ABSTRACT: Late Alzheimer disease is characterized by severe impair-ment in cognitive and physical functions with increased risk of behavioral disturbance. Baseline assessment should include a comprehensive review of the patient’s cognition, basic and instrumental activities of daily living, mood and behavior, safety hazards, and care planning. While collateral information can be helpful, performance-based observations are more objective. Disease-specific treatments, including the use of cholinesterase inhibitors and glutamatergic modulating drugs, may slow down cognitive decline in some individuals with late Alzheimer disease, although their effects on behavior and function remain inconclusive. Nonpharmacological interventions can provide functional assistance, optimize safety, reduce caregiver burden, and improve overall quality of life. Further research is needed to address many uncertainties that remain in the management of late Alzheimer disease.

A lzheimer disease (AD) is a progressive, neurodegenerative illness and its prevalence increases with age.1 The Alzheimer Society of Canada uses a staging system that divides the progression of AD into early, middle, and late disease.2 No single pathognomonic clinical event has been found to characterize late AD. Features of late disease are summarized in Table 1.

In a recent longitudinal cohort study, median survival from the time of diagnosis ranged from 8.3 years for people diagnosed with AD at age 65 years to 3.4 years for those diagnosed at age 90 years.3 The duration of late disease may vary among individuals. Patients with late AD are more likely to experience impairment in their basic activities of daily living, develop medical complications such as pneumonia and delirium, and demonstrate disturbance in their behavior.

Tracking the progression of impairment in people with late AD can be difficult because of many measurement challenges from both the clinical and research perspectives. There are multiple possible confounders that can influence the interpretation of measurement results. Despite these difficulties, clinicians should assess several areas, including cognition, behavior, function, safety, and to obtain a gestalt view of the patient and determine which pharmacological and non-pharmacological approaches are appropriate.

Cognition in late AD
People with late disease experience deficits in multiple cognitive domains. However, measuring cognition in this population can be difficult. Self-reported history is invariably unreliable, and collateral information is only as good as the informant’s ability to provide an accurate account. There is no specific neurological sign to look for in the physical examination, and traditional cognitive screening instruments have limited use in late AD. The Folstein Mini-Mental State Examination (MMSE) is a rating of cognitive function that measures a variety of domains and assesses orientation to time and place, verbal recall,

Roger Y.M. Wong, MD, FACP, FRCPC
Dr. Wong is associate program director of Postgraduate Medical Education, Department of Medicine, and clinical assistant professor in the Division of Geriatric Medicine at the University of British Columbia. He is also director of the Geriatric Consultation Program and medical manager of the ACE Unit at Vancouver General Hospital.
attention and calculation, language, and visual construction. Although the MMSE is commonly used in clinical settings, it is limited by its “floor” effects and low responsiveness to change when the score is less than 12. There are inadequate data to support the routine use of the Clock Drawing Test in late AD. An instrument that is more useful in late disease is the Severe Impairment Battery (SIB), although its application in day-to-day conditions may not be practical.

Most clinical trials of disease-specific treatment for AD include cognition either as a primary or secondary outcome. Historically, cholinesterase inhibitors (ChEIs) have been the main pharmacological treatment in persons in the ambulatory setting with mild to moderate AD (MMSE score 10 to 26). The three agents available in Canada are donepezil, galantamine, and rivastigmine. The efficacy studies of ChEIs now extend to ambulatory persons with moderate to severe AD. In a multicentre, randomized controlled trial in AD patients with a mean MMSE score of 12 (range 5 to 17), the use of donepezil was associated with improvements in cognition, function, and behavior. All of the published data on ChEIs so far indicate that their main cognitive effect is delaying symptomatic losses. Other clinical trials of cholinesterase inhibitor use in late AD are ongoing. In many parts of the world, including Canada, ChEIs constitute a standard of care for AD patients with early and middle disease, although there are no guidelines for the routine use of these drugs in late disease.

Recently, another class of pharmacological treatment with a different mechanism of action has been used to treat AD. It is hypothesized that excess excitatory action of glutamate on neurons can lead to overstimulation of postsynaptic N-methyl-D-aspartate (NMDA) receptors, which in turn can accelerate neurodegeneration and neuronal death. In a recent randomized controlled trial, the use of memantine (an uncompetitive NMDA receptor antagonist with antiglutamatergic effect) was associated with improved global function and cognition in people with moderate to severe AD (mean MMSE score 7.9, range 3 to 14, cognition measured by SIB). Another memantine trial involving persons with severe dementia (MMSE score <10, mean 6.3) also showed global improvement in the treatment group. Information exists to suggest that the use of memantine and donepezil is efficacious and safe. There is an unanswered question as to whether memantine’s effects extend to nursing home residents with late AD. Memantine has recently been approved for clinical use in Canada.

There are a variety of nonpharmacological interventions proposed to improve cognition in people with late AD. Support for these interventions is anecdotal or unpublished. None of the published evidence is based on randomized controlled trials. For example, playing games is a cognitive strategy that may promote personal enjoyment, but there are no data to support the cognitive benefit of this.

Reminiscence therapy and other emotion-oriented methods are often used in the care of people with AD, including those with late disease. A recent literature review concludes that these methods can produce favorable results, such as increased social interaction and decreased behavioral disturbance. Unfortunately, many of the original studies have methodological limitations, and there is insufficient evidence to justify the implementation of emotion-oriented methods on a large scale. Another common approach, especially when a group of AD patients is present, involves cognitive-linguistic stimulation using music, pets, memory boxes, the Montessori method, or other types of activity programming. Again, only observational data are available, and the data are non-specific for late AD.

**Behavior in late AD**

People with late AD are more likely to develop behavioral and psychiatric symptoms of dementia (BPSD). The assessment and treatment of which are
discussed elsewhere in this issue (“Behavioral and psychological disturbances in Alzheimer disease”). When considering aspects of BPSD in late AD, the effects of disease-specific treatments on behavior in nursing home residents, and the importance of the behavioral program management approach need to be highlighted.

In a recent well-designed randomized controlled trial, behavioral problems in nursing home residents with late AD proved to be resistant to disease-specific treatments such as donepezil. The study was powered primarily to detect differences in behavior among nursing home residents with AD and found that donepezil did not demonstrate any superior impact over the control group on modifying neuropsychiatric disturbances during the 24-week study period. In fact, both the ChEI treatment group and the control group demonstrated similar improvements by the fourth week based on measurement with the nursing home version of the Neuropsychiatric Inventory (NPI-NH), but there were no statistically or clinically significant differences between the groups at any assessment time point.

The behavioral effects of memantine in late AD remain inconclusive. Whereas the use of memantine was associated with improvement in behavior (measured by the behavioral rating scale for geriatric patients) in one trial of severe dementia, there was no benefit (measured by the Neuropsychiatric Inventory) in another trial of moderate to severe AD. More studies are needed.

A comprehensive approach to BPSD involves behavioral management programs that include pharmacological therapy as one component of many. These programs, which require systematic educational initiatives for caregivers in nursing homes, have proven effective in randomized controlled trials. Common features of successful programs include a multi-component approach, combined use of pharmacological and nonpharmacological interventions, involvement and education of multidisciplinary teams, and adoption of a program management model.

The Eden Alternative (EA) involves the systematic introduction of pets, plants, and children into nursing homes. The impact of the EA on the behavior of people with severe AD remains unclear. A recent prospective cohort study of EA did not demonstrate any statistical benefit in cognition, function, survival, or cost of care after 1 year of implementing the program. Whether there is truly no benefit, or whether the benefit only becomes measurable beyond 1 year, remains to be seen.

**Function in late AD**

Functional impairment is prevalent in persons with late AD. Most instrumental activities of daily living (financial management, meal preparation, shopping, homemaking, using the telephone) are likely affected, and many of the basic activities of daily living (bathing, dressing, continence, mobility, feeding) also become impaired.

When assessing a patient with late AD, it is important to document the exact nature of the functional loss so that specific interventions can be tailored accordingly. Access to a multidisciplinary team can be of assistance. These teams are available through referral to the community health units, or specialty geriatric programs if more complex issues are involved. Direct performance-based observations include kitchen assessments and home visits.

There is no single pharmacological treatment that definitively improves function in late AD. The use of memantine and donepezil has been shown to benefit the activities of daily living in people with moderate to severe AD and reduce the amount of time spent by their caregivers. In nursing homes, functional benefits with ChEIs are undetermined.

Whereas difficulty with bathing and dressing are usually tolerated and managed by family members of patients with late AD, the challenges of incontinence (both urinary and fecal), poor feeding resulting in weight loss, and mobility failure are more stressful to deal with and often become the precipitating reasons for institutionalization. In some cases, the cause of urinary incontinence, such as infection in the genitourinary tract, may be remediable.

Fecal incontinence often occurs in conjunction with urinary incontinence, and the most common reason is fecal impaction from severe constipation. Individuals with severe AD are especially at risk of developing fecal overflow incontinence as a result of fecal impaction because of their poor dietary intake of fluid and fibre, reduced mobility, and use of medications that can slow intestinal action. Sometimes there is occult gastrointestinal pathology. Managing fecal overflow incontinence involves disimpaction (either manually or by enema) followed by treatment of constipation.

Unintentional loss of body weight is common in late AD, especially in nursing home residents. A proper nutritional and swallowing assessment should be performed by a dietitian and occupational therapist or speech pathologist. Such an assessment can find potentially reversible causes of weight loss and improve the patient’s overall nutritional status by selecting appropriate types and consistency of food, bedside snacks, and nutritional supplements, allowing adequate feeding time, and devising creative feeding techniques.
Safety issues

Many safety issues are pertinent to people with late AD. Difficulty with transfer and ambulation is more common in late disease, resulting in an increased risk of falls. Contributing factors include poor judgment and the gait abnormalities that can result from AD, visual and hearing deficits, and the use of benzodiazepines, antidepressants, or other psychoactive drugs. Prevention of falls is a broad topic that has been recently reviewed.18 Persons with late AD should undergo assessment to rule out treatable diseases that impair mobility. All unnecessary medications should be eliminated. The use of environmental modifications, such as handrails and raised toilet seats, can reduce the likelihood of falls in high-risk areas such as the bathroom. Although walking aids can provide increased stability and support, how successful they are at doing this depends on the patient’s ability to adhere to their use. Similarly, the patient’s response to gait and balance training exercises can be limited by difficulty in following and recalling instructions.

A common misperception in managing the risk of falls among people with AD involves the use of physical restraints. There is no evidence in the literature that restraints reduce the frequency of falls. To the contrary, studies have shown that avoiding restraint use can reduce the probability of serious injuries.19 Physical restraints should be used as little as possible; ideally they should not be used at all.

Medication safety is another important issue. People with late AD are at risk of making medication errors (including overdosing themselves) and experiencing adverse drug reactions, especially in cases of polypharmacy. It is important to obtain a complete medication and allergy history for patients with AD, and to check the computerized medication profile or PharmaNet. The indication for every medication should be frequently reassessed. The administration of medications should be closely supervised, if not taken over, by caregivers. Before initiating a new medication, special attention should be paid to possible drug-drug interactions (for instance, cholinesterase inhibitors may interact with negative chronotropic drugs such as beta-blockers and produce significant bradycardia) and drug-disease interactions (for instance, many drugs can produce delirium in AD patients). The “start low and go slow” approach applies here as in any older adult patient.

A final safety issue involves motor vehicle use. People with late AD should not drive because of the high risk of accidents.20

Care planning

For many individuals with late AD and their families, a common question is whether (or when) to move into a care facility. The answer will vary according to individual situations, but nursing home placement is commonly precipitated by incontinence, immobility, safety concerns, or significant caregiver stress. Many families use the respite service as an interim step before placement. To facilitate the placement process, referral to the appropriate community health unit is needed.

There are many issues about the advance directives of people with late AD that physicians can help discuss and address. Some examples are the use of no code blue orders (do not resuscitate), the risks and benefits of artificial feeding, mental capacity and the process of substitute decision making, and the degree of medical interventions in the event of illness such as pneumonia.21 Ideally, the issues should be discussed and the decisions clearly documented before a crisis (such as hospitalization) occurs.

Finally, a word about those providing care for people with late AD. The stress for caregivers can be significant. We know that they are at increased risk of major depression,22 and that caregiver burden can be assessed by direct interviews or psychometric scales such as the Zarit Burden Interview.23 Support for caregivers is important for the well-being of the caregivers themselves and those they care for. Caregivers should be strongly encouraged to contact the local chapters.
of the Alzheimer Society of BC for information on the resources that are available.

Conclusions
A practical approach to managing patients with late AD includes assessment in areas of cognition, behavior, function, safety, and care planning. Concurrent medical illnesses should be treated and particular attention paid to medication adherence and safety. There is currently no clinical guideline to indicate routine use of pharmacological treatments such as ChEIs or memantine, although the published evidence is promising. It is reasonable to consider using these medications in selected individuals after weighing the potential risks and benefits. Many nonpharmacological strategies are available to address the functional and behavioral issues faced by people with late AD. It is also important to provide adequate support for caregivers to reduce the likelihood of burnout.

Competing interests
Dr Wong has received CME speaker honoraria from Merck Frosst, and consultant honoraria from Pfizer and Janssen Ortho.

References