Dementia: What pharmacists need to know

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As primary care professionals who see patients regularly, pharmacists can recognize early signs of dementia and encourage patients to seek assessment. If a patient receives a diagnosis of dementia, pharmacists can continue to provide care, from recommending support services to managing medications.

En tant que professionnels des soins primaires qui voient régulièrement des patients, les pharmaciens sont à même de reconnaître les premiers signes de démence et d'encourager les patients à recevoir une évaluation. Si un patient reçoit un diagnostic de démence, le pharmacien peut continuer à fournir des soins, de la recommandation de services de soutien jusqu'à la gestion des médicaments.

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"Of all the things I've lost, I miss my mind the most."

—Mark Twain

Introduction

Dementia is a devastating disease that places a significant physical, emotional and financial burden on patients, their caregivers and society. About 564,000 Canadians have dementia today, and by 2031, the figure is projected to increase to 937,000.[1] Its management is particularly costly: the combined health care system and out-of-pocket caregiver costs of dementia in Canada are estimated to be $10.4 billion in 2016, a figure expected to double by 2031.[1]

Pharmacists are trusted health care providers who play a vital role in patient education, medication counselling and drug therapy management and monitoring—a broad spectrum of professional services that benefit both patients with dementia and their caregivers. This article is part of a series[2] that aims to identify roles, strategies and resources pharmacists can use and apply in daily clinical practice when caring for patients with dementia. More specifically, this therapeutic update focuses on current approaches used in the diagnosis of dementia, the assessment of cognitive function and the pharmacotherapy of dementia. To prepare this article, the authors reviewed literature on dementia, its diagnosis and treatment and assessment of cognitive function. The studies deemed most relevant to a pharmacist's clinical practice were included in this article.

What is dementia?

Dementia refers to a clinical syndrome characterized by progressive cognitive decline that interferes with the ability to function independently.[3,4] Symptoms of dementia are gradual, persistent and progressive. Individuals suffering from dementia experience changes in cognition, function and behaviour. The clinical presentation of dementia varies greatly among individuals, and the cognitive deficits it causes can present as memory loss, communication and language impairments, agnosia (inability to recognize objects), apraxia (inability to perform previously learned tasks) and impaired executive function (reasoning, judgement and planning). Cognitive impairment stems from injury to the cerebral cortex caused by synaptic failure, inflammation and change in cerebral metabolism.[5]

Patients with mild deficits who do not meet the criteria for dementia are considered to have mild cognitive impairment (MCI), an objective cognitive impairment with preserved function.[5] People with MCI may experience difficulties with memory, language, thinking or judgement that are greater than the cognitive changes expected with normal aging.[6] While MCI can be assessed objectively with cognitive tests, the impairments are considered to be insufficient to interfere with an individual's daily life and independence.[6] As Alzheimer's disease (AD) is a progressive condition, in its early stages, individuals may present with MCI. Moreover, individuals with MCI are at higher risk of developing Alzheimer's disease and other dementias than those without MCI.[7-10] The reported annual conversion rate ranges from 1.6% to 28%, depending on definitions and operational criteria and settings within these definitions.[7,11-14] A meta-analysis of cohort studies indicated that in specialist settings, a cumulative proportion of 39.2% of individuals with MCI deteriorated to dementia, but in

population studies, 21.9% deteriorated.[14] A significant number of individuals with MCI remain cognitively unchanged or return to normal cognition status.[10,14,15]

Behavioural and psychological symptoms of dementia are complications of dementia. The most common symptoms (agitation, apathy, aggression, psychosis, hallucinations and delusions) cause considerable distress and may pose a safety risk for patients and their caregivers. Unfortunately, many behavioural and psychological symptoms, such as wandering, hoarding, inappropriate behaviours (e.g., sexual disinhibition, eating inappropriate objects), repetitive behaviour and restlessness, do not respond well to pharmacotherapy. In the most recent *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the term *neurocognitive disorder* was introduced and replaced the term *dementia*,[16] which was referred to in the DSM-IV as "dementia, delirium, amnestic and other cognitive disorders."[17] The 6 cognitive domains affected by dementia are learning and memory, language, complex attention, executive function, perceptual-motor and social cognition. The neurocognitive disorder is classified as mild or major, depending on the severity of symptoms.[16] More precisely, patients with mild neurocognitive disorder have modest cognitive decline from previous levels of performance in 1 domain or more. In contrast, major neurocognitive disorder is diagnosed when deficits in 1 domain or more interfere with independence in everyday activities.[16]

KNOWLEDGE INTO PRACTICE

- As the Canadian population ages, the prevalence of dementia is increasing exponentially and with it the demands placed on individuals, society and health care providers.
- Pharmacists can take on a larger role in treating and supporting individuals with dementia, in particular educating patients and caregivers about the condition and its progression, becoming familiar with screening tools that can be used in pharmacy practice to assess cognitive function and helping to manage medications for patients in different stages of dementia.

Subtypes of dementia

Dementia is an umbrella term used to describe a clinical syndrome of progressive cognitive decline, but its subtypes are classified according to the cause of dementia. The 4 common types of dementia—AD, vascular dementia, Lewy body dementia and frontotemporal dementia—are described below and summarized in Table 1.

TABLE 1 Distinguishing features of subtypes of dementia[18]

Dementia subtype	Clinical presentation*
Alzheimer's disease	• Insidious onset and slow progressive decline • Short-term memory impairment in early stage; deficit on 3-word or 5-word recall; executive function impairment in later stages
Vascular dementia	• Sudden or gradual onset • Usually correlated with cerebrovascular disease (stroke, lacunar infarcts) and atherosclerotic comorbidities (diabetes, hypertension, coronary heart disease) • Mild memory impairment in early stage • Possible gait difficulties and falls (depending on the extent of the stroke)
Lewy body dementia	• Fluctuating cognition associated with parkinsonism • Poor executive function and visual hallucinations in early stage; deficits on tests designed to examine visual perception (pentagons, cube, trails, clock face)
Frontotemporal dementia	• More prominent personality changes (disinhibition) and behavioural disturbances (apathy, aggression, agitation with less memory impairment in early stage)

*Clinical presentation summaries from Muangpaisan W. Clinical differences among 4 common dementia syndromes. *Geriatr Aging* 2007;10(425):9.

MISE EN PRATIQUE DES CONNAISSANCES

- À mesure que la population canadienne vieillit, la prévalence de la démence augmente de façon exponentielle et les demandes auxquelles doivent répondre les individus, la société et les fournisseurs de soins de santé s'accroissent en conséquence.
- Les pharmaciens peuvent jouer un plus grand rôle dans le traitement et le soutien des personnes atteintes de démence, en particulier en informant les patients et les aidants sur la maladie et sa progression, en se familiarisant avec les outils de dépistage qui peuvent être utilisés dans la pratique de la pharmacie pour évaluer la fonction cognitive, et en gérant les médicaments des patients à différents stades de la démence.

Alzheimer's disease

AD is the most common neurodegenerative disease responsible for dementia, comprising 60% to 80% of cases. It is believed to derive from the accumulation of beta-amyloid plaques and neurofibrillary tangles, first in the brain areas of the entorhinal cortex and the hippocampus, which induces neuronal injury and, subsequently, neuronal death. The resulting decrease in cholinergic neurotransmission gives rise to loss of memory and cognition. More precisely, neurotransmitter abnormalities include reduced activity of choline acetyltransferase (involved in the synthesis of acetylcholine) and a reduced number of cholinergic neurons. As it spreads to other parts of the brain, neurons progressively die in affected regions, thereby worsening the symptoms of AD. Genetics is a contributing factor to the development of AD. While late-onset AD is most commonly diagnosed in patients after the age of 60, early-onset AD (diagnosed in individuals age 30 to 60) is associated with autosomal dominant mutations in 3 genes: *PSEN1, APP* and *PSEN2*.[19] Apolipoprotein E has been identified as a genetic risk factor in late-onset AD.[19]

While the onset of AD is usually undetectable, short-term memory loss is most commonly the first sign. Gradual deficits in cognitive function occur progressively over time, affecting multiple cognitive domains. For treatment and assessment, AD symptoms are classified as cognitive and noncognitive. While the former are usually present throughout the illness, the latter are less predictable in the course of the disorder. More specifically, cognitive symptoms include memory loss (poor recall, losing items), aphasia, agnosia, apraxia, disorientation (impaired perception of time, unable to recognize familiar people) and impaired visuospatial function and executive function. Patients with AD may also present noncognitive symptoms such as depression, psychotic symptoms (hallucinations, delusions) and behavioural symptoms (such as physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities and combativeness). AD is usually characterized by early problems in memory and visuospatial abilities (e.g., becoming lost in a familiar environment). Personality changes and behavioural difficulties may develop as the disease progresses. Hallucinations may occur in moderate to severe dementia. At the end stage, patients may present with near mutism, lacking the ability to sit up, hold up their head or track objects with their eyes.

Vascular dementia

Vascular dementia is the second most prevalent form of dementia (20%).[20] Also called *multi-infarct dementia*, vascular dementia results from neuronal deprivation of oxygen caused by conditions that either block or reduce blood flow to the brain. Stroke is the most common cause of vascular dementia. Its symptoms can vary widely, depending on the affected regions of the brain and the severity of the blood vessel damage. After a major stroke, the most prominent symptoms include confusion, disorientation, difficulty with speaking, understanding speech and vision loss. Memory may not be affected in vascular dementia, but a sudden change in executive function (e.g., thinking, reasoning) might surface after a stroke. In contrast, multiple small strokes lead to a more gradual decline in executive function as damage accumulates. *Mixed dementia* refers to the co-existence of AD and vascular dementia.

Lewy body dementia

Lewy body dementia (LBD) is a form of dementia caused by abnormal deposits of alpha-synuclein protein (Lewy bodies) inside neurons. It accounts for 5% to 15% of all dementias.[21] The most distinctive features of LBD include fluctuating cognitive impairment with variations in attention and alertness, recurrent complex visual hallucinations and spontaneous parkinsonism.[21,22] The prevalence of fluctuating mental

status in LBD is between 30% and 89%. In contrast to AD, caregivers of patients with LBD may observe lethargy, daytime somnolence, sustained periods of staring into space (episodes of blank staring with disengagement from the environment), periods of improved memory, episodes of disorganized speech and periods of decreased attention.[22] Furthermore, rigidity, bradykinesia and rapid eye movement (REM) sleep disorders are more commonly observed in early stages of LBD. Although memory loss tends to be a complaint in early AD, it is more frequently observed in advanced LBD.[21] More than 80% of individuals with LBD develop parkinsonism. To differentiate LBD from Parkinson's disease dementia (PDD), the temporal course of the disease and the clinical presentation are considered: with LBD, the onset of dementia occurs up to 12 months before parkinsonism, but PDD patients demonstrate parkinsonian symptoms at the time of dementia diagnosis. Moreover, tremor is more commonly observed in PDD, while postural instability and gait difficulty are more frequent extrapyramidal symptoms associated with LBD.[18]

Frontotemporal dementia

Frontotemporal dementia (FTD) is a general term used to describe disorders, such as Pick's disease, that affect the frontal and temporal lobes of the brain.[23] FTD tends to occur at a younger age (40-75 years) than does AD. Personality changes and behavioural disturbances are key features of FTD and occur early in the disease. In contrast to AD, visuospatial function is usually not affected.

Clinical evaluation

In clinical practice, the diagnosis of dementia and its subtype is based on a detailed patient history, physical examination, cognitive assessment and laboratory testing. Neuroimaging tools, such as magnetic resonance imaging or computed tomography scans, establish the diagnosis. Since cognitive impairment is usually multifactorial, a detailed history is essential. The clinician gathers information from the patient and collateral history from a reliable informant about the history of present illness (details, timing and progression of complaints), functional status (basic activities of daily living), safety (driving, finances, ability to use appliances), medical history (cardiovascular disease, neurologic disease, history of head trauma or concussions) and social history (current living arrangement, support network). Risk factors for dementia include a positive family history, repetitive head trauma, cardiometabolic factors (diabetes, hypertension, obesity and dyslipidemia), atrial fibrillation, sleep apnea and previous depression.[5,24-27]

A medication review and review of systems should be part of the evaluation. Several conditions may contribute to cognitive impairment, including adverse drug effects, depression, thyroid disease, vitamin B_{12} deficiency, hypercalcemia, sleep apnea, atrial fibrillation, subdural hematoma and delirium. The latter can be distinguished from dementia by their acute onset, fluctuating course and deficits in attention rather than memory. Older patients are particularly vulnerable to the sedating effects of medications such as benzodiazepines, sedative hypnotics, anticholinergics, opioid analgesics and antipsychotics. Since medications may be reversible causes of cognitive impairment, pharmacists should evaluate the benefits of these medications vs their possible contribution to cognitive impairment for each patient with dementia symptoms.

Assessment scales for primary care

Many types of assessment scales have been developed for dementia in the domains of cognition, function, behaviour, quality of life, depression, caregiver burden and severity of illness.[3] Examples of cognitive tests and the types of symptoms they could be used to assess are presented in Table 2. These scales can use reports from patients, their caregivers or observers. In primary care, brief cognitive screening instruments are commonly used to detect cognitive impairment, as such impairment is the core factor in dementia diagnosis.[16] In Canada, the Mini-Mental State Exam (MMSE),[28] Montreal Cognitive Assessment (MoCA),[29] Clock Drawing Test[30] and delayed word recall are the most frequently used tools by family physicians and psychogeriatric clinicians.[31,32] These instruments, which can be administered quickly by trained personnel, are used consecutively, because dementia is multidimensional and use of a single scale is insufficient to make a diagnosis. A detailed comparison of tools for use in primary care is presented in Table 3.

The MMSE is the most commonly used cognitive screening tool worldwide and remains the most thoroughly studied instrument to date.[28] The MMSE requires 5 to 10 minutes to

TABLE 2 Examples of cognitive assessment tools

Symptoms	Examples within cognitive tests
Immediate memory Recent memory (including free recall, cued recall and recognition memory) Very long-term memory (semantic, autobiographical)	3-word recall (MMSE) 5-word recall (MoCA)
Expressive language (naming, word finding, fluency) Grammar and syntax Receptive language (comprehension)	Recognizing pen or watch (MMSE) Animals (MoCA)
Sustained attention Selective attention Divided attention	Serial 7s, numbers backward
Planning Decision making Working memory (ability to hold information briefly and to manipulate it) Feedback/error correction Overriding habits Mental flexibility (ability to shift between 2 concepts, tasks or response rules)	Mini trials (MoCA)
Visual perception Visuoconstructional Perceptual-motor (integrating perception with purposeful movement) Praxis (integrity of learning movements, such as ability to imitate gestures) Gnosis (perceptual integrity of awareness and recognition)	Pentagons, cube, trails, clock face Blowing candle, waving goodbye

MMSE = Mini-Mental State Exam (MMSE); MoCA = Montreal Cognitive Assessment.

administer, is available in different languages and requires minimal training by a clinical assessor. It provides a global assessment of various cognitive domains: orientation to time and place, registration of words, calculation, attention, concentration, recall of words, language and visual construction. The MMSE has high sensitivity and specificity, and a score of 23 or lower indicates cognitive impairment.[28] However, the subject's educational level affects the score strongly, so interpretation must consider this factor.[33] The test is copyrighted by Psychological Assessment Resources, which does not grant open permission to reproduce the MMSE in its entirety, diminishing its value as a practice tool.

The Abbreviated Mental Test Score is a 10-point scale that assesses patients' orientation, attention, memory and general knowledge.[34] The test takes only 5 minutes to administer; a score from 0 to 3 indicates severe cognitive impairment, 4 to 6 indicates moderate impairment, and greater than 6 indicates normal cognitive function.[35]

The MoCA was created as a rapid screening instrument for MCI.[29] It requires 10 to 15 minutes to complete and evaluates cognitive domains such as attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. A score ≤25 out of 30 is considered to be indicative of significant cognitive impairment.[29] The MoCA has been shown to be more sensitive than the MMSE in differentiating between mild dementia and normal cognition.[24]

The Mini-Cog is a short test that is not influenced by income or education levels and takes only 3 minutes to complete.[36] It starts with a 3-item word recall test, followed by a clock drawing test.

The Clock Drawing Test typically requires patients to draw a clock face with numbers and

TABLE 3 Comparison of cognitive assessment tools

Tools	Sensitivity	Specificity	Total scores	Time to administer	Access link	Areas of assessment	Comments
Mini-Mental State Examination (MMSE)[4,28,33]	0.87	0.82	30	5-10 min	https://www.mountsinai.on.ca/care/psych/on-call-resources/on-call-resources/mmse.pdf	Orientation, registration, recall, attention and calculation, language	Educational level strongly affects the score; insensitive to delirium
Abbreviated Mental Test Score (AMTS)[4,34,35]	0.81/0.91	0.85/0.75	10	5 min	www.ncbi.nlm.nih.gov/pmc/articles/PMC2560932/pdf/occpaper00113-0035.pdf	Orientation, attention, memory, general knowledge	
Montreal Cognitive Assessment (MoCA)[4,29]	1	0.87	30	10-15 min	www.mocatest.org/	Memory, attention and concentration, executive functions, language, visuoconstructional skills, conceptual thinking, calculations and orientation	
Mini-Cog[4,36]	0.99	0.93	5	3 min	www.alz.org/documents_custom/minicog.pdf	Recall of memory, clock drawing	Often accompanied with a clock-drawing test; best choice for low-income and low-education groups
Clock-Drawing Test (CDT)[4,37]	0.86	0.96	6	3 min	https://www.healthcare.uiowa.edu/igec/tools/cognitive/clockDrawing.pdf	Clock drawing	
General Practitioner Assessment of Cognition (GPCOG)[4,38]	0.82	0.83	9	6 min	www.alz.org/documents_custom/gpcog(english).pdf	Recall, time orientation, clock drawing, information	
7-minute screen (7MS)[39]	0.92	0.96		6-10 min		Memory, orientation, verbal frequency, visuoconstruction	Insensitive to age, sex, education
Memory Impairment Screen (MIS)[4,40]	0.86	0.91	8	5 min	www.alz.org/documents_custom/mis.pdf	Recall	Alternative to GPCOG, clock-drawing test, Mini-Cog or AMTS

hands indicating a prespecified time. The test was designed as a quick screen for dementia by focusing on the cognitive domains of executive functioning and visuoconstruction.[4,24] Based on the Shulman scoring system, a cutoff score of 3 generates the preferred sensitivity (0.86) and specificity (0.96).[37] This scale may be used on its own or with other screening tools to assess patients.

The General Practitioner assessment of Cognition (GPCOG) is a brief dementia screening scale designed for use in primary care.[38] It consists of a patient examination and informant interview and takes about 6 minutes. A score of 10 or lower indicates cognitive impairment.

As its name implies, the 7-minute screen takes about 7 minutes to administer and consists of 4 tests that assess memory, verbal frequency, visuospatial skills and visuoconstruction and orientation.[39] The test demonstrates a competitive sensitivity and specificity in distinguishing between patients with dementia and normal controls, and its accuracy is not affected by age, sex or educational level.

The Memory Impairment Screen is a 4-item scale designed to detect various types of dementia in different settings.[40] The scale has shown good sensitivity and specificity in classifying dementia. A score of 5 or below indicates dementia.

Pharmacists should become familiar with these assessment tools so they can use them quickly and proficiently in patient care. The MMSE and the MoCA can be used to screen for cognitive impairment in patients with memory complaints. If cognitive impairment is suspected, patients can then be referred to their physicians for in-depth assessment. These tools can also be used to monitor the efficacy of pharmacological treatment by comparing scores before and after initiation of therapy. The Mini-Cog, a 3-minute screening test involving clock drawing and 3-word recall, can be used as part of patient counselling to detect cognitive impairments in older adults.

Treatment for dementia

Prevention

To date, studies evaluating the role of statins and omega-3 fatty acids in preventing AD have provided conflicting results.[41,42] Randomized controlled trials have not supported the use of ginkgo biloba to reduce the risk of developing AD in elderly patients with or without MCI.[43,44] Since oxidative stress is considered a factor in neurodegeneration and neuronal death in AD, oxidants such as selenium and vitamin E have been investigated, but they did not demonstrate a preventive role in AD.[45]

Nonpharmacological strategies

Although various cognitive training and exercise programs have been proposed to improve or preserve cognition and function in patients with mild to moderate dementia, multiple studies have not provided sufficient evidence to support any particular beneficial intervention.[46-49] However, while exercise does not improve cognition, neuropsychiatric symptoms or depression, it may improve the ability to perform activities of daily living in individuals with dementia.[48]

Pharmacological options

Cholinesterase inhibitors prevent breakdown of acetylcholine in the brain, a key neurotransmitter involved in learning and memory, thus increasing the level of acetylcholine in brains of individuals with dementia. Donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon) are cholinesterase inhibitors indicated for treatment of mild to moderate AD in Canada (Table 4). Donepezil may also be used in severe forms of AD, and rivastigmine is indicated for treatment of patients with PDD and mild to moderate AD.

Cholinesterase inhibitors should be used cautiously in patients with bradycardia (heart rate <55 beats per minute), cardiac conduction abnormalities (e.g., left bundle branch block or sick sinus rhythm), epilepsy and seizure disorders. The most common adverse effects associated with this class of medication are gastrointestinal (e.g., nausea, vomiting, diarrhea) and stem from a rise in the central and peripheral concentration of acetylcholine. These adverse effects are usually transient and present when therapy starts or when the dose is increased. Other notable possible adverse effects that require monitoring include insomnia, somnolence, weight loss and syncope. Although no cholinesterase inhibitor has been shown to be superior to another to treat mild to moderate dementia, oral rivastigmine seems to be associated with the highest risk of gastrointestinal side effects.[50-52] Transdermal rivastigmine provides a higher gastrointestinal tolerability than the oral formulation.[53] Several studies have found that switching from an oral cholinesterase inhibitor to transdermal rivastigmine can be an effective

TABLE 4 Pharmacological options for dementia

Drug	Strength	Dosing	Dosing in renal impairment	Dosing in hepatic impairment	Pharmacokinetics	Monograph access link
Donepezil (Aricept, Aricept RDT)	Tablet: 5 mg or 10 mg	Initial dose: 2.5–5 mg po daily Titration: increase by 2.5-5 mg every 4 wk Therapeutic dose: 5-10 mg/d Maximum dose: 10 mg/d	No	No	Metabolized by CYP 3A4 and 2D6	www.pfizer.ca/sites/g/files/g10017036/f/201505/ARICEPT_PM_E_177353_18Dec2014_R.pdf
Galantamine (Reminyl ER)	Capsule: 8 mg, 16 mg, 24 mg	Initial dose: 8 mg po daily × 4 wk Titration: increase by 8 mg every 4 wk Therapeutic dose: 16-24 mg/d Maximum dose: 24 mg/d	CrCl 9-60 mL/min: max 16 mg/d CrCl <9 mL/min: not recommended	Moderate: max 16 mg/d Severe: not recommended	Metabolized by CYP 3A4 and 2D6	http://auropharma.ca/products/monograph/Auro-Galantamine-PM.pdf
Rivastigmine (Exelon)	Capsule: 1.5 mg, 3 mg, 4.5 mg, 6 mg Oral solution: 2 mg/mL	Initial dose: 1.5 mg po bid Titration: increase by 1.5 mg every 2-4 wk Therapeutic dose: 3-6 mg po bid Maximum dose: 6 mg po bid		Mild-moderate: use with caution Severe: not recommended	Not metabolized by CYP P450	www.ask.novartispharma.ca/download.htm?res=exelon_scrip_e.pdf&resTitleId=740
Rivastigmine patch (Exelon patch)	Exelon Patch 5 Exelon Patch 10 Exelon Patch 15	Initial dose: Exelon Patch 5: apply once daily Titration: increase to Exelon Patch 10 once daily every 4 wk Therapeutic dose: Exelon Patch 10: apply once daily Maximum dose: Exelon Patch 15: apply once daily If switching from oral rivastigmine, use Exelon Patch 5 for patients taking <3 mg bid and Exelon Patch 10 for patients taking 3-6 mg bid	Dose titration with caution	Mild-moderate: use with caution Severe: not recommended		https://www.novartis.ca/sites/www.novartis.ca/files/exelon%20patch_scrip_e.pdf
Memantine (Ebixa)	Tablet 10 mg	Initial dose: 5 mg po daily Titration: increase by 5 mg every 1 wk Therapeutic dose: 5-10 mg po bid Maximum dose: 10 mg po bid	CrCl 30-49 mL/min: daily dose should be 10 mg/d; if well tolerated after ≥7 d of treatment and based on clinical response, dose may be titrated to 20 mg/d CrCl <30 mL/min: daily dosage should be 10 mg/d	Mild-moderate: no dosage adjustment Severe: not recommended (lack of data)	Metabolism: no appreciable CYP450 enzyme system involvement	https://www.lundbeck.com/upload/ca/en/files/pdf/product_monograph/EBIXA_PM_MKT_ctrl_138778_eng_v2_20Apr2011.pdf

po = by mouth; bid = twice daily.

therapeutic strategy after lack or loss of efficacy to a first agent or to improve gastrointestinal tolerability.[54-57] Furthermore, as older adults are likely to have multiple comorbidities requiring treatment, a common clinical scenario is concurrent treatment of dementia and urinary incontinence. Anticholinergic drugs exert a pharmacological opposition with cholinesterase inhibitors. A prospective cohort study of older adults in nursing homes indicated that concurrent use of bladder anticholinergic drugs with cholinesterase inhibitors is associated with a greater rate of functional decline than use of a cholinesterase inhibitor alone.[58]

Memantine (Ebixa), an N-methyl-D-aspartate receptor antagonist, inhibits prolonged influx of calcium ions, thereby minimizing neuronal excitotoxicity, a mechanism involved in the neurodegenerative process of AD (Table 4). Memantine is indicated for the treatment of moderate to severe AD.[59,60] Memantine is generally well tolerated, and its most common adverse effects include dizziness, drowsiness, constipation, agitation and headaches. Furthermore, a recent meta-analysis of 4 trials showed that combining a cholinesterase inhibitor with memantine in individuals with moderate to severe dementia provided modest benefits in the global clinical impression scale, cognition, behaviour and ability to perform activities of daily living than did monotherapy with a cholinesterase inhibitor.[61]

It is important to recognize that current pharmacological treatment options do not prevent advancement of dementia. Pharmacotherapy can delay the progression of cognitive, functional and behavioural outcomes and thereby improve quality of life for patients and caregivers, but it is essential that clinicians set realistic expectations of treatment outcomes. Furthermore, not every individual will respond to treatment. The efficacy of these therapeutic options is modest. Studies show that even though these medications can improve the global cognitive function in patients with AD by 1 to 3 points on the Alzheimer's Disease Assessment Scale–Cognitive Subscale, a 4-point improvement over 6 months is required to be considered clinically meaningful.[62] Moreover, the duration of most trials was only 23 to 26 weeks, so the efficacy of these agents over a period of years is unknown.

While the occurrence of adverse effects should be assessed within the first month of therapy, the efficacy of treatment should be evaluated about 3 to 6 months after its initiation. Observational studies suggest that continuing therapy with a cholinesterase inhibitor over a year is associated with reduced cognitive and functional decline,[63-65] so the duration of therapy should be individualized.

Trials evaluating low-dose aspirin, statins, nonsteroidal anti-inflammatory drugs and hormonal replacement therapy showed no benefit on global cognitive and physical function in individuals with MCI or with mild to moderate dementia.[62,66]

Cholinesterase inhibitors and memantine offer symptomatic pharmacological treatment of AD but do not affect neurodegenerative processes. Emerging therapeutic strategies to treat dementia are designed to prevent or interrupt the pathological mechanisms involved. Since AD is linked to amyloid-beta protein aggregation, the use of humanized monoclonal antibodies directed against the amyloid-beta peptide are posited to interfere with the amyloid cascade by preventing the accumulation of amyloid-beta plaques, thus slowing disease progression.[67] Bapineuzumab and solanezumab have advanced furthest in clinical trials, but recent phase 3 trials (EXPEDITION, EXPEDITION2) indicate that solanezumab does not improve cognition and functional ability in individuals with mild-to-moderate AD (MMSE score 16-26).[68] However, as solanezumab is superior to placebo in preventing cognitive and functional decline (MMSE score 20-26) in participants with mild dementia, a third trial (EXPEDITION3) has been launched to evaluate the efficacy of solanezumab in a population with mild AD.[69]

Conclusion

Managing dementia is particularly challenging because of the complexity of the disorder and limitations in current pharmacological options. The treatment plan for each patient should be individualized to provide the most effective and safe drug therapy. Subsequent articles will focus on the role of the pharmacist in assessing and applying this knowledge into practice. ■

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