Drug Therapy for Dementia—Affecting More Than Just the Mind

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Pharmacologic agents used for dementia and its associated symptoms are effective for many patients; however, each medication is capable of causing a variety of adverse effects that may hinder the individual from reaching physical goals. Adverse drug events can manifest physically as gait disturbances or tremors, whereas cognitive effects may present as sedation or confusion. Therapists and rehabilitation specialists are in optimal positions to recognize sometimes subtle physical and cognitive changes resulting from a drug-related adverse event. Early identification of adverse events allows the healthcare team to promptly address these issues, so patients may progress with the best treatment possible. Key words: adverse effects, dementia, drug therapy, geriatrics, rehabilitation

Although modern science provides drug therapy options for dementia and the associated behavioral issues, using any of these medications possesses a certain degree of risk. Any drug therapy, from natural products to modern pharmaceuticals, has the ability to cause adverse effects or may interact with other medications. Although no current therapy can reverse the progressive cognitive decline of dementia, pharmacotherapy may produce cognitive stabilization or behavioral improvement in many patients. Pharmacologic agents have been shown to provide relief for the depression, psychosis, and agitation often associated with dementia; however, use of these agents may result in adverse effects that can hinder therapy and rehabilitation.

Medications such as cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists, antipsychotics, benzodiazepines, and sedative hypnotics can improve the quality of life and functioning in the person with dementia; however, cognitive adverse effects like confusion, sedation, dizziness, hallucinations, and agitation as well as physical manifestations such as falls, ataxia, and tremors can hinder progress in reaching personal goals. A decline in physical or cognitive functioning in the person with dementia may be a result of disease progression; however, the deterioration could also be a result of a medication-related problem. Awareness of the common adverse effects from medications used in the person with dementia will assist members of the healthcare team to detect drug-related alterations in physical and cognitive functioning.

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PATHOPHYSIOLOGY OF DEMENTIA

Approximately 4 to 5 million people in the United States have some degree of dementia; this number will steadily increase over the next several decades as the “baby boomer” population ages. Dementia begins most frequently in late life, generally after the age of 60 years. Approximately 6% to 8% of all persons older than 65 years have Alzheimer's disease, with the prevalence of the disease doubling every 5 years after the age of 60 years. Consequently, nearly 30% of the population older than 85 years has Alzheimer's
Disease progression is gradual and continuous, and the average patient may expect to live from 8 to 10 years after symptom onset. Dementia is one of the leading reasons for skilled nursing facility placement; the prevalence among elderly nursing home residents is estimated to be 60% to 80%.

*Dementia* refers to the loss of intellectual reasoning and cognitive function due to changes in the brain caused by disease or trauma. The changes can affect thinking, memory, and reasoning, and may occur gradually or quickly depending on the underlying pathophysiology. Alzheimer’s disease is the most common cause of dementia, and other types of dementia such as vascular dementia and Lewy body dementia stem from different pathologies:

- **Alzheimer’s disease** is characterized by the formation of β-amyloid plaques that develop between neurons in the brain and neurofibrillary tangles that develop within neurons. These changes result in a gradual breakdown of the neurons and a decrease of neurotransmitters in the brain (eg, acetylcholine), causing loss of brain function. In addition, overstimulation of neurons by the neurotransmitter glutamate may contribute to the pathogenesis of Alzheimer’s disease. Continual overstimulation of glutamate receptors in the brain leads to excitotoxicity, and eventually neuronal cell death. Consequently, the target of therapy for Alzheimer’s disease currently focuses on modulating the acetylcholine and glutamate pathways in the brain.

- **Vascular dementia**, or multi-infarct dementia, is caused by decreased or interrupted blood flow to parts of the brain. Small clots obstruct the tiny blood vessels in the brain, resulting in *ischemia* that destroys brain tissue. Often the person with vascular dementia may exhibit cycles of cognitive decline, plateau, and then decline again; this is in contrast to the steady decline a person with Alzheimer’s disease experiences. Consequently, the treatment of vascular dementia frequently focuses on managing hypertension and cholesterol to reduce the risk for future cerebrovascular events. It is possible for a combination of pathologies to contribute to the clinical presentation of dementia; for example, vascular dementia can result from small strokes that then may unmask underlying Alzheimer’s disease. Therefore, some patients may have dementia caused by multiple diseases.

- **Lewy body dementia** is a less common form of dementia, resulting from progressive destruction of brain cells by protein deposits called Lewy bodies. The symptoms are similar to Alzheimer’s disease, including memory problems, confusion, language problems, and difficulty with current events. Alertness and cognitive function may fluctuate over time, and these individuals may experience visual hallucinations and Parkinson’s-like features.

**SYMPTOMS AND BEHAVIORAL ISSUES OF DEMENTIA**

Alzheimer’s disease and other forms of dementia are disorders that progressively destroy cells in the brain, resulting in decline of brain function. The regions of the brain that control memory, logical thinking, and personality are generally the most affected. Psychological changes and mood changes may also occur, and can fluctuate throughout disease progression. Symptoms of dementia include the following:

- Loss of memory
- Depression
- Anxiety
- Personality changes
- Agitation and aggression
- Irrational thinking
- Suspicion
- Delusions
- Hallucinations
- Psychosis
• Disturbed affect/mood
• Withdrawn/passive behavior
• Sleep disturbances
• Sundowning

As dementia progresses, behavioral and psychological issues may intensify. Agitation is a general term that refers to a range of behavioral disturbances, including aggression, combative ness, shouting, hyperactivity, and loss of inhibitions. As many as 50% of all persons with dementia exhibit agitation, particularly in middle and later stages of the illness. Psychosis (paranoia, delusions, and hallucinations) is less frequent but can cause distress to patients and caregivers, and lead to violence. These symptoms can overlap, may be difficult to distinguish, and are among the most common causes of institutionalization or specialist referral.

DRUG THERAPY CONSIDERATIONS FOR THE GERIATRIC PERSON WITH DEMENTIA

Drug therapy in any older person is a balance of benefits and risks. The elderly person has declining functions of many organ systems, multiple diseases, and altered responses to medications. They often receive care from more than one doctor, which adds to the complexity of their therapeutic regimen. The older adult often presents with 2 or more chronic disease states, many of which are progressive in nature. Multiple disease processes are usually coupled with multiple pharmaceutical interventions. Medications are prescribed to enhance the older adult’s well-being and general health, improving function, and increasing longevity. However, as the number of medications prescribed increases, the rates of adverse drug reactions (including drug-drug, drug-disease, and drug-nutrient interactions) also increase. Add to the effects of aging and increased disease burden the neurochemical complexities of a dementia process, and the balancing of medication risks versus benefits becomes even more tenuous.

Although medications can help improve the quality of life of persons with dementia, all medications carry the risk for adverse effects. Elderly persons with dementia are more sensitive to certain medication side effects, including anticholinergic effects, orthostasis, central nervous system sedation, and parkinsonism. Medications should be used with considerable care, and all members of the treatment team should actively observe for possible medication-related adverse events.

TREATMENTS USED IN THE MANAGEMENT OF DEMENTIA: FOCUS ON MEDICATIONS

Drug therapy for dementia can be separated into 2 main categories: (1) medications that alter the dementia process and (2) medications used to manage the behavioral issues resulting from the dementia. Acetylcholinesterase inhibitors, NMDA-receptor antagonists, vitamin E, and selegiline hydrochloride work either to prevent neuron cell death or to increase neurotransmitters lost from neuronal cell death. Consequently, these medications can temporarily stabilize or slow the disease progression. Drugs such as donepezil, galantamine, rivastigmine, and memantine alter neurotransmitters by increasing acetylcholine or decreasing glutamate’s effects in the brain. These medications may be initiated early in the dementia process, and are often continued indefinitely.

Medications for behavioral issues including antidepressants, antipsychotics, and benzodiazepines are initiated when depression, anxiety, agitation, or psychosis develop. When treating a patient with agitation or psychosis, other possible causes for the behavior must be ruled out—for example medical problems, pain, depression, anxiety, loss of sleep, or delirium. Unaddressed interpersonal or emotional issues such as fear of abandonment may also lie at the root of the disturbance. Non-drug therapies to manage the behavior and psychological problems are the ideal frontline
treatments for persons with dementia. Treatment of underlying medical conditions, reassurance, attention to the environment, or emotion-oriented psychotherapy may reduce agitation before drug therapy is attempted. When nonpharmacologic plans are no longer adequate to manage behaviors or the person is unable to achieve his or her highest level of function, psychoactive medications are added to improve the person’s quality of life.

Acetylcholinesterase inhibitors

Although no drug has been shown to completely protect neurons, agents that inhibit the degradation of acetylcholine within the synapses of the brain are the foundation of treatment of Alzheimer’s disease. Alzheimer’s disease is characterized by a deficiency of the neurotransmitter acetylcholine in the cortex and basal forebrain, which contributes to cognitive deficits. Acetylcholinesterase inhibitors including rivastigmine, donepezil, and galantamine prevent the enzyme acetylcholinesterase from degrading acetylcholine in the brain. This appears to result in increased concentrations of acetylcholine available for synaptic transmission in the central nervous system. Currently, treatment of acetylcholine deficiency is the primary focus of drug therapy for Alzheimer’s disease. Although acetylcholinesterase inhibitors increase the amount of acetylcholine in the brain, they are in no way a cure for Alzheimer’s disease; the primary use of acetylcholinesterase inhibitors is to slow the progression of Alzheimer’s disease. Studies suggest beneficial effects on behavioral symptoms in some patients, and prolonged cholinergic therapy may delay nursing home placement. Clinically, acetylcholinesterase inhibitors may result in improved memory to a small degree, but more often caregivers report a slower decline in the patient’s functional abilities and behaviors.

Adverse effects

A majority of the adverse effects from acetylcholinesterase inhibitors occur during initiation of therapy or dose escalation, and are due to the general increase in cholinergic activity in the body. Side effects may occur more often in persons older than 85 years, women, and of low body weight. Common side effects include nausea, vomiting, loss of appetite, diarrhea, and increased urinary frequency or urinary incontinence. These side effects may attenuate with time. The drug may occasionally need to be discontinued or the dose lowered because of adverse gastrointestinal effects in some people.

Effects on rehabilitation

Acetylcholinesterase inhibitors can affect the cardiovascular system, causing bradycardia that may lead to syncope and falls. In addition, orthostatic hypotension, dizziness, and sedation have been reported. Overall, the use of acetylcholinesterase inhibitor can be beneficial in improving behavior and function, but the improvement in most cases is modest.

Dosing/titration

Acetylcholinesterase inhibitors are initiated at varying times in the disease course; there are no set determinants as to when these medications should be started or stopped. Typically, acetylcholinesterase inhibitors are initiated in the mild to moderate stages of dementia. Doses are often started lower, and then titrated up slowly over the course of weeks to avoid gastrointestinal side effects. Some practitioners may discontinue the medication if no benefit is concretely demonstrated, whereas others will maintain acetylcholinesterase inhibitors use for the duration of the disease process.

NMDA receptor antagonists

Memantine is indicated for the treatment of moderate to severe dementia of the Alzheimer’s type, and has been shown to bring about improvement in performance deficits and behavioral changes in persons with dementia. Glutamate, the primary excitatory amino acid in the central nervous system, is believed to play a role in the development of symptoms associated with Alzheimer’s disease. Memantine is thought to act by blocking the functioning of the NMDA receptor, thereby reducing the excitatory effects of glutamate. Although memantine has been shown to improve certain aspects of cognitive function, its overall impact on disease progression is limited. Memantine is typically started in lower doses and gradually increased to a maximum of 20 mg per day. Side effects of memantine are relatively mild and include nausea, diarrhea, and dizziness. The primary goal of treating dementia with memantine is to slow the progression of the disease and improve the quality of life for the patient and their caregivers.
system, may contribute to the pathogenesis of Alzheimer’s disease by overstimulating various glutamate receptors, thus leading to toxicity and neuron death. Memantine is an antagonist of the NMDA type of glutamate receptors in brain; in effect, memantine blocks the binding of glutamate to the neurons, and thus prevents overstimulation of the nerve that leads to cell death. In clinical trials, persons taking memantine had less of a decline in cognitive function and activities of daily living as compared to placebo. This was true for monotherapy with memantine, as well as combination therapy with the acetylcholinesterase inhibitor donepezil. Although not a cure for the disease, memantine may reduce clinical deterioration in persons with moderate to severe disease. In these persons, any improvement in cognitive, affective, and motor function that allows them to remain self-reliant and able to perform everyday tasks without or with only minimal external help is of great value.

**Adverse effects**

Common side effects reported during the use of memantine include somnolence, headaches, and insomnia. More severe side effects may include confusion, hallucinations, aggression, and psychosis.

**Effects on rehabilitation**

Adverse effects of memantine that may impact rehabilitation include somnolence, vertigo, gait abnormalities, and motor restlessness. These effects may be transient and occur during the initiation or dose escalation phase of treatment. Persistent functional problems should be evaluated and a risk versus benefit analysis performed to determine whether the benefit of memantine is substantial enough to warrant continued therapy.

**Dose reduction/titration**

Memantine requires a multi-week dose titration, increasing doses over the course of 4 to 6 weeks. If discontinued, doses should be titrated down incrementally, if possible. Response to memantine varies by individual, and clinical improvements may be minimal at best. Persons who experience adverse effects or limited response may have memantine titrated down or discontinued altogether. If beneficial, memantine treatment may continue indefinitely.

**Antipsychotics**

Psychosis of Alzheimer’s disease manifests as delusions and/or hallucinations, whereas symptoms of agitation include restlessness, verbal and physical aggression, forced motor behavior such as pacing, and irritability and resistance to care. These behaviors appear in up to 50% of persons with Alzheimer’s disease, may interfere with the delivery of basic care, and can cause distress and even endangerment to caregivers and other residents in institutional settings. Antipsychotic drugs can produce a modest improvement of some behavioral symptoms related to dementia. A shift from older “typical” antipsychotics (eg, haloperidol and chlorpromazine) to the newer “atypical” antipsychotics (eg, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone) has occurred in the past decade due to the improved safety profile of atypical antipsychotics. Atypical antipsychotic agents are preferred over conventional antipsychotics in elderly persons due to the lower incidence of extrapyramidal symptoms and tardive dyskinesias compared to conventional antipsychotics.

Older, typical antipsychotics work mainly in blocking the action of dopamine in the central nervous system by binding to the postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain. This binding is thought to help regulate the effects of dopamine in the brain, but can also affect dopamine-related motor functions.

Newer, atypical antipsychotics differ from the typical antipsychotics in the central nervous system receptors they affect. While typical antipsychotic agents focus mainly on
blocking dopamine receptors, atypical agents affect a variety of brain receptors. The true mechanism of action of atypical antipsychotics such as risperidone, quetiapine, olanzapine, aripiprazole, and ziprasidone is unknown; however, it is proposed that atypical antipsychotics’ activities are mediated through a combination of dopamine and serotonin-type blocking. Atypical antipsychotics, depending on the individual agent, may block various neurotransmitter receptors in different degrees: serotonin, dopamine, histamine, α-adrenergic receptors, cholinergic receptors, γ-aminobutyric acid (GABA), and β-adrenergic receptors can all be involved. Clinical trial data indicate comparable efficacies among antipsychotic drugs; therefore, clinicians usually base their choice of specific agents on the profile of adverse effects.

**Adverse effects**

Elderly individuals are sensitive to several of the serious nonmotor side effects that can result from the use of antipsychotic agents including sedation, orthostatic hypotension, changes in heart rate and rhythm, incontinence, and reduced appetite. In addition, the elderly are especially sensitive to anticholinergic effects (eg, constipation, confusion, blurred vision, dry mouth, urinary retention) of antipsychotics (Table 1).

**Typical antipsychotics (haloperidol, chlorpromazine, perphenazine, thioridizine)**

Typical and atypical antipsychotics each carry their own unique array of side effects; common adverse events associated with typical antipsychotics include Parkinsonian symptoms, sedation, postural hypotension, and anticholinergic effects (dry mouth, constipation, urinary retention). Less frequent, but more serious adverse events are tardive dyskinesias and neuroleptic syndrome (a medical emergency indicated by rigidity, altered mental status, diaphoresis, and fever).

**Atypical antipsychotics (risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone)**

Adverse effects including somnolence, dizziness, insomnia, agitation or hostility, personality changes, and speech disorders can occur with newer antipsychotics. Blocking of histamine H₁ receptors may result in the somnolence observed with atypical agents, and binding to α₁-adrenergic receptors may explain the orthostatic hypotension that may occur. These newer agents can cause extrapyramidal symptoms including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia, though the risk of these reactions is very low relative to older drugs. Prolonged use of atypical antipsychotics may cause hyperglycemia and/or weight gain. Moreover, the Food and Drug Administration recently issued a public health advisory describing a 1.6- to 1.7-fold increase in death rate of elderly persons with dementia receiving atypical antipsychotics for the treatment of behavioral disorders (compared with placebo). Causes of death mainly included cardiovascular events (eg, heart failure) and infection (eg, pneumonia) (Table 1).

**Effects on rehabilitation**

Antipsychotic drugs are very useful in the treatment of psychosis and severe agitation in dementia, but adverse events may limit their use. Common neuromotor side effects of all antipsychotic drugs can be grouped into 2 basic categories: (1) reversible effects, which usually disappear after the dose is lowered or the drug is discontinued and (2) potentially irreversible effects, which may persist even after discontinuation of drug therapy. Prevention of serious adverse events, by using the minimum dose and duration of treatment possible, is the key to managing motor side effects. If prevention fails, drug-induced parkinsonism and dystonia may improve with the use of anticholinergics and akathisia may improve with the use of benzodiazepines or low-dose propranolol. There is no proven
Table 1. Antipsychotic agents: Comparison of side effects

<table>
<thead>
<tr>
<th>Antipsychotic agent</th>
<th>Sedation</th>
<th>Extrapyramidal side effects</th>
<th>Anticholinergic side effects</th>
<th>Orthostatic hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>1+</td>
<td>0/1+</td>
<td>0/1+</td>
<td>0/1+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>4+</td>
<td>3+</td>
<td>3+/4+</td>
<td>3+/4+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>4+</td>
<td>0/1+</td>
<td>4+</td>
<td>4+</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1+</td>
<td>4+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1+</td>
<td>4+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>4+</td>
<td>1+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3+/4+</td>
<td>1+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Perhanzine</td>
<td>1+</td>
<td>3+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3+/4+</td>
<td>0/1+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2+</td>
<td>1+</td>
<td>0/1+</td>
<td>3+</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>4+</td>
<td>1+</td>
<td>4+</td>
<td>3+/4+</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>1+</td>
<td>4+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>1+</td>
<td>4+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2+</td>
<td>1+</td>
<td>0/1+</td>
<td>2+</td>
</tr>
</tbody>
</table>

*0 to 4+ = absent or rare to relatively common.
†Anticholinergic effects: dry mouth, urinary retention, constipation, blurred vision.

Table 2. Neuromotor side effects of antipsychotic medications

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Reversible</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>Usually</td>
<td>Tremor, increased muscle tone, bradykinesia or akinesia, drooling, postural instability, loss of spontaneity, micrographia</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Usually</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Usually</td>
<td>Sustained muscle contractions</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Sometimes</td>
<td>Involuntary body movements (usually choreiform), hyperkinesia</td>
</tr>
</tbody>
</table>

Treatment of tardive dyskinesias, which is most likely to be observed during dose reduction or after discontinuation of antipsychotic drugs (Table 2). Treatment of tardive dyskinesias, which is most likely to be observed during dose reduction or after discontinuation of antipsychotic drugs (Table 2). **Typical antipsychotics.** The most severe effects of conventional antipsychotics are tardive dyskinesia and extrapyramidal symptoms; these conditions can affect functional performance to a greater extent than the psychosis itself. Neuroleptic malignant syndrome, a medical emergency indicated by rigidity, altered mental status, diaphoresis, and fever, should be evaluated immediately. Restlessness, akathisia, lethargy, confusion, and vertigo have been reported with conventional antipsychotics, and may also hinder rehabilitation efforts.

**Atypical antipsychotics.** This group of antipsychotics can cause dizziness, swallowing difficulties, neck rigidity, twitching or tremors, hypertonia, abnormal gait, akathisia, and falls, especially in older persons.
**Dose reductions**

Antipsychotic agents can be successful in treating severe behavioral and psychological symptoms that present in the person with dementia. However, routine re-evaluation of drug therapy is needed as the course of dementia progresses. For residents in a nursing facility, appropriate indications for the use of antipsychotic medications are outlined in the Healthcare Finance Administration’s Omnibus Reconciliation Act of 1987. These regulations require that antipsychotics be used to treat specific problems and not solely for vague behavioral control. Gradual dosage reductions are to be attempted twice in 1 year if prescribed for symptoms of dementia. If symptoms for which the drug has been prescribed return and both reduction attempts have proven unsuccessful, the physician may indicate further that reductions are clinically contraindicated. “ Clinically contraindicated” means that a resident who has had a history of recurrence of psychotic symptoms (eg, delusions, hallucinations), which have been stabilized with a maintenance dose of an antipsychotic drug without incurring significant side effects (such as tardive dyskinesia), should not receive gradual dose reductions. Adverse effects that may surface during a dose reduction or discontinuation of antipsychotic therapy include myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia.

**Antidepressants**

Depression in Alzheimer’s disease is associated with excess disability, increased patient irritability, altered appetite, physical aggression, exacerbation of cognitive impairment, and generally impaired quality of life. Epidemiological studies of depression associated with Alzheimer’s disease report a prevalence of major and minor depression at 30% to 50%. Treatment of depression in the elderly can be accomplished using psychotherapy, family therapy, drug therapy, and electroconvulsive therapy. Clinical evidence supports the use of antidepressants in persons with depression superimposed on Alzheimer’s disease. The most useful medications are those with minimal anticholinergic side effects, such as the selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs). These medicines can improve the symptoms of sadness and apathy, and they may also improve appetite and sleep problems. Drug therapy is generally well tolerated, with the adage, “start low, go slow, and persist.”

Selective serotonin reuptake inhibitors such as fluoxetine, sertraline, escitalopram, paroxetine, citalopram, and fluvoxamine and SNRIs such as duloxetine and venlafaxine appear to be well tolerated and effective in treating geriatric depression. These medications work by blocking the reuptake mechanism of neurotransmitters from the synaptic cleft between neurons in the brain, leaving the neurotransmitters available to act in the brain for a longer period. Depending on the particular agent used, the result will be more available serotonin and/or norepinephrine in the brain.Selective serotonin reuptake inhibitors and SNRIs have become the drugs of choice for the treatment of depression in the elderly; having advantages in persons with dementia who are at particular risk of sedation and anticholinergic effects.

Older tricyclic antidepressants (amitriptyline, nortriptyline, doxepin, desipramine) work by increasing the synaptic concentration of neurotransmitters serotonin and/or norepinephrine in the central nervous system. This is accomplished by inhibition of the neurotransmitter’s reuptake by the presynaptic neuronal membrane. Tricyclic antidepressants are generally considered therapeutically equivalent to each other, although some older persons may respond better to one drug than another. The selection of an individual agent is based primarily on the side effect profile rather than the differential therapeutic efficacy. Older persons are particularly sensitive to the sedating, hypotensive, and anticholinergic side effects of all tricyclic antidepressants.
**Table 3. Antidepressant agents: Comparison of adverse effects**

<table>
<thead>
<tr>
<th>Antidepressant agents</th>
<th>Anticholinergic effects†</th>
<th>Drowsiness</th>
<th>Orthostatic hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>4+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Citalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Desipramine</td>
<td>1+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Doxepin</td>
<td>3+</td>
<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3+</td>
<td>3+</td>
<td>4+</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1+</td>
<td>3+</td>
<td>1+</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trazodone</td>
<td>0</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
</tr>
</tbody>
</table>

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†Anticholinergic effects: dry mouth, urinary retention, constipation, blurred vision.

**Adverse effects**

Tricyclic antidepressants (amitriptyline, nortriptyline) have significant anticholinergic properties, often causing dry mouth, constipation, blurred vision, and urinary retention. Central anticholinergic symptoms include agitation, confusion, hallucinations, and impairment of concentration, attention, and memory. Because of the frequency and severity of these side effects, tricyclic antidepressants are not the first choice agents for treatment of depression in the elderly; however, these agents are often used in the treatment of neuropathic pain. Newer antidepressants, the SSRIs and SNRIs, do not exhibit the extent of anticholinergic side effects in the elderly, but constipation and dry mouth are possible. Most common side effects of SSRIs are gastrointestinal disturbances (including nausea, vomiting, and diarrhea), central nervous symptoms (eg, agitation, anxiety, insomnia), and sexual dysfunction including decreased libido and impotence. Gastrointestinal complaints often resolve after the first month of therapy and may be minimized by taking SSRI medication with/after meals. Although some patients experience weight loss when SSRIs are initiated, weight gain may occur with long-term use of SSRIs (Table 3).

**Effects on rehabilitation**

Tricyclic antidepressants can be very sedating, and in fact are occasionally used as sleep-inducing agents; consequently, drowsiness and lethargy are of concern. In addition, these agents may cause orthostatic hypotension, impaired coordination, ataxia, tremors, and weakness. Side effects of SSRIs and SNRIs include dizziness, weakness, and tremor. Considering most antidepressants affect the amount of serotonin in the brain, there is a potential for serotonin syndrome—a severe reaction manifesting as hyperthermia, muscular rigidity, change in mental status, and autonomic instability. Serotonin syndrome is considered a medical emergency and any person exhibiting these symptoms should be evaluated immediately.

**Dose reduction**

Antidepressants should be continued at full therapeutic dosage for 6 to 12 months after resolution of depression.
with a history of recurrent depression, severe symptoms of depression, or suicide attempts, may require long-term continuation therapy. If the decision is made to discontinue antidepressant therapy, the medication should be slowly tapered over several weeks. Abruptly discontinuing shorter acting antidepressants may cause a withdraw reaction of dysphoric mood, irritability, anxiety, confusion, dizziness, and lethargy.16

**Benzodiazepines**

Benzodiazepines, indicated for anxiety and panic disorders, are also clinically used as sedative-hypnotics, anticonvulsants, and muscle relaxants. They are often used in the treatment of behavioral disorders associated with dementia including agitated states (that either endangers the patient or others, or is a source of distress or dysfunction), panic disorder, and symptomatic anxiety. Benzodiazepines work by binding to receptors on the postsynaptic GABA neuron at several sites within the central nervous system. Enhancement of the inhibitory effect of GABA on neurons results in a less excitable neuron and resultant stabilization. This stabilization creates the sedative/hypnotic/anticonvulsant/muscle relaxant properties of the benzodiazepines.15 Short-acting benzodiazepines such as oxazepam and lorazepam are preferred over long-acting drugs (eg, diazepam, chlordiazepoxide, and flurazepam). Long-acting benzodiazepines and their metabolites can accumulate in the body and last for days, increasing the chance for adverse effects.34 Long-acting benzodiazepine drugs should generally not be used in nursing facility residents or any elderly patient unless an attempt with a shorter acting drug has failed.24

**Adverse effects**

The most frequently reported adverse effects of benzodiazepines include sedation, confusion, ataxia, amnesia, and disinhibition.15 Long-acting benzodiazepines (diazepam, chlordiazepoxide, flurazepam, and chlortizepate) have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures.35 Short- and intermediate-acting benzodiazepines (lorazepam, alprazolam, oxazepam, triazolam) are preferred if a benzodiazepine is required.36

**Effects on rehabilitation**

Benzodiazepines cause central nervous depression, resulting in sedation, dizziness, confusion, and ataxia that may impair physical and mental capabilities.16 These effects may be most pronounced at the start of benzodiazepine therapy or when a dose is increased. Benzodiazepines have been associated with falls and traumatic injury, and should be used with extreme caution in persons who are at risk of these events.28

**Dose reduction**

Regulations from the Healthcare Finance Administration’s Omnibus Reconciliation Act of 1987 recommends that daily use of a benzodiazepine should be less than 4-continuous months unless an attempt at a gradual dose reduction is unsuccessful.24 Nursing facility residents using benzodiazepines should have a gradual dose reduction attempted at least twice within 1 year before it can be concluded that this dose reduction is clinically contraindicated. Rebound or withdrawal symptoms including confusion, heightened sensory perception, muscle cramping or twitches, numbness or tingling, and seizures may occur up to 3 days following abrupt discontinuation or large decreases in dose. Dose reductions or tapering should be approached with extreme caution in the person with dementia.16

**Other agents used in the treatment of Alzheimer’s disease: Selegiline and vitamin E**

Other agents explored in the treatment of dementia include selegiline and vitamin E. Vitamin E, an antioxidant, is thought to reduce the inflammatory effects of Alzheimer’s-related plaque formation in the brain.15 The argument for the use of vitamin E comes from
the Alzheimer’s Disease Cooperative Study,\textsuperscript{37} which evaluated the effects of 10 mg of selegiline once daily and/or 1000 IU of vitamin E twice daily as treatments of Alzheimer’s disease. The researchers concluded that these agents delayed disability and nursing home placement but not deterioration of cognitive function. Potential adverse effects with vitamin E are minimal but may include gastrointestinal upset, diarrhea, and weakness.\textsuperscript{16} Selegiline is an MAO-type B inhibitor. The enzyme MAO-B plays a major role in the metabolism of dopamine, and is possibly involved with neuroprotection.\textsuperscript{15} By inhibiting MAO-B, selegiline is thought to increase the effect of dopamine in the brain activity by preventing dopamine reuptake at the synapse. Selegiline is metabolized to amphetamine and methamphetamine in the body; consequently, possible side effects include orthostatic hypotension, hallucinations, dizziness, confusion, anxiety, and tremor.\textsuperscript{15} Because of the risk of serotonin syndrome (indicated by rigidity, severe agitation, and elevated temperature), selegiline therapy is contraindicated in persons who are taking meperidine, and this precaution is often extended to other opioids. Concurrent use of selegiline with tricyclic antidepressants and SSRIs also should be avoided.\textsuperscript{15} These restrictions and adverse effects may limit the use of selegiline in persons with Alzheimer’s disease.

### Anticholinergic medications: Potentially problematic for persons with dementia

Medications with anticholinergic activity block the action of acetylcholine at various sites in the body, including muscles, secretory glands, and the brain. Keeping in mind that Alzheimer’s disease is thought to be partly as a result of an acetylcholine deficiency, it follows that blocking the action of available acetylcholine in a person with Alzheimer’s disease is not an optimal therapeutic effect. In theory, the use of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) to increase the amount of acetylcholine and slow Alzheimer’s disease may be inhibited or negated by concomitant use of anticholinergic drugs.\textsuperscript{15} The concurrent use of anticholinergics is fairly common, as many medications used in the elderly have mild to moderate anticholinergic properties.\textsuperscript{38} Agents including diphenhydramine,\textsuperscript{39} gastrointestinal antispasmodics, urinary incontinence agents, muscle relaxants, and antidepressants have significant anticholinergic activity.\textsuperscript{16} Adverse effects such as agitation, confusion, delirium, behavioral problems, or impairment of activities of daily living may be exacerbated in elderly persons, especially those with dementia. Whenever possible, persons with dementia should avoid anticholinergic medications.\textsuperscript{38}

### SURVEILLANCE FOR ADVERSE MEDICATION EFFECTS: TEAM RESPONSIBILITY

As with any treatment, the use of pharmacologic agents to treat dementia and the associated behavioral issues requires a determination of the relative risks and benefits. Some central nervous system effects (e.g., sedation, gait disturbances, tremors) may be hazardous or damaging depending on the clinical situation. However, when therapeutic options are limited, the benefits may outweigh relatively minor side effects. In this regard, a great deal of individual variability in tolerance or intolerance may be seen with older persons depending on the mix of drugs, diseases, and medication sensitivities of each individual. Because of this unpredictability, all members of the healthcare team should maintain a high level of surveillance for medication-induced cognitive or physical adverse effects.

### REFERENCES


