Update on Alzheimer Disease

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Lesson description

This lesson reviews the most pertinent information that pharmacists should know to help optimize the care of patients with Alzheimer disease. It includes a review of prevention, diagnosis, and monitoring; medication therapies for maintenance of cognitive functioning; and medication therapies and principles of management for behavioural and psychological symptoms of dementia (BPSD). The most current Canadian dementia guidelines are reviewed and practical information is included to assist pharmacists in performing medication reviews for these patients as well as to allow them to monitor therapy outcomes.

Learning objectives

Upon completion of this lesson, the participant should be able to:

- describe the symptoms and progression of Alzheimer disease
- discuss methods of diagnosing and monitoring progression of Alzheimer disease
- describe the evidence to support strategies to prevent Alzheimer disease
- review the medications that can exacerbate cognitive impairment and discuss how this impact can be managed
- summarize the principles of appropriate use of cognitive enhancing medications for patients with Alzheimer disease, taking into consideration evidence of efficacy, duration of use, monitoring, adherence, potential toxicity, and management of adverse effects
- describe the more common types of behavioural and psychological symptoms associated with dementia (BPSD)
- review current management principles for BPSD, taking into consideration appropriate use of medication therapies
- outline the role of the pharmacist in the management of patients with Alzheimer disease and in consultation with families and other health care providers

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Rosemarie has been a Certified Geriatric Pharmacist since 1998. She has worked in geriatrics at Sunnybrook Health Science Centre, and in the community long-term care setting in her role as Manager of Healthcare Facilities Clinical Services at Shoppers Drug Mart. She has developed and taught a program in geriatric pharmacotherapy for Shoppers Drug Mart pharmacists across Canada. She is currently Manager of Pharmacy Marketing and Professional Services at Shoppers Drug Mart and continues to work in the community setting, conducting medication reviews for elderly patients.

Rosemarie has facilitated various modules within the Ontario Pharmacists' Association Certified Geriatric Pharmacist Preparation Course since its conception in 2004. She has published articles and continuing education lessons, and has spoken to various professional and public groups on topics related to seniors' health care, including Parkinson disease, hypertension, stroke, dementia, and osteoporosis.

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Dr. Cheryl Sadowski started her career in pharmacy in Manitoba, where she graduated from the University of Manitoba with her BSc(Pharm). She completed her Doctor of Pharmacy degree at Wayne State University (Detroit, Michigan), and a one-year post-doctoral residency in geriatrics through Campbell University (North Carolina).

Dr. Sadowski has worked in community, hospital, and ambulatory clinic settings. She currently is a team member of the geriatrics clinic at the Misericordia Community Hospital in Edmonton, Alberta. Over three quarters of patients seen in this clinic are assessed for cognitive impairment.

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Contents

1. Introduction

According to Statistics Canada, the steadily aging population will result in people over 65 making up about 26% of the population by 2025, with the numbers over 85 years of age increasing most.[1] This greying of the population will no doubt also lead to an increase in health conditions that occur most commonly with aging, such as osteoporosis, certain cancers, Parkinson disease, and Alzheimer disease (AD). Today, 7% of Canadians over 65 years of have Alzheimer disease, with a doubling of incidence and prevalence of the condition every 5 years past age 65.[2]

This lesson will provide pharmacists with an overview of the most current guidelines, evidence, and practices that support the care of individuals with Alzheimer disease. Contrary to common belief, most people with this condition live at home; a minority live in long-term care facilities.[3] Thus pharmacists working in both community and institutional pharmacy-based settings can impact on the quality of life of patients with AD, albeit at different stages in the progression of this condition.

2. What is Alzheimer disease?

Alzheimer disease is the most common type of dementia. It is a progressive neurological condition that occurs most commonly later in life; however, it can occur in earlier years, usually if associated with family history.[4] There are roughly 300,000 people in Canada with Alzheimer disease today. According to the Canadian Study of Health and Aging Working Group, that number is projected to grow to over 750,000 by 2031.[2]

While classically Alzheimer disease was differentiated from vascular dementia based on hallmark symptoms and pathology, research has suggested that it is not uncommon for older people to have both vascular and Alzheimer disease pathologies.[5] Vascular dementia has been defined as a group of syndromes related to vascular pathology; for example, a stroke increases the risk of vascular dementia. *Vascular cognitive impairment* is a newer terminology that encompasses vascular cognitive impairment with or without dementia and Alzheimer disease with cerebrovascular pathology.[5,6] Thus the distinction between vascular and Alzheimer dementia has become less clear. Other types of dementia identified include dementia with Lewy bodies (DLB), frontotemporal dementia, and Binswanger's dementia.[5,6]

The pathophysiology of Alzheimer disease involves three factors: amyloid plaques, neurofibrillary tangles, and progressive loss of connections between neurons – eventually leading to brain atrophy. Amyloid plaques are hardened pieces of beta amyloid protein that accumulate, as opposed to being eliminated as in a healthy brain.[7] Neurofibrillary tangles are dysfunctional fibres of tau protein (a normal protein in the brain) that are not able to carry nutrients from one nerve cell to another.[7] The apolipoprotein E gene, found on chromosome 19, has been associated with greater risk of developing Alzheimer disease. Most cases of early-onset Alzheimer disease are associated with a genetic link.[4] Corder et al. demonstrated that an increased number of apolipoprotein E4 alleles increased the risk of Alzheimer disease from 20% to 90% in 42 families studied, and the higher the number of alleles, the lower the age of onset of Alzheimer disease.[8] Although this association is well established, current guidelines do not recommend genetic testing for the general population to determine risk of Alzheimer disease.

It is also understood that reduced levels of acetylcholine in the brain of patients with Alzheimer disease, discovered on autopsy, contribute to the severity of the condition, depending on how reduced they are. In addition to lower levels of acetylcholine, increased levels of glutamate, an excitatory neurotransmitter in the brain, have been associated with neuronal death and subsequent cognitive symptoms of Alzheimer disease.[9]

There are several risk factors that have been identified for Alzheimer disease. Some are uncontrollable, including older age, the presence of apolipoprotein E4, family history, and mild cognitive impairment. Also, being female and having a lower educational level seem to be associated with Alzheimer disease. Other risk factors are less definitive but can be changed, for example vascular risks including hypertension, diabetes, and dyslipidemia. It is still questionable as to what role (outside of vascular protection) smoking cessation, aluminum, NSAIDs, and estrogen play in protecting against Alzheimer disease.[10]

2.1 Diagnosis

According to the third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, there are a number of different tests that should be done to adequately diagnose any type of dementia, including Alzheimer disease.

There is no laboratory test or marker to identify AD, so clinicians rely on validated tools and exclusion of other potential diagnoses to confirm that a patient has AD. This may partially explain why less than 25% of people with Alzheimer disease in Canada are actually diagnosed.[11]

There are a number of warning signs that may indicate the presence of Alzheimer disease. These warning signs include memory loss that affects daily functioning (e.g., forgetting to pay bills); difficulty performing tasks that the person is familiar with; language problems; disorientation to time and place (e.g., inability to find their way home); impaired judgment; difficulty with abstract thought; misplacing items; mood, behavioural, or personality changes; and loss of initiative (i.e., requiring prompting to get involved in an activity).[12]

Cognitive tests that could be performed by a primary care practitioner can help to identify dementia; however, they are not necessarily diagnostic on their own. These tests are used together with the clinical picture to refine the clinical investigation of the patient.[11]

The most common of these tools is the Folstein Mini Mental Status Exam (MMSE). The MMSE was first published in 1975 and created as a tool to allow clinicians to screen and monitor cognitive functioning in 4 areas: memory, attention, construction, and orientation. This is a brief questionnaire that is rated out of a possible 30 points. Although lower scores are usually attributed to some level of cognitive impairment, it is important to note that language barriers and education level can affect scores in the absence of cognitive impairment. An MMSE score of less than 26 is often associated with individuals with mild dementia, with lower scores correlating with severity of dementia; however, the score in itself is not diagnostic.[11,13]

Other brief tests are thought to be more accurate than the MMSE, including the Montreal Cognitive Assessment (MoCA), the DemTect, the 7-Minute Screen, the General Practitioner Assessment of Cognition, and the Behavioural Neurology Assessment Short Form.[11] The MoCA is more sensitive than the MMSE for detecting mild cognitive impairment and is also scored out of a possible 30 points. It is available in 15 different languages and has been adapted to a 5-minute version in addition to the standard version that takes roughly 10 minutes to complete. It can be accessed online at www.mocatest.org.[14] For a review of cognitive screening tests used in Alzheimer disease, refer to the Canadian Medical Association Journal article at www.cmaj.ca/cgi/content/full/178/7/825/T115.

The Diagnostic and Statistical Manual (version 4) provides a summary of diagnostic criteria for Alzheimer disease. The criteria are outlined in Table 1.

The National Institute of Neurological Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) also outlines diagnostic criteria for Alzheimer disease:[16]

Table 1. DSM-IV Criteria for Alzheimer Disease[15]

- Cognitive deficits including memory impairment and one of the following:
  - aphasia (difficulty with language), e.g. difficulty articulating medication side effects
  - apraxia (difficulty with motor tasks despite motor function intact), e.g., difficulty opening a vial
  - agnosia (inability to recognize things despite all senses intact), e.g., patient cannot recognize you even though you have known the patient for years
  - disturbance in executive function, e.g., inability to take their blood pressure reading and write it down
- Causes significant impairment in social or work functioning
- Gradual onset and ongoing cognitive decline
- Not accounted for by another central nervous system condition, systemic condition, or substance abuse
- Symptoms do not occur exclusively during a delirium
- Symptoms not accounted for by another psychiatric condition

- dementia established by examination and cognitive tests
- deficits in two or more cognitive domains (e.g., memory, attention, executive function)
- progressive worsening of memory and other cognitive functions
- no disturbance in consciousness
- onset between ages 40 and 90

A diagnosis of Alzheimer disease is more likely if the patient presents with altered behavioural patterns and family history. It is less likely to be Alzheimer disease if it occurs suddenly or if the patient presents with visual or other sensory changes, incoordination, hemiparesis (defined as weakness on one side of the body), or early gait disturbances or seizures.[11]

Clinicians should also rule out systemic disorders or other brain diseases that could cause memory or cognitive impairment. The third Canadian Consensus Conference on Dementia recommends the use of the NINDS-ADRDA criteria to help make the clinical diagnosis of Alzheimer disease.[11]

Laboratory tests are required to rule out other possible causes of dementia symptoms. The tests that are recommended include complete blood count (CBC) to rule out anemia, TSH to

rule out hypothyroidism, electrolytes to rule out hyponatremia, serum calcium to rule out hypercalcemia, and fasting blood glucose to rule out hyperglycemia. Also, serum vitamin B_{12} levels should be taken and deficiency corrected with vitamin B_{12} supplementation, as this can potentially improve cognitive function.[11]

Computed tomography (CT) scan of the head may be useful to rule out other potential causes or complicating medical conditions in patients who present with dementia symptoms who are less than 60 years of age, have a rapid decline in cognitive function, have head trauma, have a history of cancer, are taking anticoagulants, have gait disturbances, or have early urinary incontinence.[11]

2.2 Progression of Alzheimer disease

As Alzheimer disease is a progressive condition, it is important for pharmacists to understand how this progression occurs, how rapidly, and what types of cognitive, behavioural, and other changes can occur. It is currently understood that Alzheimer disease progresses slowly, and patients generally live with this condition for up to 10 years, depending on when the diagnosis occurs.

Mild cognitive impairment (often referred to as MCI) can precede a diagnosis of Alzheimer disease. A patient with MCI may have impaired memory for their age and level of education, intact cognitive functioning, and minimally or not impaired ADL functioning. MCI is not dementia but may be a cause of decrease in memory. Patients can also have other issues including changes in attention, visuospatial functioning, problems with instrumental activities of daily living (e.g., finances), and depression.[17]

The stages of progression of Alzheimer disease have been well documented. The Functional Assessment Staging system has been validated as a tool to determine the stage of Alzheimer disease.[18] MMSE scores have been associated with the different stages of the condition. See the table below for this information.

Functional Assessment Staging Tool (FAST)[19]

Stage	Description	MMSE Average Score
1	Normal	29–30
2	Normal aged forgetfulness	28–29
3	Mild cognitive impairment	24–28
4	Mild Alzheimer disease	19–20
5	Moderate Alzheimer disease	15
6	Moderately severe Alzheimer disease	1–9
7	Severe Alzheimer disease	0

In the early stages of Alzheimer disease, in the first few years, cognitive symptoms are most prominent, notably short-term memory loss (for recent events). The cognitive changes at this stage may not be noticed by patients and family members, and therefore, the patient may not see a physician until later stages.[18]

The next stage, characterized by functional changes, occurs in the mild-to-moderate phase of Alzheimer disease. Functional changes include difficulty performing instrumental activities of daily living (IADL), including managing finances and medications, driving, and preparing meals. Personal activities of daily living (ADL) become difficult at the disease progresses, leading to inability to bathe, eat independently, use the toilet, and dress. [18]

Behavioural changes can occur at different stages but more commonly in the later stages of disease. Behavioural changes are described in more detail below. In the earlier stages of Alzheimer disease, depression and apathy are more common. In the later stages of disease, aggressive behaviours and psychosis can occur.[18]

In the severe stage of Alzheimer disease, patients become unable to perform ADLs, even with prompting by another person.[18]

Nursing home placement tends to coincide with the onset of significant behavioural changes. It is most typically in the later stages of disease but not always. Eventually patients die of conditions that are secondary to the decline of Alzheimer disease (e.g., pneumonia).[20]

2.3 Monitoring

The goals of management of Alzheimer disease are slowing of cognitive decline and improving quality of life. Monitoring of the patient with Alzheimer disease should include an ongoing assessment of cognitive status, including changes in MMSE and MoCA scores and alterations in other assessment tool scores. Even though cholinesterase inhibitor therapy may be used, Alzheimer disease results in decline in cognitive status, as seen through the MMSE and MoCA, for example. Also, patients and family members or caregivers should be interviewed to check for onset of behavioural and psychological symptoms associated with dementia. Specific behaviours and realistic expectations for changes in these behaviours should be determined with the patient and caregiver, allowing for subsequent and ongoing monitoring for improvement, worsening, or no change. Caregiver burden and need for additional assistance for patients living at home are important to consider as the Alzheimer disease progresses. Patients and family members should be referred to local support groups or branches of the Alzheimer Society for ongoing support.[21]

3. Prevention strategies

The association of Alzheimer disease with cerebrovascular pathology suggests the need to address vascular risk factors for primary prevention. This includes ensuring that hypertension is controlled, achieving a target of less than 140/90 mmHg or less than 130/80 mmHg in people with diabetes. Blood pressure reduction must be approached carefully in older patients to minimize the risks of orthostatic hypotension and falls. Also in people with diabetes, it is important to strive for A1c levels of less than 7% to reduce vascular risks. Cholesterol levels should also be controlled, with a target LDL less than 2.5 mmol/L and target total-cholesterol-to-HDL ratio less than 4. Lifestyle changes are critical to helping meet these targets and reduce vascular risks; this includes smoking cessation, reduction in alcohol consumption, weight management, low-fat and low-sodium diet, physical activity, and stress reduction.[22] Although it is important to manage cholesterol levels and blood glucose for overall vascular health, there is insufficient evidence that these strategies can reduce the incidence of AD.[11]

According to the 3rd Canadian Consensus Conference on dementia, it is useful to recommend that patients with and without memory loss participate in cognitively stimulating activities as part of a healthy lifestyle.[11]

A recent prospective cohort study of elderly people living in the community demonstrated that regular exercise and a Mediterranean diet were independently associated with a decreased risk of developing Alzheimer disease.[23] Other published studies have demonstrated the benefits of a healthy diet and exercise on reducing the risk of Alzheimer disease.[24,25,26] Where possible, all patients should be encouraged to adopt a healthy lifestyle.

Independent of the association of high blood pressure and dementia, ACE inhibitors have demonstrated a protective role against Alzheimer disease. In a comparative study of patients with hypertension taking ACE inhibitors enrolled in the Cardiovascular Health Study Cognition Substudy, a 6-year follow-up demonstrated that those taking centrally acting ACE inhibitors (e.g., perindopril) had 65% less decline in MMSE scores over time than did those taking other antihypertensives.[27] The study authors suggest that the effect of these agents on central renin-angiotensin activity (which affects memory and cognition) may play a role in this proposed protective effect. Randomized controlled trials are needed to obtain more conclusive evidence.

The use of NSAIDs has been associated with a reduced risk of developing Alzheimer disease, and it was thought that this could be due to the effects of prostaglandin inhibition. The ADAPT study was a randomized, double-masked chemoprevention trial in the US that tested the hypothesis that NSAIDs can reduce the risk of Alzheimer disease. In patients with a family history of Alzheimer disease, neither celecoxib 200 mg twice daily nor naproxen 220 mg twice daily showed benefits related to cognitive functioning compared to placebo.[28] As there are conflicting study results, current recommendations for prevention do not include the use of NSAIDs.

Some studies have shown that cholesterol can play a role in the development of Alzheimer disease.[29,30] At this time, there is inadequate evidence to recommend a cholesterol-lowering agent for the purpose of preventing Alzheimer disease. However, as previously mentioned, it is prudent for all patients to maintain healthy cholesterol levels to reduce vascular risks.[11]

A vaccine to protect against Alzheimer disease was developed and studied in clinical trials until 2002. Unfortunately, 6% of patients in the trials with the vaccine developed encephalitis and others developed brain shrinkage. The vaccine studies were stopped and further development is ongoing.[31]

Ongoing study is required to fully understand how best to prevent Alzheimer disease. There is little evidence to support specific interventions for prevention, even though risks have been well defined.

4. The medication review for the Alzheimer disease patient

With the increasing demand for pharmacist medication review in the community setting for patients at high risk of medication-related problems, pharmacists should consider patients with Alzheimer disease as potential candidates for ongoing review and follow-up. The pharmacist's medication review should target high-risk medications in this population, which have been well-defined within the Beers criteria.[32] Some examples of these medications include:

- certain tricyclic antidepressants (e.g., amitriptyline, doxepin)
- long-acting benzodiazepines (e.g., flurazepam, chlordiazepoxide)
- digoxin in a dose greater than 0.125 mg per day
- meperidine
- methyldopa
- pentazocine

Although there are often caregivers administering medications, cognitive impairment as well as the older age of most of these individuals increases their risks of medication-related problems. Pharmacists should identify unnecessary use of any medication and recommend discontinuation to the patient's physician when appropriate.

In general, consider the physiological changes that occur with aging that can have bearing on therapies related to Alzheimer disease. Renal and hepatic function can be compromised in an older person, thus decreasing their dose requirements of certain medications (e.g., benzodiazepines) and increasing the risk of toxicity. Older people are generally more sensitive than younger adults to the side effects of psychotropic medications, so prudent use of these types of medications is critical. For example, long-term use of benzodiazepines should be investigated and tapering to discontinue the medication considered where appropriate. Fat-to-muscle ratio increases with age, thus leading to accumulation of fat-soluble medications (e.g., psychotropic medications). Also, pharmacists should consider changes in the ability to swallow oral medications and how to facilitate this depending on the specific medication.[33]

People with cognitive impairment are at risk of worsening of cognition if their medication profile has a high anticholinergic load.[34] One of the most important medication characteristics to flag in the medication review of the patient with Alzheimer disease is anticholinergic effects. Pharmacists should be aware of medications that are anticholinergics and those that have anticholinergic properties. A list of some medications with anticholinergic effects is provided in Table 2. Where potentially offending medications exist on the profile, pharmacists should discuss discontinuation or alternatives with the patient and their physician where appropriate. In some cases, an anticholinergic agent may be indicated (e.g., overactive bladder) and risks and benefits must be weighed for that patient. It is also important to note that anticholinergics can interact with cholinesterase inhibitors, resulting in a reduced effect of the cholinesterase inhibitor.[35]

Another aspect of the medication review to focus on in patients with Alzheimer disease is appropriate management of cerebrovascular risk factors. If required, it is important to ensure that the patient is taking (or caregiver is providing) medications to control blood pressure, cholesterol, and diabetes as prescribed. Pharmacists should encourage patients to keep a log of relevant readings (i.e., blood pressure, lipids, and blood glucose) to track their progress and promote adherence.

Appropriate use of medications in general is a consideration for any medication review. For patients with Alzheimer disease, continuing to take cholinesterase inhibitors if benefits continue to be realized can help to optimize quality of life. It is common to stop the medication prematurely. According to the guidelines published in 2008 by the American College of Physicians and the American Academy of Family Physicians, benefits can continue for 3 to 5 years and patients should continue on therapy, if tolerated, for as long as the benefit is noted.[36] It is important to note that patients should be monitored carefully for improvement or stabilization of cognition (through tests such as the MoCA) or behaviours to help determine how long to continue therapy. Other factors to consider when determining whether or not to continue therapy include the ability to pay for the medication if not covered by a plan, tolerability of adverse effects, and physician and caregiver opinions on the benefit of the medication. Although little evidence supports the ongoing use of cholinesterase inhibitors beyond one to two years, clinical experience and some studies have shown that ongoing benefits can be achieved in some patients. Pharmacists should also consider recommendations to discontinue medications that are no longer required or beneficial, and provision of written medication schedules to assist in medication adherence.

Memory impairment, even in early stages, can affect the ability to take medications properly. Pharmacists should work with the patient and/or their caregiver(s) to determine the best approach to ensuring appropriate medication use. This might include blister packaging; special labelling on prescription vials, dossettes, or pill boxes; switching to once-daily medications where possible; and optimization of medication schedules.

Any medication review should include a discussion of over-the-counter products and supplements. In addition to noting non-prescription medications with anticholinergic effects such as

Table 2. Medications with anticholinergic properties

- Tricyclic antidepressants (e.g., amitriptyline)
- Antipsychotics (e.g., chlorpromazine)
- Antiparkinsonian agents (e.g., trihexiphenidyl)
- Antihistamines (e.g., diphenhydramine)
- Antispasmodics (e.g., cyclobenzaprine)

Note that not all medications within the categories above have significant anticholinergic effects; thus, specific agents must be considered when reviewing the patient's medications, rather than the class of medications.

antihistamines, pharmacists should review the benefits and risks of supplements such as ginkgo biloba and ginseng. With limited evidence to support the benefits of ginkgo and ginseng in improving cognition in people with Alzheimer disease, patients should be aware of potential drug interactions of these two supplements with warfarin if applicable.

5. Medications to treat cognitive and functional symptoms of AD

Current medication therapy for Alzheimer disease is focused on enabling the patient to maintain quality of life for as long as possible; it does not stop the progression of the dementia. Cholinesterase inhibitors and N-methyl-D-aspartate antagonists can slow the progression of the Alzheimer disease symptoms and may reduce the behavioural and psychological symptoms of dementia.[37]

5.1 Cholinesterase inhibitors

Cholinesterase is the enzyme responsible for the breakdown of acetylcholine. Acetylcholinesterase and butyrylcholinesterase are two types of this enzyme, and butylcholinesterase is thought to play an important role when acetylcholinesterase is no longer available. Nicotinic modulation that occurs with galantamine enhances the effects of acetylcholine. In Alzheimer disease, the brain is lacking acetylcholine, and cholinesterase inhibitors play an important role in enhancing cholinergic function. The cholinesterase inhibitors available in Canada include donepezil, rivastigmine, and galantamine. They are all reversible inhibitors of both types of cholinesterase, with varying degrees of specificity for the two types of enzyme.[38]

These agents have been demonstrated to be efficacious for patients with mild-to-moderate Alzheimer disease. The cholinesterase inhibitors have shown benefits in global clinical state and cognition (e.g., memory, language).[39] In most trials of cholinesterase inhibitors, the cognitive portion of the Alzheimer Disease Assessment Scale is used to assess changes in cognitive function. A clinically significant improvement is considered a change of 4 points (out of a total possible score of 70).[40]

An important consideration with cholinesterase inhibitors is duration of therapy. Most trials of cholinesterase inhibitors have lasted up to 6 months, with very few trials lasting a year or more. This may not be sufficient to demonstrate benefits over time.[40]

Observational studies have demonstrated benefit of the cholinesterase inhibitors for up to 5 years; however, this type of evidence is considered weak relative to that obtained from placebo-controlled, double-blinded randomized trials. The current recommendations indicate that cholinesterase inhibitors should be continued, if tolerated by the patient, for as long as cognitive function is maintained at an acceptable level to that patient and their family.[40]

All cholinesterase inhibitors have the potential to interact with other medications that have anticholinergic effects, or with medications that have cholinergic agonist effects.[21]

Monitoring of patients taking cholinesterase inhibitors involves the expected positive outcomes as well as adverse effects of the medication. A baseline cognitive assessment should be used as a comparator to subsequent tests. Commonly, the MMSE is used to evaluate changes in cognitive function for the patient taking a cholinesterase inhibitor. Adverse effects are similar amongst the cholinesterase inhibitors, including nausea and bradycardia. [40]

Tacrine was the first available cholinesterase inhibitor in Canada; however, it is used under only extraordinary circumstances as compassionate release due to the high risk of hepatotoxicity associated with this medication.[41]

Donepezil is more specific for acetylcholinesterase and is currently labelled for use in mild, moderate, and severe Alzheimer disease. This medication is very specific for centrally acting acetylcholinesterase, and thus has limited peripheral adverse effects. The usual dose of donepezil is 5 mg once daily, with or without food, later in the day, titrating to 10 mg if tolerated. The most common adverse effects noted with donepezil are nausea, vomiting, and diarrhea related to cholinergic activity. Patients who experience vivid dreams should be instructed to take donepezil earlier in the day. Generally, these adverse effects resolve with time and do not require patients to reduce the dose or switch to another cholinesterase inhibitor. This cholinesterase inhibitor is metabolized in the liver by cytochrome p450 2D6 and 3A4, thus potentially interacting with ketoconazole and quinidine.[42]

Clinical trials with donepezil have demonstrated a slowing of cognitive decline when the medication is used continuously. Placebo-controlled trials of donepezil have been done for up to 1 year and open-label trials for as long as three years.[43,44,45] Donepezil has also shown to be beneficial, compared to placebo, in a number of trials that assessed functioning.[43,44] Increasingly, cholinesterase inhibitors are being used to help manage behavioural and psychological symptoms associated with Alzheimer disease. Two separate placebo-controlled

trials with donepezil in patients with Alzheimer disease showed improvements in NPI (Neuropsychiatric Inventory – a tool that assesses behaviours and their severity in people with dementia) scores that were significantly greater than that seen with placebo.[46,47]

Rivastigmine is only approved for the treatment of mild-to-moderate Alzheimer disease. Unlike donepezil, it is a nonspecific inhibitor of both centrally acting acetylcholinesterase and butyrylcholinesterase. The usual starting dose of rivastigmine is 1.5 mg twice daily, titrating slowly over 2-week periods up to a maximum of 6 mg twice daily. It can cause nausea, vomiting, diarrhea, weight loss, and loss of appetite, but these effects tend to be minimized over time. A case of severe vomiting leading to esophageal rupture in a patient who had therapy with rivastigmine has led to a warning in the product monograph related to reinstating therapy once it has been discontinued.[74] The product monograph states that severe vomiting and nausea are more likely to occur in the titration phase, so patients should be started at a low dose (1.5 mg bid) even if therapy is being reinstated after several days without the medication.[48] The rivastigmine patch is an alternative dosage form that has been shown to reduce gastrointestinal adverse effects.[49] Rivastigmine is not affected by other drugs metabolized by cytochrome p450, as it is not largely metabolized by this enzyme system.[42]

Placebo-controlled trials with rivastigmine have demonstrated benefits in cognition, functioning, and behaviour. Open-label trials have shown continued benefits of rivastigmine in patients with Alzheimer disease for up to 5 years.[50,51,52]

Galantamine is also approved for the treatment of mild-to-moderate Alzheimer disease. It is specific for both central and peripheral acetylcholinesterase, with nicotinic cholinergic agonist effects. The initial dose is 8 mg daily or 4 mg twice daily, titrating over 4-week intervals up to a maximum of 24 mg daily. It is recommended that galantamine be taken with food to minimize adverse gastrointestinal effects, including diarrhea, nausea, vomiting, and weight loss. Adverse effects tend to be more pronounced when the dose is titrated upwards. Galantamine is metabolized by cytochrome p450 2D6 and 3A4, thus having the same potential drug interactions as donepezil, in addition to a possible interaction with paroxetine (inhibition of galantamine metabolism).[42]

Similar to donepezil and rivastigmine, trials of galantamine in patients with Alzheimer disease have demonstrated improvements in cognition, functioning, and behaviour. Open-label trials have shown continued benefits of galantamine for up to 3 years.[53,54]

All available cholinesterase inhibitors are similar in many aspects. The differentiating features include dosing regimen, adverse effects incidence, cost, and titration schedule. Also, it is important to note that donepezil is the only agent approved for severe Alzheimer disease. Since there are no significant differences in efficacy (or direct comparative trials to show differences) between the available agents, other differentiating features would be the most important considerations in the choice of agent.[39]

Should a patient not respond to a particular cholinesterase inhibitor, the recommendation is to switch to another agent in this class or to consider using memantine as an alternative. Although the target dose of a cholinesterase inhibitor is the maximum dose, if the patient cannot tolerate the cholinesterase inhibitor that they have been prescribed, the dose should be decreased if possible, or the medication should be stopped.[39]

5.2 Memantine

The excitatory neurotransmitter glutamate plays a role in learning and memory processes, and overstimulation of n-methyl-d-aspartate (NMDA) receptors by glutamate leads to destruction of neurons. Memantine is an NMDA receptor antagonist that is approved for the treatment of moderate-to-severe Alzheimer disease. The initial dose is 5 mg daily, titrating up to a maximum of 10 mg twice daily (or 5 mg twice daily in patients with severe renal impairment), with or without food. Adverse effects include headache, dizziness, and constipation. Memantine is excreted unchanged by the kidneys and is not affected by other medications metabolized by liver enzymes. Drug interactions may include H2 receptor blockers, hydrochlorothiazide, carbonic anhydrase inhibitors, quinidine, amantadine, and dextromethorphan.[42]

Double-blind, placebo-controlled randomized trials of memantine in patients with moderate-to-severe Alzheimer disease have demonstrated small benefits in cognition and activities of daily living at 6 months of therapy.[55] There is some evidence that memantine can also be beneficial in mild-to-moderate Alzheimer disease. [56]

Memantine can play a role in the treatment of the patient with Alzheimer disease as a monotherapy or together with a cholinesterase inhibitor, although the evidence is inconsistent on the benefits of combination therapy.[39] There is some evidence that memantine may be beneficial for the management of behavioural symptoms in patients with Alzheimer disease.[57]

Table 3 provides an overview of the dosage

Table 3. Dosing and availability of approved therapies for Alzheimer disease[42,58,59,60,61,62]

Medication	Dosage forms	Dosing and titration
Donepezil (Aricept®)	5 mg, 10 mg tablet 5 mg, 10 mg rapidly disintegrating tablet	5 mg daily. Increase to maximum of 10 mg daily after 4 to 6 weeks.
Rivastigmine (Exelon®)	1.5 mg, 3 mg, 4.5 mg, 6 mg capsule Transdermal patch 5 (4.6 mg/24hr), 10 (9.6 mg/24hr) Oral solution 2 mg/mL	1.5 mg twice a day with food. Increase to 3 mg BID after 2 weeks. Exercise caution in doses higher than 6 mg BID. Increase to maximum of 6 mg BID in two week intervals. For patch, start at 4.6 mg and if tolerated, titrate to 9.6 mg after 4 weeks. To switch from capsules to patch, use 5 mg patch for oral doses < 6 mg per day and 10 mg patch for oral doses 6 mg or higher per day. In patients with renal or hepatic impairment, start with once daily low dosing and titrate more slowly.
Galantamine (Reminyl®, Reminyl® ER)	4 mg, 8 mg, 12 mg tablets 8 mg, 16 mg, 24 mg capsules extended release	8 mg daily in the morning with food. (Regular release tablets are usually BID.) Increase to 16 mg daily after 4 weeks. Can increase to a maximum of 24 mg daily after 4 weeks.
Memantine (Ebixa®)	5 mg tablet	5 mg daily in the morning. Weekly increments of 5 mg. Maximum dose of 10 mg BID. Decrease dose in moderate renal impairment. Should not be used in severe renal impairment. Despite long terminal half-life (60–100 hours), dosing is BID.

forms and dosing of the available cholinesterase inhibitors and memantine. Pharmacists should take note of the products with unique dosage forms, including rivastigmine transdermal patch and oral solution as well as galantamine extended release capsules.

The cholinesterase inhibitors and memantine are the only agents approved for the treatment of Alzheimer disease. Patients should be given an adequate trial of 3 to 6 months of these therapies before the determination of effectiveness is made, with the goal of therapy being disease stabilization (i.e., maintenance of similar level of cognition as prior to starting therapy) rather than improvement. If the medication is not effective over this time period, it should be discontinued. Other reasons to stop therapy, from the Canadian dementia guidelines, include nonadherence to therapy, patient/caregiver choice, intolerable adverse effects, or disease progression or other interacting comorbidities.[39]

5.3 Other medications

Several other types of medications, vitamins, and natural health products have been considered for the treatment and prevention of Alzheimer disease.

Vitamin E is an antioxidant substance that has been studied at various dosages for the prevention and treatment of cognitive impairment and progression to Alzheimer disease. A recent Cochrane review showed no consistent benefit of supplementation with vitamin E, regardless of dose, in the prevention or treatment of Alzheimer disease.[63] In general, supplements with less than 400 IU of vitamin E are considered safe. According to the Canadian Consensus Conference on Diagnosis and Treatment of Dementia, authors conclude that doses of vitamin E higher than 400 IU per day are associated with excess mortality and should not be used.

It has been proposed that ginkgo biloba can improve cognition as a result of effects on blood flow in the brain. A recent 8-year trial of over 3000 people at 4 clinical sites, 75 years or older with no or mild cognitive impairment, tested the benefits of 120 mg ginkgo twice daily for reducing the incidence or rate of incidence of Alzheimer disease. The study showed no benefits at this dose. Pharmacists should be aware of potential drug interactions with gingko, most notably with warfarin (resulting

in a potential increase in bleeding risk).[64]

Several studies have attempted to demonstrate the benefits of ginseng for Alzheimer disease. In a recent review, only 2 studies were identified as methodologically sound. Although these studies showed improvement in MMSE and ADAS-cog, overall the evidence for ginseng is not sufficient to support the use of ginseng to prevent or manage Alzheimer disease. [65]

Regular use of NSAIDs has been shown to be associated with a lower risk of dementia and specifically, Alzheimer disease. A study of people 65 years of age and older using NSAIDs demonstrated the reduced risk of Alzheimer disease; however, this effect was largely seen in individuals who had the apolipoprotein E4 allele.[66] In a trial of 2736 people over 65 years of age without dementia, NSAID use was identified through pharmacy records and subjects were followed up biennially up to 12 years. The results of this study conflicted with most other evidence for the benefits of NSAIDs; "heavy users" of NSAIDs had a higher incidence of dementia and Alzheimer disease.[67] Currently there is no recommendation regarding using NSAIDs to prevent Alzheimer dementia.

6. Behavioural and psychological symptoms of dementia (BPSD)

Up to 90% of patients with Alzheimer disease will develop additional symptoms that further complicate the management of their condition.[68] Behavioural and psychological symptoms of dementia encompass a number of different types of symptoms. Table 4 outlines the types of symptoms that are referred to as BPSD.

In a study that compared behavioural changes in patients with Alzheimer disease and age-matched controls, it was found that apathy was the most common behaviour seen in the Alzheimer group. Agitation, anxiety, and irritability were the next most common behaviours noted. In this study, anxiety, agitation, apathy, and dsyphoria were highly correlated with cognitive impairment. Some patients may develop depression and social withdrawal even before the diagnosis of Alzheimer disease. In general, anxiety along with mood changes are most common in the early stages of Alzheimer disease. Later, delusions, wandering, agitation, and sexual disinhibition can occur. In later stages of disease, aggressive behaviours and hallucinations may be more common.[69]

Pharmacists who work in long-term care or hospital settings may be more likely to encounter these behaviours in their practice because it is often the onset of these symptoms that results in institutionalization. It becomes difficult for caregivers to manage the patient at home and ensure their safety.

Initially and in patients with mild BPSD, behaviours should be managed without the use of medications. It is important to try to identify and manage specific causes for the behaviour – for instance, uncontrolled pain, urinary tract infection, hunger – to avoid unnecessary medication therapy. For example, modifying the environment can help to reduce vocalizations and wandering, which would not respond to medication therapy. Table 5 outlines behaviours that will not respond to medication therapy and those that may. Support groups and scheduled activities can help patients and caregivers cope with the changes in their functioning

Table 4. Behavioural and psychological symptoms of dementia[68]

Earlier symptoms

- apathy (withdrawal, lack of interest)
- sleep disturbances (e.g., insomnia)
- mood disturbances (depression)

Later symptoms

- aggressive behaviour (e.g., striking out, pushing, verbal)
- anxiety
- agitation (e.g., pacing, repetitive actions)
- disinhibition
- dysphoria
- vocalizations (e.g., crying, shouting)
- wandering
- psychotic behaviours (e.g., hallucinations, delusions)

Table 5. Behaviours and their response to medication therapy[70]

Behaviours that do not respond to medications	Behaviours that might respond to medications
• Wandering • Inappropriate dressing or undressing • Nuisance behaviours such as repetitive vocalizations • Hoarding items • Eating inappropriate items	• Anxiety • Depressive symptoms • Sexually inappropriate behaviours • Verbal and physical aggression • Delusions and hallucinations • Mania • Sleep disturbances

and subsequently reduce some mild BPSD.[70]

6.1 Types of behaviour

6.1.1 Delusions and hallucinations

Psychotic symptoms such as delusions and hallucinations can occur in patients with Alzheimer disease. Although it is important to identify other conditions (e.g., delirium, pain) that could be contributing to the symptoms, antipsychotics are the drugs of choice for treatment.[71]

6.1.2 Sleep disturbances

Sleep disturbances are common in patients with Alzheimer disease, commonly manifested as sleeping more than usual and waking early. These changes can be difficult for caregivers and are often a contributing factor to nursing home placement. Sleep structure can be changed, resulting in day-night sleep pattern reversals and greater likelihood of napping during the day. As with all behaviours associated with dementia, caregivers should evaluate other potential causes (e.g., untreated pain or depression) before initiating other treatments. Three non-pharmacological modalities have shown some benefits in one clinical trial – light therapy, exercise, and sleep hygiene. Light therapy involves the use of a high intensity "light box" to increase exposure to light during the day, for 30 to 90 minutes. This light can impact on the circadian system to reduce nighttime awakenings. Physical activity for at least 30 minutes per day can help to improve sleep and reduce functional dependence and depression. This can be as simple as going for a daily walk. Sleep hygiene measures have been shown to contribute to a consistent bedtime and waking time and fewer daytime naps. Strategies such as limiting fluids and caffeine-containing foods and beverages in the evening, maintaining a dark environment, and reducing noise were effective in one trial.[72]

6.1.3 Anxiety and Agitation

As with most behaviours, nonpharmacologic strategies should be used prior to starting any medications to specifically treat symptoms of anxiety. Patients commonly present with agitation that can often be managed by creating a daily routine and simplifying tasks to minimize frustration. Also, reducing stimulation and providing reassurance and redirection often can reduce anxiety.[71]

6.1.4 Depression

Patients with Alzheimer disease commonly have symptoms of depression, and 20–40% of them are diagnosed with depression. Although these patients may not present with suicidal ideation, they may have apathy, lack of interest in activities, and loss of appetite.[73] Symptoms of depression can be managed with nonpharmacological approaches as well as the use of antidepressants. Non-pharmacological strategies can include establishing a daily routine that is appropriate for that patient; providing reassurance and encouragement; increasing exposure to the patient's favourite people, places, and things; and psychotherapy for early-stage Alzheimer disease.[74]

6.2 Guidelines for the use of medication therapies for BPSD

Guidelines for the use of pharmacological therapies for the treatment of BPSD suggest[71]:

- use the lowest possible dose of psychotropic agent to manage the symptoms
- re-evaluate the treatment strategy regularly (i.e., every 12 weeks)
- attempt discontinuation of the psychotropic medication used for BPSD every few months

It is important to titrate the dose slowly to avoid adverse effects, reduce the dose if the patient experiences adverse effects, and use regularly scheduled doses rather than as-needed doses (if the patient has intermittent symptoms, use non-pharmacological treatment strategies).[71]

6.2.1 Antipsychotics

If the patient is dangerous to themself or others around them, or if they present with psychotic symptoms, antipsychotic medications may be prescribed. Antipsychotics are the most commonly used medications to treat BPSD. Although only one of the atypical antipsychotics, risperidone, is approved in Canada for the treatment of BPSD, other agents in this class are commonly used for this indication.

There are several cautions that must be considered prior to starting antipsychotic therapy for a patient with Alzheimer disease. Weight gain is associated with atypical antipsychotics, subsequently leading to greater insulin resistance, cholesterol abnormalities, and blood pressure changes. Metabolic adverse effects were demonstrated in an analysis of subjects in the CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease) study who had Alzheimer disease. This analysis showed that clinically significant weight gain occurred in 20% of outpatients with Alzheimer disease, increasing over 36 weeks with antipsychotic treatment. It is important to note that the CATIE-AD trial initially demonstrated minimal efficacy for BPSD, so the authors of the analysis suggest that clinicians consider these

Table 6. Dosing for atypical antipsychotics[78,79,80]

Agent	Dose	Availability
Risperidone	0.25 mg BID up to 0.5 mg BID; some patients may benefit from 2 mg per day	Oral tablets, orally disintegrating tablet, liquid
Olanzapine	2.5–5 mg per day, up to 10 mg per day	Oral tablets, orally disintegrating tablet, intramuscular injection
Quetiapine	12.5–25 mg daily, up to 150 mg per day	Oral tablets

adverse effects when using atypical antipsychotics in these patients, and if they are used, to monitor the patient closely. Olanzapine demonstrated the greatest changes in cholesterol and waist circumference in this study.[75]

The risk of stroke and mortality with atypical antipsychotics has been documented and debated. Due to the nature of Alzheimer disease and the high likelihood that cerebrovascular risk factors exist in these patients, it is advisable to monitor these factors closely in patients that require antipsychotic therapy and ensure that strict adherence with preventative therapies (e.g., ASA, antihypertensives, lipid-lowering agents) is followed. [76]

When considering the choice of atypical antipsychotic for a patient with Alzheimer disease, note that risperidone may be most likely to cause extrapyramidal symptoms (e.g., parkinsonian symptoms). This is an important consideration in patients with Parkinson disease or other movement-related disorders. Olanzapine may be more likely to cause anticholinergic effects and has been associated with vascular risk factors. Quetiapine may cause hypotension and sedation.[77]

Table 6 outlines the dosing of the atypical antipsychotics for the acute treatment of BPSD. It is important to start with the lowest possible dose as older patients with AD may be very sensitive to the effects of antipsychotics.

6.2.2 Other agents used to treat BPSD

Anxiolytics

Benzodiazepines are commonly used to help manage anxiety and agitation associated with dementia. The behaviours that seem to respond best to benzodiazepine therapy include anxiety, tension, irritability, and insomnia.[81] In light of the significant adverse effects associated with these agents in older patients (e.g., falls, confusion, ataxia), only short-acting benzodiazepines should be used if necessary in the lowest effective dose for a short period of time. The agents that could be tried include low doses of lorazepam (0.5 mg), oxazepam (15 mg), and temazepam (15 mg). When discontinuing benzodiazepines that have been used for over one month, it is important to taper the dose gradually to minimize the risk of withdrawal symptoms.[81] Zopiclone is an alternative to benzodiazepines for insomnia.

Although buspirone has not been shown to be as effective as benzodiazepines for the management of agitation in dementia, it can be used as an alternative for the management of mild anxiety. It is generally well tolerated compared to benzodiazepines.[81]

Anticonvulsants

Anticonvulsants are reserved for difficult behaviours and psychosis associated with Alzheimer disease. The most frequently used agents in this class include carbamazepine and divalproex sodium or valproic acid. Although they can be effective in reducing agitation and behaviours, they can cause significant side effects (i.e., leucopenia with carbamazepine or abnormal liver function with both agents); therefore, close monitoring including blood levels is required. Valproic acid may have fewer drug interactions and therefore can be a more suitable choice in patients with BPSD on multiple medications.[82]

Antidepressants

Trazodone is an antidepressant that is used mostly for sundowning in patients with Alzheimer disease. This is a phenomenon in which patients exhibit increased confusion and agitation in the early evening and nighttime hours. It is generally used in low doses (e.g., 25–50 mg) rather than typical antidepressant doses. Trazodone can be sedating and can cause hypotension.[83]

Most tricyclic antidepressants are not recommended for older patients with Alzheimer disease in light of the fact that these patients are at higher risk of significant issues associated with the anticholinergic effects of these medications. Anticholinergic effects can exacerbate confusion and can cause urinary retention, blurred vision, and cardiac conduction abnormalities. Secondary amine tricyclic antidepressants are less likely to have anticholinergic effects and may be considered in this population. These agents include nortriptyline and desipramine.

Selective serotonin reuptake inhibitors (SSRIs) are generally well-tolerated in patients with Alz-

heimer disease with depressive symptoms. Citalopram has been shown, in placebo-controlled trials in older people, to improve depressive symptoms, anxiety, agitation, and social interaction.[84,85] Other experience shows that most SSRIs can improve mood and are well tolerated in the elderly Alzheimer disease patient.[86]

In general, SSRIs (e.g., citalopram, sertraline), secondary amine tricyclic antidepressants, mirtazapine, and moclobemide are considered safer options for the management of depression in patients with Alzheimer disease. The choice of agent depends on past response to any therapy, other medical conditions, and other medications.

Pharmacists should consider the monitoring parameters for patients with Alzheimer disease taking an antidepressant. Specifically, patients should expect to see related symptom changes, including sleep alterations, appetite changes and enhanced energy level before changes in mood occur.

Cholinesterase inhibitors and memantine

Cholinesterase inhibitors and memantine have both demonstrated some efficacy in reducing behavioural and psychological symptoms associated with dementia. A trial of one or both of these agents can be utilized as an option for difficult behaviours.

There is evidence of the efficacy of cholinesterase inhibitors on specific types of BPSD, including apathy, hallucinations, delusions, anxiety, and depression.[87,88,89]

Other agents

Lithium is a mood stabilizer that is usually indicated for bipolar disorder. It has been used to treat certain types of behaviours associated with dementia, but has little evidence to support efficacy and safety in the Alzheimer disease population. Uncontrolled studies have shown conflicting results with high risk of toxicity in patients with BPSD.[82]

Uncontrolled studies of beta-blockers have shown some benefits for the treatment of BPSD. There have been no controlled studies in patients with Alzheimer disease with BPSD, so there are no specific recommendations for their use in this population.[82]

7. Other considerations for the care of the patient with AD

In addition to medical management of the patient with Alzheimer disease, clinicians and caregivers must consider other factors that can affect the safety and well-being of these patients.

It is important that any caregiver, whether a health care provider (e.g., nurse or aide) or family member, be informed about the condition and what to expect. Through learning about the natural progression of Alzheimer disease, caregivers can prepare themselves, the patient, and the living environment for the expected changes. Pharmacists can play an important role in educating caregivers as a result of their day-to-day interactions with patients and/or their caregivers.

Support groups and day programs can help patients and caregivers adapt to cognitive, memory, and behavioural changes, and can facilitate some of the learning that is required. The Alzheimer Society of Canada (www.alzheimer.ca) is a good source of information about support groups and local programs.

Everyone caring for a person with Alzheimer disease should consider safety issues and take the necessary steps to reduce risks to that person in their care. It can be a difficult time when driving privileges are revoked as a result of the dementia, and wandering is common when disorientation occurs. Activities of daily living can present dangers, and caregivers should consider risks associated with food preparation or the use of appliances in the home.

As an individual with Alzheimer disease progressively loses cognitive functioning, it is most important that legal matters are organized, particularly by planning advanced directives including the naming of a substitute decision maker.

8. Pharmacist's role in the management of the patient with AD

In the community setting, where the majority of patients with earlier stages of AD receive health care, pharmacists are important sources of knowledge and support for them and their caregivers. Pharmacists should review medications of these patients regularly to identify drugs that can worsen cognitive impairment, such as anticholinergics and benzodiazepines. Where feasible, pharmacists should collaborate with the patient and their physician to find effective alternatives to the potential offending agents.

Where cognitive function appears to worsen acutely, pharmacists should consider other potential causes, including drug interactions, blood glucose disparities, or infections (e.g., urinary tract). As drug experts, pharmacists have a responsibility

to inform patients, family, other caregivers, and other health care providers about medications that can aggravate the cognitive impairment of Alzheimer disease, including over-the-counter products and natural health products.

Pharmacists play an important role in helping patients with medication adherence. Patients with Alzheimer disease are at risk of nonadherence with therapies, particularly with therapies for cognitive and functional symptoms. This can be due to the perceived lack of efficacy, memory impairment, or health care provider lack of knowledge of duration of therapy. As patients are seen most frequently in community pharmacies, ongoing follow-up, reminders, and monitoring of outcomes is an important role of the pharmacist. The pharmacist can assist with monitoring for target goals and side effects on a regular basis. This can be achieved by a patient or caregiver interview, MMSE, MoCA, or other simple cognitive assessment tool.

Blister cards or other specialized medication packaging may be required for many patients with Alzheimer disease and their caregivers to simplify medication administration and reduce the number of missed doses. Pharmacists should be proactive and discuss available options that can facilitate medication taking, including recommendations to reduce the number of medications or doses for the patient and providing medication schedules.

For patients taking antipsychotics or other therapies for BPSD, pharmacists should reassess the need for these medications on a regular basis, especially since most BPSD eventually diminish as the disease becomes more severe.

Pharmacists can also assist patients and their families in obtaining drug coverage for certain therapies (e.g., cholinesterase inhibitors), and by referring to home care and other supportive resources in their community. A useful website for patients is www.dementiaguide.com. The content of this website is interactive and credible and the Chief Scientific Officer is Dr. Kenneth Rockwood, a Canadian geriatrician and dementia expert.

With a growing body of evidence to support prevention of Alzheimer disease by reducing vascular risk factors, pharmacists must focus on helping all patients, particularly those at highest risk, reduce these risks. This includes counselling on hypertension management, normalizing lipid levels, and maintaining good control of blood glucose levels.

9. Summary

Alzheimer disease is a progressive neurological condition that occurs mostly in older individuals. It is the most common type of dementia and it appears to be associated with many risk factors, including vascular risks such as hypertension and diabetes.

Alzheimer disease is characterized by cognitive decline over time, including initial memory impairment. The condition progresses and most patients experience behaviour and psychological symptoms of dementia, including apathy, agitation, and aggression.

Pharmacists play an important role in education and medication management. A medication review is an important part of the care plan for patients with Alzheimer disease to ensure that adherence and outcomes are optimal and that no drug interactions exist.

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Questions

Questions 1–3 refer to the following case:
GH is an 82-year-old male living on his own. He comes to the pharmacy to ask about taking ginkgo to help improve his memory. When you engage him in a dialogue about his history, you find that he has high blood pressure, and he indicates that he has been forgetting things more lately. Despite learning from you that gingko is likely not effective for dementia, GH insists on taking this supplement.

1. Which of the following should be the pharmacist's first consideration when counselling GH on the use of ginkgo biloba?
   a. a medication history to determine whether or not there may be any potential interactions
   b. an MMSE score to determine his level of cognitive impairment
   c. a determination of whether or not his blood pressure is well controlled
   d. the most appropriate dose of ginkgo to improve his memory

2. What should the pharmacist do on the patient's next medication review?
   a. recommend to the physician discontinuation of any drugs with anticholinergic properties when possible, or switching to another more suitable agent
   b. check blood pressure medication and whether or not blood pressure is well controlled
   c. assess GH's ability to take medications on his own and provide support if necessary
   d. all of the above

3. What can the pharmacist recommend that GH do to prevent Alzheimer disease?
   a. ask for a referral to a neurologist for assessment
   b. avoid using aluminum pots and pans when cooking
   c. take his blood pressure medications regularly as prescribed
   d. take a pain medication such as naproxen regularly

Questions 4–6 refer to the following case:
RT is a 76-year-old female who has been diagnosed with Alzheimer disease. She was prescribed donepezil 5 mg daily and has been taking it for 2 months. She complains of nausea and tells you that she sometimes skips the medication because of this side effect.

4. How should the pharmacist counsel RT?
   a. Tell RT to continue to take the donepezil despite the nausea.
   b. Advise RT to take the medication at bedtime to minimize the feeling of nausea.
   c. Tell RT to stop taking the donepezil and contact her doctor to switch to another agent.
   d. Tell RT to continue to take the donepezil and contact her doctor to increase the dose.

5. Eventually, RT's physician decides to switch to rivastigmine. What is a potential benefit of switching RT from donepezil to rivastigmine?
   a. Rivastigmine is less likely to cause nausea than donepezil.
   b. Rivastigmine may be more effective for the management of AD.
   c. Rivastigmine has a longer dosing interval than donepezil.
   d. Rivastigmine may be less likely to have drug interactions than donepezil.

6. RT continued to take rivastigmine for 7 months, and according to her husband, her level of functioning and memory have declined substantially and they think that she should not take the medication anymore. What should be considered as part of the decision of whether or not to stop cholinesterase therapy?
   a. whether or not documented benefits continue to occur
   b. whether or not the patient tolerates the medication
   c. whether or not the patient can be adherent to the medication schedule
   d. all of the above

Questions 7–9 refer to the following case:
TM is a 75-year-old male with AD living on his own in the community who has scheduled a medication review with his pharmacist. He is currently taking the following medications: digoxin 0.0625 mg daily, hydrochlorothiazide 25 mg daily, senna 2 tablets at bedtime, ranitidine 150 mg at bedtime, atorvastatin 10 mg at suppertime, lorazepam 0.5 mg at bedtime, and galantamine 8 mg daily.

7. Which of the following is an important consideration for the pharmacist's medication review with TM?
   a. The digoxin dose may be too high, contributing to cognitive impairment.
   b. Moderate-acting benzodiazepines, such as lorazepam, should be avoided in elderly patients.
   c. Assess TM's medication adherence and take into consideration living arrangements and sensory impairment.
   d. Histamine-2 blockers such as ranitidine should be avoided in patients with Alzheimer disease.

8. TM has been taking galantamine at the current dose for 2 months. He says that he has not had any problems with it. Which of the following is the correct titration?
   a. Increase to 16 mg daily for 2 weeks, then 16 mg BID.
   b. Increase to 16 mg daily and maintain at this maximum dose.
   c. Increase to 8 mg BID for 2 weeks, then 8 mg TID.
   d. Increase to 16 mg daily, then up to 24 mg daily in 4 weeks if tolerated.

9. TM asks the pharmacist about taking vitamin E. He says that he has heard that it can help maintain his memory. How should the pharmacist advise TM?
   a. TM should take vitamin E at a dose of 2000 IU to slow progression of AD.
   b. TM can take vitamin E less than 400 IU daily but it has not been proven to slow progression of AD.
   c. TM should not take vitamin E, as it can worsen his AD symptoms.
   d. At a dose of 400 IU daily, vitamin E can interact with galantamine.

Questions 10–12 refer to the following case:
SJ is an 80-year-old female resident of a nursing home. She has had AD for 5 years and was recently admitted to the facility because of the onset of behavioural and psychological symptoms of dementia (BPSD). Specifically, SJ has begun to wander and become quite agitated often.

10. Which of the following is correct about the management of SJ's behavioural problems?
    a. Wandering can be managed with a benzodiazepine such as lorazepam.
    b. Caregivers should consider reasons for behaviours to ensure the most appropriate choice of medication.
    c. Drug therapy should only be used in the lowest possible doses for behaviours such as agitation that respond to medications.
    d. Antipsychotic drugs are the treatments of choice for SJ's behavioural problems.

11. Which of the following is an example of an appropriate non-pharmacological approach to managing TM's symptoms?
    a. physical restraint to eliminate wandering
    b. modifying the environment to allow for safe wandering
    c. psychotherapy to address agitation
    d. none of the above

12. TM begins to get more agitated and strikes at the other nursing home residents and staff. The physician decides to start an antipsychotic. Which of the following is correct about antipsychotic therapy for TM?
    a. Traditional antipsychotics are not the best choice because they are most likely to cause extrapyramidal symptoms.
    b. The most likely atypical antipsychotic to cause anticholinergic effects is quetiapine.
    c. Antipsychotic use should be re-evaluated every year and discontinuation considered at that time.
    d. all of the above

Questions 13–15 refer to the following case:
JB is an 87-year-old male resident of a long-term care facility. He is currently taking donepezil 10 mg daily for AD, ASA 325 mg daily, ramipril 10 mg daily, furosemide 40 mg daily, and oxybutynin 2.5 mg twice daily. JB's mood has changed in the past few weeks, and he appears to be depressed.

13. JB's physician would like to treat him with an antidepressant. Which agent would be most appropriate for him?
    a. clomipramine
    b. citalopram
    c. fluoxetine
    d. doxepin

14. Which medication should be re-evaluated in light of his medical conditions?
    a. ASA
    b. furosemide
    c. ramipril
    d. oxybutynin

15. JB's family asks whether or not he should continue to use donepezil. How should the pharmacist determine whether or not JB's donepezil should be continued?
    a. The donepezil should be continued if JB's MMSE score is less than 18.
    b. Donepezil should be continued for at least 3 years.
    c. If JB's cognition and other target symptoms continue to be favourably maintained, donepezil therapy is likely still benefiting the patient and can be continued if he is tolerating it well.
    d. The pharmacist should suggest that the medication be discontinued after 1 year.

Questions 16 and 17 refer to the following case:
RC is an 85-year-old female who lives with her husband in her own home. She is quite independent and wants to stay that way. She visits the pharmacy to pick up her prescriptions (naproxen 250 mg BID, alendronate 70 mg once weekly, simvastatin 40 mg daily, diltiazem CD 240 mg daily) and asks for the pharmacist's advice on how to prevent Alzheimer disease.

16. What should the pharmacist advise RC with regards to prevention of AD?
a. She should continue to take naproxen regularly, as it can prevent AD.
b. She should check her blood pressure regularly.
c. She should consider taking estrogen therapy to prevent AD.
d. All of the above.

17. RC says that she has heard that taking vitamin B supplements can prevent dementia. How should the pharmacist respond?
a. If you have a deficiency of vitamin B_{12}, it can result in symptoms like confusion. It is important to take vitamin B_{12} supplementation if a deficiency is present.
b. Vitamin B supplements should be taken by people over the age of 65 to prevent dementia.
c. Vitamin B is not associated with any of the symptoms of dementia.
d. Vitamin B_6 levels can be reduced in people with Alzheimer disease, so it is a good idea to supplement with this vitamin.

Question 18 refers to the following case:
MR is a 77-year-old male living in the community with a caregiver. He was recently diagnosed with AD and was put on rivastigmine 1.5 mg twice daily. His initial MMSE score was 23.

18. MR's caregiver indicates that he is experiencing nausea and diarrhea and refusing to take the rivastigmine. What should the pharmacist recommend?
a. Take dimenhydrinate to minimize the side effects of the medication and continue to take it for 2 more weeks.
b. Switch to another cholinesterase inhibitor, such as donepezil.
c. Titrate the dose of rivastigmine to 3 mg BID after at least 2 weeks of therapy, as the nausea and diarrhea should dissipate.
d. Add memantine to this therapy.

Questions 19 and 20 refer to the following case:
PT is an 88-year-old female with AD who has been taking galantamine 16 mg daily for the past 4 months. The medication has been generally well tolerated and her physician would like to add memantine to her treatment regimen to achieve optimal benefits.

19. Which of the following pharmacist recommendations regarding memantine is correct?
a. It should be started at 10 mg daily and titrated every 2 weeks.
b. The dose of galantamine should be decreased to 8 mg daily and memantine started at 5 mg daily.
c. Memantine can be started at 5 mg daily and titrated every week.
d. The physician should discontinue the galantamine prior to starting memantine to reduce the patient's risk of diarrhea.

20. PT starts to develop confusion and agitation in the evening hours after dinner. Which of the following is the most appropriate treatment for this type of symptom?
a. risperidone
b. valproic acid
c. buspirone
d. trazodone