have demonstrated its efficacy in treating

hallucinations and delusions in patients with Alzheimer's disease with little negative impact on cognition or safety [56–58]. However, head-to-head studies with other antipsychotics will be needed to test whether it really is safer than older agents.

In summary, atypical antipsychotic agents may be useful in treating psychosis, agitation, and aggression in some patients with dementia without harming cognition, but the treatments must be individualized, and it would be prudent to start slowly with low doses to minimize the chance of adverse effects.

Sedative-Hypnotics and Anxiolytics

Insomnia occurs frequently in older patients and may have various causes. These include a consequence of aging, sleep apnea, restless leg syndrome, or various parasomnias, such as periodic leg movement disorder. Overnight sleep studies that monitor brain electrical activity, movements, and breathing are sometimes required for diagnosing sleep disorders. Depression and anxiety are among the most common causes of insomnia, so accurate diagnosis and directed therapy should be attempted before treating sleeplessness with more generalized sleep aids. Dementia is often associated with inverted sleep-wake cycles that result in daytime sleepiness and nighttime restlessness or wandering.

In managing insomnia, a trial of non-pharmacological therapy should be completed before prescribing hypnotics or sedatives. This includes counseling on good "sleep hygiene." The patient should be told to avoid caffeinated beverages in the afternoon and evening, refrain from napping, get regular exercise, set regular bedtime and awakening hours, and restrict the bed at night for sleeping and not watching television or reading. Cognitive-behavioral therapy has also been shown to improve sleep in elderly patients with chronic insomnia [59] and was shown in a randomized controlled trial to be superior to zopiclone in this patient population [60]. Such non-pharmacological interventions are underutilized despite their effectiveness [61]. When needed, sleep aids should be used judiciously (e.g., only 1–2 nights/week when a patient really needs to catch up on sleep) and should not be taken nightly.

Although they are still commonly prescribed for the treatment of anxiety, the use of short-acting benzodiazepines (e.g., estazolam, triazolam, temazepam) as sleep aids has largely been supplanted by the development of non-benzodiazepines or "Z-drugs" (i.e., zolpidem, zaleplon, eszopiclone) that also act as $GABA_A$ agonists but which are believed to have fewer side effects. It should be noted that the perceived safety vis-à-vis reduced daytime sleepiness of the latter group of medications might be due to the fact they have been unfairly compared to longer-acting benzodiazepines (e.g., nitrazepam) or inappropriate doses of short-acting agents such as temazepam [62].

Benzodiazepines are more potent in elderly patients due to target organ sensitivity, are cleared less efficiently due to reduced hepatic clearance and increased distribution volume, and can accumulate, resulting in cognitive impairment, psychomotor slowing, delirium, or sedation [3]. In the elderly, short-acting agents are preferred, and high-potency benzodiazepines (e.g., alprazolam) should be avoided due to increased risk of side effects, such as overuse and withdrawal symptoms upon discontinuation [63]. Two large epidemiological studies in older French men and women demonstrated an association between benzodiazepine use and cognitive decline [64, 65], whereas a third did not [66]. Benzodiazepines can impair reaction time, attention, and memory [67]. Longer-acting agents are more likely to produce impairment [68]. Whenever the clinician makes a decision to stop benzodiazepines, they should be withdrawn gradually (i.e., dose tapered over one to several weeks) to lessen the risk of delirium associated with drug withdrawal in the elderly [69].

When treating anxiety, SSRIs or SNRIs should be considered before prescribing benzodiazepines. In addition, buspirone has been shown to be at least as effective as sertraline in treating anxiety in the elderly without significant adverse effects [70]. In healthy older subjects, buspirone did not affect reaction time, psychomotor speed, or memory [71]. Nefazodone seems to be a safe

choice in treating elderly patients with anxiety and comorbid depression [72].

The so-called Z-drugs are the most commonly prescribed sleep aids in the elderly population. They are not without side effects and can produce hallucinations, delirium, and amnesia [73–75]. Most studies of these drugs have been conducted in younger individuals, with some showing cognitive impairment at commonly used doses [76] and others showing no significant effects [77–79]. Studies in the elderly have been limited. Following a single dose, zolpidem did not appear to affect attention or memory in healthy elderly individuals [80]. Weeklong administration of zolpidem also did not significantly impair psychomotor or cognitive functioning [81]. In contrast, another study demonstrated that older subjects experience memory impairment the day following dosing with zolpidem [82].

The antihistamine diphenhydramine is often prescribed as a sleep aid, especially by hospital staff, or taken by patients seeking over-the-counter remedies. It possesses anticholinergic activity and can induce delirium in elderly patients and can impair attention and memory [83–85]. Chloral hydrate can be an effective sleep aid in older patients that carries little risk of delirium but may increase the free concentrations of certain other drugs (e.g., warfarin) due to displacement from plasma proteins [3]. Although trazodone is commonly prescribed as a sleep aid in elderly patients due to its perception as a "safe" drug, a comprehensive review of the evidence for trazodone in insomnia identified few trials that were mostly performed in depressed patients. There was also evidence of possible tolerance and side effects that included daytime sedation, dizziness, and psychomotor impairment [86].

The orexin receptor antagonist suvorexant was recently approved for treating insomnia. The most common side effects of the medication include headaches, dry mouth, and excessive daytime sleepiness, and it should be used with caution in patients at risk for delirium [87]. In a meta-analysis of four clinical trials of the drug, suvorexant was demonstrated to be superior to placebo on subjective measures of time-to-sleep onset and total sleep time [88]. It remains to be determined whether the drug is safe and effective in patients with cognitive impairment or dementia.

Ramelteon is a selective melatonin receptor agonist that was recently approved by the FDA for treating insomnia. In one open-label study in subjects over age 65 with primary insomnia, ramelteon (8 mg) each night improved subjective measures of sleep latency and total sleep time over the course of 1 year [89]. This drug also appears to be safer and better tolerated than Z-drugs. In a placebo-controlled crossover study comparing ramelteon and zolpidem, older adults performed worse on middle-of-the-night balance tests and immediate recall tests when taking zolpidem, but there was no significant impairment when taking ramelteon [90].

Lastly, melatonin has been shown to improve sleep quality and possibly cognitive functioning in healthy elderly individuals [91]. It also appears to be an effective sleep aid in patients with dementia, reducing sleep latency and prolonging sleep duration, though long-term use may predispose to worsening affect [92]. In a randomized, crossover study comparing melatonin and zolpidem in healthy older individuals, a prolonged-release formulation of melatonin did not impact psychomotor functioning, memory, or driving skills, whereas zolpidem negatively affected all three measures [82].

Parkinson's Disease Medications

Multiple classes of medications are used in treating Parkinson's disease, including L-dopa, dopamine agonists (e.g., pramipexole, ropinirole), MAO-B (monoamine oxidase inhibitor, class B) and COMT (catechol-*O*-methyltransferase) enzyme inhibitors (which increase the bioavailability of dopamine), and anticholinergic agents (e.g., trihexyphenidyl). It should be kept in mind that cognitive dysfunction is common in patients with Parkinson's disease, either in the form of dementia with Lewy bodies, as a later complication of idiopathic Parkinson's disease, or due to depression, which occurs in more than half of Parkinson's patients during some point in their illness. As such, these patients may be particularly susceptible to untoward cognitive effects of medications described in this chapter. However,

drugs used specifically to treat Parkinson's disease might also have the potential for negatively impacting cognition.

L-dopa did not seem to impair cognition after 3 months of treatment in patients with Parkinson's disease with or without comorbid dementia [93]. The absence of negative cognitive effects of L-dopa seems to carry over into moderate or severe Parkinson's disease [94]. However, an earlier study failed to show any cognitive benefit of L-dopa in Parkinson's patients [95]. In patients with early Parkinson's disease, treatment either with L-dopa or the dopamine agonist bromocriptine improved cognition, whereas anticholinergic therapy worsened it [96]. Addition of the MAO-B inhibitor selegiline to L-dopa treatment may help improve cognition in Parkinson's patients without dementia [97]. The newer MAO-B inhibitor rasagiline does not seem to be associated with any significant cognitive or behavioral worsening [98].

In a randomized study of patients with early/mild Parkinson's disease, the D2/D3 dopamine agonist pramipexole significantly impaired verbal memory, attention, and executive function compared to L-dopa [99]. The same study group also showed that the D1/D2 dopamine agonist pergolide was comparable to L-dopa in its effects on cognition [100]. However, both pergolide and pramipexole might improve working memory in medically naïve Parkinson's patients [101]. It should be noted that dopamine agonists such as pramipexole or ropinirole have been linked to impulse control disorders in patients with Parkinson's disease (e.g., pathological gambling, compulsive sexual behavior, binge eating), the risk being perhaps 2–3 times higher than in patients not treated with dopamine agonists [102]. In a small study of patients with advanced Parkinson's disease, treatment with tolcapone, a COMT inhibitor, resulted in improved scores for attention, verbal and visual-spatial memory, and praxis [103].

The anticholinergic agent trihexyphenidyl is useful in treating tremors in Parkinson's disease [104, 105] and may also be of use in patients with tardive dyskinesia [106]. Trihexyphenidyl was shown to worsen executive function in patients with Parkinson's, an effect that is mediated by subcortical frontal circuits [107]. This medication was also demonstrated to impair cognitive shifting and memory [108]. In a crossover study of patients with drug-induced EPS, cognitive performance was better on the Parkinson's medication amantadine than in trihexyphenidyl [109]. Lastly, an uncontrolled study of elderly patients with schizophrenia demonstrated a dose-dependent correlation between global cognitive and memory impairment and chronic use of trihexyphenidyl [110].

Anticonvulsants

Anticonvulsants or antiepileptic drugs (AEDs) are used primarily in treating seizure disorders but also play an important role in the management of mood disorders, neuropathic pain syndromes (e.g., trigeminal neuralgia), and migraine headaches. Since these drugs function to reduce neuronal irritability, such as cortical seizure foci, vis-à-vis inhibiting neuronal excitability, they have the potential for impairing cognition, as well as other brain and spinal cord functions such as balance [111]. This is especially true in elderly patients, in whom the pharmacokinetics of AEDs may be different than in younger patients and who might be taking other medications that interact with AEDs [112]. Note also that the type of epilepsy (e.g., focal-onset versus primary generalized) may restrict the choice of appropriate AEDs. There should be a low threshold for seeking the guidance of an epileptologist when managing epilepsy in older patients who do not respond to monotherapy with first-line AEDs or who experience significant side effects.

At normal therapeutic doses, use of phenytoin, valproate, or carbamazepine did not seem to affect cognition significantly in most adult patients, though their safety in the elderly is less well established [113]. Carbamazepine seemed to produce fewer adverse effects on cognition compared to phenytoin, primidone, or phenobarbital in a large study of veterans [114], and a subsequent study in the same population showed no difference between carbamazepine and valproate [115].

In elderly patients on monotherapy for epilepsy (carbamazepine, phenytoin, or valproate), increasing the dose of their AED to a higher level within the normal dose range did not induce cognitive impairment or sedation [116]. A randomized study comparing valproate and phenytoin in elderly patients with new-onset epilepsy found no significant adverse cognitive effects and no difference between the two drugs [117]. However, a tolerability study of valproate in non-epileptic patients with Alzheimer's disease demonstrated cognitive worsening at a dose of 1500 mg/day, though doses less than 1000 mg/day might be safe [118]. Carbamazepine was shown to be superior to placebo in treating agitation and aggression in demented nursing home patients with no effects on cognition or functionality [119].

A large, randomized, double-blinded clinical trial comparing lamotrigine, gabapentin, and carbamazepine in geriatric patients with new-onset epilepsy showed similarly efficacy on seizure control among the three medications but significantly fewer adverse effects in the lamotrigine and gabapentin groups [120]. In a randomized, case-control study of Alzheimer's patients with seizures, levetiracetam improved attention and oral fluency and lamotrigine had a positive effect on mood, but phenobarbital caused persistent cognitive impairment [121]. Topiramate has been shown to impair cognitive speed, verbal fluency, and short-term memory in patients with epilepsy, whereas levetiracetam or lamotrigine seems to lack cognitive side effects [122, 123]. Other studies have demonstrated negative effects of topiramate on verbal fluency and attention in adults with migraines [124, 125]. In a small study of elderly patients with seizures comparing two different doses of topiramate (50 or 200 mg/day), approximately 13% of patients reported negative cognitive effects [126].

Vagus nerve stimulation (VNS) by means of an implanted electronic device is an approved therapy for medication-refractory forms of epilepsy and major depression. It has been shown to be effective in treating epilepsy in older adults and is associated with only mild, transient side effects [127]. Although only a small number of patients have been formally studied, patients with Alzheimer's disease who received VNS demonstrated improvement or stability at 1 year on several measures of cognition [128].

Opiates

The geriatric population is particularly susceptible to musculoskeletal and rheumatologic illnesses associated with pain. Although studies directly addressing this issue are lacking, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and topical agents (e.g., fentanyl patch or capsaicin lotion) are effective therapies that only rarely produce cognitive effects in elderly patients [129–132] (for some exceptions, see section on corticosteroids and NSAIDs).

For more severe or intractable pain, patients may be prescribed opiates (e.g., morphine, codeine, oxycodone) or combination medications (e.g., acetaminophen-hydrocodone). Though any opiate may of course produce sedation or cognitive impairment in patients of any age, one study of primary care patients with non-malignant pain found that problems with cognitive functioning were more likely related to psychological health and pain control than with specific opiate medications [133]. A review of postoperative pain management in elderly patients concluded that meperidine has consistently been shown to be associated with an increased risk of delirium, whereas this has not been shown for other commonly used opiates (e.g., morphine, fentanyl, hydromorphone) [134].

In using opiates, it should be kept in mind that tolerance for a dose administered chronically may subsequently be too high and result in delirium, sedation, or cognitive impairment following another intervention to reduce absolute pain levels (e.g., spinal nerve block, surgery). Also, given the substantial risk of abuse and addiction associated with opiates, physicians should attempt to substitute non-opiate analgesics or non-pharmacologic treatments (e.g., physical therapy) whenever possible.

Anti-Vertigo and Motion Sickness Agents

Anticholinergic and antihistaminergic agents are widely used to treat vertigo and motion sickness (e.g., seasickness). Dimenhydrinate and meclizine are antihistamines that are effective in relieving motion sickness and vertigo but which can produce psychometric slowing and sleepiness [135]. Although a case report noted memory loss and confusion in an elderly woman taking meclizine, there have been no studies specifically examining this drug's or dimenhydrinate's effects on cognition in older patients [136].

Scopolamine is an anticholinergic medication used to treat motion sickness and has been associated with memory impairment. In a blinded placebo-controlled study, it was shown to worsen cognition and behavior in a dose-dependent fashion in patients with Alzheimer's disease [137]. It has also been demonstrated to worsen memory in Parkinson's patients without pre-existing cognitive impairment [138]. In a comparison between healthy individuals of different ages, scopolamine impaired memory and constructional praxis in old but not young subjects [139].

Systemic Drugs

Cardiovascular Drugs

Hypertension is a common risk factor for carotid atherosclerosis and cerebrovascular disease. Ischemic changes in the brain may in themselves produce cognitive impairment or dementia (e.g., "subcortical dementia," Binswanger's disease) or contribute to the pathogenesis or potentiate the effects of other dementias (e.g., Alzheimer's disease). However, overaggressive lowering of blood pressure in treating hypertension can also cause cognitive changes. Elderly patients with a long history of hypertension might have cervical or cerebral blood arteries with poor compliance that require pressures greater than those considered normal in order to adequately perfuse the brain. Cerebral hypoperfusion can also occur with atrial fibrillation, congestive heart failure, myocardial infarction, or coronary artery bypass grafting (CABG) [140]. As such, it can sometimes be difficult to gauge the extent to which either underlying cardiovascular pathology versus therapies used to treat them may be contributing to cognitive worsening. With the possible exception of beta-blockers (see below), antihypertensives are not thought to affect cognition significantly. A review of several randomized, placebo-controlled studies and a meta-analysis examining the effects of antihypertension medications on dementia suggested that these medications, and angiotensin-converting enzyme (ACE) inhibitors and diuretics in particular, may help prevent or slow the progression of dementia [141, 142].

Beta-Blockers

Although propranolol is also used to treat essential tremor and prevent migraine headaches, the clinician is most likely to use beta-adrenergic antagonists, or beta-blockers, in elderly patients with hypertension or cardiac disease. Beta-blockers may exert biological effects in the CNS either specifically via activity at downstream receptors of central adrenergic pathways (e.g., projections from the locus coeruleus) or nonspecifically via neuronal membrane stabilization [143]. Lipophilic beta-blockers such as propranolol and metoprolol cross the blood-brain barrier and accumulate in brain tissue compared to hydrophilic agents like atenolol [144]. These differences in lipophilicity seem to correspond to the relative risk of CNS effects. Switching from a lipophilic beta-blocker to a less lipophilic agent was associated with improved sleep, concentration, and memory, and atenolol was less likely to produce sleep disturbances than metoprolol [145].

However, a comprehensive review of beta-blockers concluded they in general have minimal or absent effects on memory function, as well as in causing sleep disturbances, nightmares, or hallucinations [146]. A large, randomized, controlled study of antihypertensives in elderly women failed to find evidence of cognitive decline after 5 years of treatment with a diuretic and atenolol [147]. Elderly patients with hypertension randomized to the angiotensin receptor antagonist losartan experienced improved memory,

but those who received atenolol showed neither improved nor worse memory function [148]. Another study compared propranolol to placebo in young or middle-aged patients with hypertension and found little or no difference in performance on a battery of cognitive tests [149]. A small study in hypertensive veterans demonstrated no decline in cognitive performance with treatment using either propranolol or atenolol [150]. However, in a study of cognitively impaired elderly patients, use of beta-blockers was associated with a trend toward worsening memory [151].

Digoxin

Digoxin is a naturally occurring glycoside used to improve cardiac output in patients with congestive heart failure. Altered mental state and delirium can occur with toxic doses of digoxin [152] and have even been reported with so-called therapeutic serum concentrations [153]. However, at therapeutic dosages, digoxin may actually improve cognitive performance [154].

H2 Blockers and Proton-Pump Inhibitors

Histamine H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine) and proton-pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole) are widely prescribed for the treatment of acid-reflux disease and peptic ulcer disease and to help reduce the gastric side effects of medications such as aspirin. Both classes of drug inhibit acid secretion from gastric parietal cells. Stomach acid is necessary for the release of vitamin B12 from ingested food, and H2 blockers may reduce B12 absorption [155, 156]. Since vitamin B12 deficiency can cause cognitive impairment, dementia, or delirium, prolonged inhibition of gastric acid secretion may increase the risk of neurobehavioral symptoms [157].

A case-control study of elderly patients demonstrated an association between chronic use (at least 12 months) of H2 blockers or proton-pump inhibitors and vitamin B12 deficiency [158]. Another study showed that prolonged use of proton-pump inhibitors, but not H2 blockers, was associated with vitamin B12 deficiency in the elderly, though the consequences of this on cognition were not examined [159]. A longitudinal study of elderly African-Americans demonstrated that H2 blocker use doubled the risk of developing cognitive impairment [160]. Thus, it might be prudent to periodically check serum B12 levels (or sensitive surrogate markers such as methylmalonic acid and homocysteine) when using H2 blockers or proton-pump inhibitors in elderly patients.

There have been numerous case reports describing mental confusion in patients taking the H2 blockers cimetidine, ranitidine, or famotidine. However, a randomized, placebo-controlled, crossover of healthy elderly individuals showed no adverse effects of cimetidine on cognition, leading the authors to conclude that earlier case reports might have been due to specific patient sensitivities to this class of medications [161]. A large cohort study, in contrast, suggested that H2 blocker use was associated with higher risk of cognitive impairment or decline in cognitive functioning [162].

Urinary Antispasmodics

Urge urinary incontinence due to an overactive or spastic bladder may be treated with medications that have the potential to produce cognitive symptoms. Simple measures such as restricting fluid intake, avoiding caffeine, or scheduling frequent visits to the toilet can reduce the need for medical treatment in some patients. Others, though, may be prescribed anticholinergic medications directed against muscarinic M3 receptors that decrease bladder detrusor muscle activity (e.g., oxybutynin, tolterodine, trospium, solifenacin, darifenacin). As with any anticholinergics, these drugs can produce dry mouth, constipation, dizziness, and drowsiness. The risk for these agents to impair cognitive functioning is related to their ability to penetrate the brain and their interaction with muscarinic M1 receptors [163].

In a study of healthy elderly volunteers, solifenacin did not seem to affect cognition, whereas oxybutynin impaired several measures of cognition [165]. After 3 weeks of treatment, healthy elderly subjects experienced significant memory

impairment on oxybutynin in contrast to those on darifenacin, which showed no difference in memory compared to the placebo group [166]. Darifenacin was found to have no effects on cognition in another trial involving healthy elderly volunteers [167]. Tolterodine was demonstrated to produce reversible memory impairment in a single case report [168] but was found to have no effect on memory in a 3-week crossover study compared to oxybutynin [163].

Mirabegron is a beta-3 adrenergic agonist that causes relaxation of the detrusor muscle and was approved for use in the United States in 2012 for the treatment of overactive bladder. It does not have the anticholinergic effects of the older medications used for incontinence, but it is contraindicated in patients with poorly controlled hypertension and should be used with caution in those with other cardiovascular conditions [164]. No significant cognitive side effects have been reported to date, but this has not been studied addressed in the elderly population.

Corticosteroids and NSAIDs

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat various conditions associated with inflammation or pain (e.g., vasculitis, arthritis). Severe psychiatric symptoms, such as affective and psychotic conditions, may occur in upward of 5% of patients treated with corticosteroids [169]. Acute corticosteroid treatment, but not chronic treatment, seemed to induce memory impairment in patients with rheumatoid arthritis [170]. Steroid use has likewise been associated with reversible dementia [171, 172]. It should be noted that too rapid withdrawal of corticosteroid therapy can also affect the brain [173].

Though non-neurological side effects of NSAIDs are quite common (e.g., dyspepsia, renal impairment), they infrequently can cause aseptic meningitis, disorientation, hallucinations, and memory or attentional impairment, and the elderly may be at increased risk [174]. A large randomized, placebo-controlled study of patients with cardiovascular disease showed no difference in performance on multiple cognitive tasks with long-term low-dose aspirin therapy [175]. Aspirin failed to prevent cognitive decline in healthy older women participating in the Women's Health Study [176]. Neither naproxen nor celecoxib prevented cognitive decline compared to placebo in elderly non-demented subjects with a family history of Alzheimer's disease [177]. In contrast, a randomized, placebo-controlled study of patients with subjective memory impairment demonstrated improvements in executive functioning and memory, as well as increased cerebral metabolism on positron-emission tomography (PET) imaging with celecoxib treatment [178].

The effects of long-term NSAID use on reducing the risk of cognitive decline and dementia have been mixed [179], with most studies showing a possible protective effect [180–186] and others providing no evidence for such protection [187, 188] or demonstrating a potential detrimental effect [189, 190]. These diverse results likely reflect differences in patient or subject groups, types and doses of NSAIDs taken, age at first use, and length of therapy. Needless to say, a disappointment for those studying Alzheimer's disease is that no prospective clinical trial has yet shown that NSAID use prevents dementia.

Hormonal Therapy

There was initial enthusiasm that estrogen therapy might help prevent cognitive decline and dementia based on epidemiological studies of estrogen-replacement therapy in younger women. However, no benefits have been demonstrated in older, postmenopausal women [191, 192]. Indeed, the large Women's Health Initiative revealed that postmenopausal estrogen therapy was associated with significant risk of dementia (hazard ratio 1.76), as well as negative effects on selective cognitive measures such as verbal memory and lower brain volumes in the frontal lobe and hippocampus [193].

Testosterone levels in men decline with aging. Evidence suggests that this drop might contribute to parallel cognitive decline and that testosterone supplementation might prevent or be useful in

treating cognitive impairment, though neither the association nor the benefits have been strongly demonstrated in large-scale, rigorous trials [194–196]. Treatment of elderly men with low serum testosterone levels and no cognitive impairment with exogenous testosterone (either alone or in combination with the 5-alpha reductase inhibitor finasteride, which blocks conversion of testosterone to dihydrotestosterone) did not impact cognition [197]. Further, a 6-month randomized, placebo-controlled trial of testosterone in older men with low normal serum testosterone levels failed to show any effects on cognition [198].

The long-term effects of antihormonal treatments for breast or prostate cancers on cognition in the elderly are uncertain [199]. Treatment with the antiestrogen drug tamoxifen in women with breast cancer may be associated with cognitive difficulties later in life [200, 201]. However, the selective estrogen receptor modulator raloxifene, which is used to treat osteoporosis and reduce the risk of breast cancer in postmenopausal women, was shown to improve verbal memory versus placebo [202]. Androgen deprivation in men with prostate cancer seems to be associated with decline in some cognitive domains [203]. In elderly men being treated with androgen blockade for prostate cancer, no decline in cognition was noted after 12 weeks of therapy, and addition of estrogen failed to improve verbal memory compared to androgen blockade alone [204].

Cholesterol-Lowering Drugs

The 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase inhibitors commonly known as statins (e.g., lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin) are effective in lowering levels of total cholesterol and low-density lipoprotein (LDL) and have been important treatments in reducing the risk of coronary and cerebrovascular disease. Statin therapy in elderly non-demented women was associated with lower risk of cognitive impairment [205]. In the large Cardiovascular Health Study ($N = 3334$ patients), cognitive decline in the elderly was less in statin users, a finding that seemed to be in part independent of lowering cholesterol levels [206]. The most recent Cochrane review on the use of statins to prevent dementia concluded that there was no convincing evidence that statins prevent cognitive decline or dementia [207]. However, a more recent study examining statin prescriptions in Medicare recipients found that the incidence of Alzheimer's disease was reduced with certain statins and in specific demographics (e.g., pravastatin and rosuvastatin only reduced dementia risk in white women) and in particular found no significant risk reduction in black men with any of the statins [208]. Further research will be needed to confirm whether the benefits of statins in reducing risk of dementia is indeed gender- and race-specific.

Less is known about the cognitive effects of other cholesterol-lowering drugs on cognition. Treatment with gemfibrozil in elderly patients with hypertriglyceridemia and stroke risk factors improved cognitive scores and cerebral blood flow after several months compared to placebo [209]. Severe niacin deficiency can produce dementia (i.e., pellagra), and dietary niacin intake was found to be inversely related to risk of cognitive decline and Alzheimer's disease [210]. However, the effects on cognition in the elderly of high-dose niacin used to treat hypercholesterolemia (usually 500–2000 mg/day) have not been examined. Ezetimibe is a second-line cholesterol-lowering agent that inhibits cholesterol absorption from the gut. In a small study of elderly patients with atrial fibrillation, those who received atorvastatin plus ezetimibe demonstrated improvements in cognitive speed and memory as well as less medial temporal lobe atrophy at 1 year compared with the placebo group [211]. A follow-up examination by the same group showed reductions in multiple markers of serum inflammatory markers in the atorvastatin plus ezetimibe patients, suggesting a protective mechanism for preservation of hippocampal volume [212].

The clinician must be vigilant in identifying medications that can cause or contribute to cognitive impairment in the elderly. In this age of polypharmacy, the potential for inappropriate or overprescribing has burgeoned, yet the increasing

use of electronic medical records might help reverse this trend. Non-pharmacologic interventions (e.g., counseling, structured environment, group activities) should be considered in treating affective and behavioral disturbances, single agents should be used whenever possible, and drugs with potential anticholinergic (i.e., TCAs) or extrapyramidal (i.e., neuroleptics) side effects should be eschewed.

Clinical Pearls

- In prescribing any medications for elderly patients, follow the rule: "start low, go slow." Elderly patients may require lower doses of a given medication than younger patients, so by starting at the lowest possible dose and titrating upward slowly, you will be more likely to identify the least amount of medication required as well as minimize any potential side effects.
- Avoid polypharmacy and keep abreast of what medications are being prescribed by other physicians. Increasing adoption of electronic medical records, patient-centered medical home (in which the multiple needs of a patient are coordinated through a primary/personal physician), and electronic prescribing are ways to help reduce the number of medications for a given patient and prevent deleterious interactions and side effects.
- When possible, select medications that may be used to treat more than one of the patient's medical conditions in order to reduce the patient's number of medications. For example, the SNRI duloxetine can be used to treat depression as well as painful diabetic neuropathy, or propranolol might be a good choice of antihypertensive for a patient with essential tremor.
- Before prescribing sleep aids in elderly patients, especially those with cognitive impairment, try promoting healthy sleep habits, so-called good sleep hygiene. That is, instruct the patient or caregiver to set regular awakening and sleep times, avoid caffeine in the afternoon and evening, and restrict the bed for sleep and not reading or watching television. In addition, recommend that the patient avoid napping and that he or she get regular exercise.
- Every attempt should be made to manage behavioral problems in patients with dementia using non-pharmacological means. Simple measures such as a structured home environment (e.g., regular routines for meals, sleep, and social activities) can sometimes reduce the likelihood of behavioral outbursts or confrontations without having to resort to sedating medications.

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