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INTRODUCTION

Dementia is an umbrella term that encompasses symptoms of a chronic progressive cognitive decline usually affecting memory and almost always judgment, decision-making, and relationships with others. Dementia can be divided into cortical and subcortical forms. Alzheimer’s disease is a form of cortical dementia, as is Creutzfeldt-Jakob disease (CJD). In subcortical dementia, structures below the cerebral cortex are affected or damaged, such as occurs in Parkinson’s disease. In multi-infarct dementia both the cortical and subcortical parts of the brain are affected. Dementia can also be divided into reversible causes such as hypothyroidism, normal pressure hydrocephalus, and vitamin B12 deficiency, and irreversible causes such as Alzheimer’s disease. The most common causes of progressive dementia are Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, fronto-temporal dementia, Parkinson’s disease, and Wernicke-Korsakoff dementia. Of those, Alzheimer’s disease is the most common type. Many layperson and some clinicians erroneously use the terms “Alzheimer” and “dementia” interchangeably.

Alzheimer’s disease (AD) is a neurodegenerative disease which involves progressive and irreversible loss of neurons in various regions of the brain. It constitutes approximately 60% of all cases of dementia (Fig. 1) and is more common in women. Histopathological changes include formation of amyloid plaques and neurofibrillary tangles resulting in neuronal cell death. It is characterized by impairment of memory and at least one cognitive domain (aphasia, apraxia, agnosia, executive function). These must represent a decline from previous levels of functioning and be severe enough to interfere with daily function and independence [1]. It mainly affects the elderly and rarely occurs before the age of 60. This review article will primarily focus on dementia of Alzheimer’s disease.

EPIDEMIOLOGY

The incidence of Alzheimer’s disease ranges from 0.5% to 4% per year depending on the age of the subjects studied [2]. A meta-analysis of estimated prevalence of Alzheimer’s disease in the United States suggests an increase from 1% at 65-69 years of age, to 13% to 17% at 85-89 years of age, and 24% to 31% at 90-94 years of age [3]. Other estimates give a slightly higher prevalence. The wide range is due to varying diagnostic criteria and the fact that AD is a diagnosis of exclusion. Worldwide prevalence of dementia, including Alzheimer’s disease (Fig. 2), is estimated at 24.3 million people, with 4.6 million new cases occurring annually [4]. This number is expected to increase by approximately fourfold by the year 2050 unless suitable interventions can be found. In Lebanon, it is estimated that over 30,000 persons suffer from all types of dementia, and this number will double within the next twenty years. AD is the sixth leading cause of death in the United States and the fifth leading cause of death for those aged 65 and above. Deaths from AD increased 66% between 2000 and 2008 [5]. Our understanding of AD and its complications has led us to categorize it into three types: • Early-onset AD: a rare form of AD diagnosed earlier than 65 years of age. Less than 10% of all AD patients are diagnosed with this type of disease. Patients with Down syndrome are particularly at risk for premature dementia. Early-onset AD appears to be linked with a genetic defect on chromosome 14. • Late-onset AD: the most common form, accounting for over 90% of cases and usually occurring after the age of 65. • Familial AD: known to be entirely inherited and accounts for less than 1% of all cases of AD. In affected families, members of at least two generations have had Alzheimer’s disease with a much earlier onset.

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**Figure 1. Approximate prevalence of Alzheimer’s disease in relation to other types of dementia.[2-6]**
AD: Alzheimer’s disease VD: vascular dementia LBD: Lewy body dementia PD: Parkinson’s disease; O/M: other or mixed dementia.
DIAGNOSIS AND CLINICAL FEATURES

Memory impairment is the most affected early feature of AD, and most patients will have amnestic problems at presentation. Pattern of memory loss includes amnestic mild cognitive impairment early in the disease (e.g., loss of recent events as episodic type of memory), followed by semantic memory loss as the disease progresses. Memory is usually tested by the recall of three objects immediately and at a 5-10 minute delay. Deficits in multiple cognitive domains are also common among patients with AD. Cognitive domains are varied and include language (verbal dysfluency, anomia, paraphasia, impaired comprehension), visuospatial (misplacement of objects, visual agnosia, prosopagnosia), insight (anosognosia), apraxia, executive function, and neuropsychiatric deficits (apathy, social disengagement, disinhibition, aggression, wandering, psychosis).

The criteria for diagnosing AD in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorder, Text Revision (DSM-IV-TR) [1], include:
A. The development of multiple cognitive deficits manifested by both
   1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
   2. One or more of the following cognitive disturbances:
      a. Aphasia (language disturbance)
      b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
      c. Agnosia (failure to recognize or identify objects despite sensory function)
      d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson’s disease, subdural hematoma, Huntington’s disease, normal-pressure hydrocephalus, brain tumor)
   2. Systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   3. Substance-induced conditions.

E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

Several practical screening tools have been devised for cognitive assessment. They variably cover the cognitive domains described above, take few minutes to complete, and are reliable for use in clinic or at the bedside. The two most widely used screening tools are the Mini Mental Status Examination (MMSE) and the St. Louis University Mental Status examination (SLUMS). Both have been translated into Arabic and can be downloaded from various websites for quick access. Once cognitive impairment has been documented, Alzheimer’s disease is essentially a diagnosis of exclusion. There are no diagnostic tests, hematologic or otherwise, to confirm the diagnosis of AD though some are in development. Brain tissue examination on autopsy is the only definitive evidence of AD at this time. The initial workup should include complete blood count, electrolytes, renal/hepatic/thyroid function tests, and vitamin levels (B12, folate, thiamine, ± 25(OH)D3). In high risk patients, syphilis and human immunodeficiency virus (HIV) testing is indicated. Brain imaging with CT scan or MRI will uncover vascular dementia, normal pressure hydrocephalus, and less commonly malignancies or intracranial bleed. Lumbar puncture is indicated in rapidly progressive dementia.

RISK FACTORS

Having some basic knowledge of risk factors for AD gives the clinician a broader understanding of means for preven-
tion and management. Many risk factors have been associated with AD, of which we have influence over while others are beyond our control.

**Non-modifiable risk factors**
Among the non-modifiable risk factors, advanced age is the strongest predisposing factor for the development of dementia, particularly Alzheimer’s disease (Fig. 2) [6]. After the age of 65 years, the incidence of Alzheimer’s disease and dementia in general increases exponentially. A useful rule of thumb to estimate the prevalence of AD is to consider it to be 1% at age 60, and assume the rate doubles every five years thereafter, resulting in a prevalence of greater than 30% by the age of 85 years. The incidence rate similarly varies widely based on diagnostic criteria and the population studied, but increases steadily with age. The incidence ranges from 0.7 to 3.5 per 1000 per year at the age of 65-69, and doubles approximately every five years thereafter.

A second powerful non-modifiable risk factor for the development of AD is family history. True familial Alzheimer’s disease accounts for less than 5% of all cases [7]. Both genetic and environmental factors play a role in diseases that cluster in families. Patients with a first-degree relative afflicted with dementia have an 10% to 30% increased risk of developing the disorder, particularly when it occurs at a relatively young age. This increased familial risk is lower in cases of Alzheimer’s disease that develop later in life (≥ 85 years of age) [8]. Specific genes (or gene combinations) involved in the transmission of familial cases of AD are still being identified. Genetics foci have been linked to both early-onset and late-onset Alzheimer’s disease. Approximately 6.5% of cases of AD are early-onset [9] (i.e. onset earlier than 60 years of age), among which only 13% exhibit autosomal dominant transmission across generations [10]. Mutations in three genes have thus far been identified as causing early-onset disease [11]. Of these mutations, approximately 30% to 70% are in the presenilin-1 gene (chromosome 14), 10% to 15% are in the beta-amyloid (Aβ) precursor protein gene (chromosome 21), and fewer than 5% are in the presenilin-2 gene (chromosome 1). People with Down syndrome (trisomy 21) have an extra copy of the amyloid precursor protein gene and almost universally exhibit AD by the age of 40. As for late-onset Alzheimer’s disease (onset past the age of 65 years), the strongest evidence for a genetic risk factor in non-familial disease exists for the ApoE ε-4 gene [12]. This gene offers neuronal protection and repair, and is found to have a role in β-amyloid (Aβ) deposition. There exist three alleles of ApoE gene: ε-2, ε-3 and ε-4. The ApoE ε-4 genotype has been linked to the development of both Alzheimer’s disease and vascular dementia. Homozygots for the ε-4 allele have up to 30 times the risk of developing AD by 75 years of age, and heterozygots carry 2-4 times the risk. The ε-2 allele may confer a protective effect. Although 40-65% of patients with AD carry at least one copy of the ε-4 allele, at least one third are ApoE ε-4 negative, and many homozygots never develop the disease. Furthermore, ApoE ε-4 does not appear to increase risk of AD in people of Hispanic or African origin. For these reasons, genetic screening, even among high-risk populations, is generally not recommended.

**Modifiable risk factors**

- **Metabolic syndrome**

There is increasing evidence that vascular disease and its risk factors play important roles in the etiology of both vascular dementia and Alzheimer’s disease [13]. Risk factors for cardiovascular disease are therefore also considered among those predisposing for Alzheimer’s disease. In fact, the overlap between AD, vascular dementia, and dementia with Lewy bodies, and their similar clinical course, has led some researchers to propose a link between these conditions – possibly different facets of a common disease pathway. For example, microvascular ischemia may trigger amyloid plaque formation, or conversely, protein deposits may lead to vascular injury and ischemia. In fact, brain tissue from patients with microvascular dementia has been shown to have significant tau protein deposition on autopsy, and tau aggregates are also found concurrently with Lewy bodies. In any case, aggressive management of vascular risk factors has been shown to reduce the risk of AD.

The metabolic syndrome, and its individual components (insulin resistance, elevated blood pressure, obesity, hypertriglyceridemia), have all been linked with dementia, including AD. In a population-based study, Vanhanen et al. showed an increase in the prevalence of Alzheimer’s disease among patients with metabolic syndrome (odds ratio 2.71; 95% confidence interval 1.44 to 5.10) [14]. This may be attributed in part to the associated cardiovascular risk and in part to increased inflammatory biomarkers (C reactive protein and interleukin-6) [15], but the exact mechanism continues to be investigated. Several studies have shown that high blood pressure is associated with higher incidence of Alzheimer’s disease and all-cause dementia. Other studies, interestingly, have shown that a low blood pressure is also possibly linked to higher risk of the disease [16]. A U-shaped curve associating blood pressure and subsequent performance on cognitive questionnaires has been shown [17]. This U-shaped (or J-shaped) curve between blood pressure and various morbidities has long been the subject of intense debate. A possible association has also been identified between cognitive decline or dementia and higher dietary intake of saturated fats, transunsaturated fats, or cholesterol. Increased blood levels of cholesterol have been associated with increased risk for dementia, including Alzheimer’s disease [18-19]. One likely explanation is that lipid metabolism is integrated in the pathway of Aβ-protein deposition, tau phosphorylation, and disruption of synaptic plasticity, resulting in neurodegenerative endpoints. These proposed mechanisms have led to studies evaluating the effect of statin drugs on the development and progression of Alzheimer’s disease. Even though there are compelling reasons to treat hyperlipidemia for other morbidities, there is no definitive evi-
dence that treatment of hyperlipidemia reduces the risk of subsequent Alzheimer’s disease.

The remaining components of the metabolic syndrome, diabetes and central obesity, have also been studied extensively, though clinical consensus has not been forthcoming. Data to confirm the association between diabetes mellitus and the increased risk for cognitive decline is variable and inconsistent. Although diabetes is associated with a 50% to 100% increased risk of AD and a 100% to 150% increased risk of vascular dementia, their causative relationship remains controversial [20]. Studies in which one component of the metabolic syndrome is modified will necessarily alter the others, making it difficult to account for confounding variables. Finally, midlife obesity is related to increased risk for Alzheimer’s disease. Again, a J-shaped relationship was observed between body mass index (BMI) and dementia. A BMI less than 20 kg/m² or greater than 23kg/m² is associated with increased risk of dementia from midlife to old age [21]. Increased BMI has also been linked to lower baseline cognitive function and increased 5-year cognitive decline [22].

■ Diet

Numerous studies have been conducted to investigate the relationship between high-fat diets (total fats, saturated fat, and total cholesterol) and declining cognitive function. Particular attention has been focused on Ω-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [23]. Results have shown lower levels of Ω-3 fatty acids in the plasma and brains of Alzheimer’s patients when compared with controls. These long-chain Ω-3 fatty acids, a type of polyunsaturated fat (PUFAs), have various beneficial properties including anti-aggregatory, antithrombotic, and anti-inflammatory properties. They are consumed almost exclusively from fish, or from vegetable oils and nuts in the form of α-linoleic acid precursor. One fish meal per week was associated with a 60% reduction in the risk of developing Alzheimer’s disease in both the Rotterdam and Chicago studies [24]. Inconsistent results, however, have been reported between high intake of Ω-3 fatty acids versus linoleic acid in association with cognitive impairment. In one study, an inverse association between high fish consumption and cognitive impairment was documented, but the association was positive (increased risk) with linoleic acid [25].

Decreased risk of Alzheimer’s disease was also observed in patients who adhered to the Mediterranean diet [26]. Most studies confirm that diets rich in fruits and vegetables are associated with overall improved cognitive performance in the elderly population [27-28]. Some studies have reported that higher dietary intake of antioxidants was associated with a lower risk of AD, however, these studies have had significant limitations [29]. Brain lesions of patients with AD have high levels of free radicals and oxidative stress [30]. Of the antioxidants, vitamin E, β-carotene, flavonoids, and vitamin C have been studied the most. Multicenter trial in patients with moderately severe Alzheimer’s disease showed that high doses of α-tocopherol (vitamin E, 2,000 IU/day) or selegiline slowed the disease progression [31]. However, in a meta-analysis of 19 trials, doses of vitamin E > 400 IU/day was shown to have an adverse cardiovascular effect and increased mortality [32]. Based on current data, consensus it to consume antioxidants in their natural form – i.e. high intake of fruits and vegetables.

The relationship between alcohol consumption and dementia is complex and more difficult to discern. However, studies have consistently shown a protective effect of moderate alcohol intake on vascular disease and dementia. Consumption of 250-500 mL/day of wine is associated with a reduced risk of subsequent all-cause dementia and of Alzheimer’s disease [33]. Again a U-shape relationship exists, and the effect is not limited to wine. Current guidelines support one “drink” per day for women (two for men) for optimal cardiovascular protection, and the same likely applies for AD.

There is some evidence that high serum levels of homocysteine, or a deficiency of vitamin B6, vitamin B12, and folate may increase the risk for dementia and Alzheimer’s disease. Homocysteine is linked to small and large vessel disease and is now commonly (if not uniformly) accepted as a risk factor for stroke and cardiovascular disease [34]. There is no conclusive evidence, however, that homocysteine-lowering therapy using supplementation of folic acid or other B vitamins improves cognitive function or prevents cognitive decline [35].

■ Smoking

Neuronal function and integrity is highly affected by the toxins contained in cigarette smoke, which may have implications for long-term neuronal function and survival [36]. Acute nicotine and tobacco consumption is associated with increased blood flow and metabolism in some parts of the brain [37], but chronic smoking has been linked to decreased global cerebral blood flow as well as accelerated cerebral atrophy and ventricular enlargement recognized in patients with dementia [38]. Stroke is one of the suggested mechanisms by which smoking may lead to dementia [39]. One study reported that smoking may actually have a protective effect on Alzheimer’s disease by reducing senile plaque formation, none the less any protective effect would be counterbalanced by the increased risk of lung cancer, chronic obstructive lung disease, and cardiovascular disease [40]. Interestingly, ApoE ε-4 carriers have been shown to have fewer nicotinic receptors, and nicotine may increase receptor density or promote the release of neurotransmitters. This suggests that there may be a direct biologic modification of the effect of smoking by ApoE ε-4 [41].

■ Other reversible factors

Neurodegenerative disorders and worsening cognitive function may be related to high levels of proinflammatory cytokines and chronic inflammation. Such changes are found in the brains of patients with dementia [42] and therefore have been the subject of many studies investigating the use of non-steroidal anti-inflammatory agents (NSAIDs) for the prevention of dementia and Alzheimer’s disease. Results have not been consistent. Some studies have shown that NSAIDs may have a protective effect
against the development of Alzheimer’s disease and cognitive decline, possibly by lowering levels of the amyloidogenic Aβ42 protein [43]. Other studies failed to show this benefit. Conflicting results regarding their efficacy may be due to the timing and duration of NSAID use, differences in tracking NSAID use, and the ApoE genotype status of the participants. In addition, the use of low-dose aspirin did not show any benefit in decreasing the decline of cognitive function [44].

Strong evidence exists supporting the role of exercise in the prevention of dementia or slowing its progression. Apoptosis (programmed cell death) as well as neurotrophic factors are enhanced with physical activity [45]. It is believed that exercise-induced apoptosis is a normal regulatory process that serves to remove damaged cells thus preserving optimal function. Exercise may benefit dementia outcome in other ways – by preserving muscle mass, preventing falls and consequent head trauma, preserving the cardiovascular function, preventing cerebrovascular accidents, and improving the cerebral blood flow [46]. In addition to exercise, social and mental activity may slow neuronal loss and preserve synaptic function, thus slowing disease progression. In fact, evidence suggests that all three aspects of lifestyle activity – physical, mental, and social – are inversely associated with the risk of developing dementia and Alzheimer’s disease [47]. It is now commonly accepted that higher levels of education and mental exercise are associated with lower risks for Alzheimer’s disease and vice versa [48]. Advanced education is believed to represent a higher cognitive “reserve” that decreases the impact of Alzheimer’s disease on cognitive function, rather than offer a protective effect against the disease [49]. Interestingly, once highly educated people develop AD, they tend to deteriorate quicker than other patients [50]. Daily mental exercises (learning to play a new musical instrument, memory games, reading, writing, playing puzzle, and sharing in discussions) were associated with relatively lower risk of all-cause dementia [51], and must be encouraged in all patients.

It is still debatable whether depression is a comorbid condition of AD, a consequence of the worsening cognitive function, or an independent risk factor for it. One theory suggests that there exists an indirect neurotoxic mechanism by which depression affects the hippocampus [52]. Other theories propose that there are common genetic pathways that predisposed for depression and Alzheimer’s disease [53]. In any case, as discussed next, depression is a common occurrence in early stages of dementia and must be screened for and treated in earnest.

COMORBIDITIES

Of the many comorbidities associated with AD, depression, apathy, anxiety, and other conduct disorders are the most common. Depression affects 20% to 32% of patients with dementia, and can occur early in the disease. It remains debatable whether this is due to increased risk of major depressive disorder in patient with AD, or if it is a response to the disease. In early stages of AD, patients might be aware of their cognitive deficits and the natural progression of the disease. This can lead to reactive depression. As the disease progresses, self-awareness diminishes as other symptoms develop. The management of late-stage dementia is complicated by behavioral and psychological symptoms of dementia (BPSD). People with dementia may experience behavioral symptoms (screaming, restlessness, aggression, agitation, wandering, disinhibition, inappropriate sexual behavior, hoarding, cursing) and psychological symptoms (anxiety, depression, hallucinations, delusions, psychosis) during the course of their illness. Anxiety affects 20% of patients with dementia, and delusions or hallucinations can be present in 15% to 20% of patients, particularly in later stages of the disease. Paranoid delusion of intruders and missing personal possession are very common. Among patients with AD, approximately 27% exhibit agitation or aggressive behavior. Agitation can occur with or without psychosis and is one of the more difficult late complications to manage. It is estimated that BPSD occur in 70-90% of people with dementia. Causes of BPSD are not yet clear, but changes in behavior may be triggered by biological, psychological, social, or environmental factors. No matter what form BPSD takes, the first step is a search for any precipitating factors. Environmental triggers (temperature, noise, noxious odors), basic needs (hunger or thirst), or social triggers (change or loss of caregiver, change of environment or placement) are common precipitating factors that must be monitored and addressed when possible. Common medical problems such as pain, constipation, infections, and sleep disturbance, among others, can trigger or exacerbate BPSD. Untreated pain must be considered when acute behavioral changes develop, and is an often overlooked cause of distress that is treatable. In advanced dementia, non-verbal cues for pain must be examined, one of which is agitation.

Other comorbidities of late-stage AD which can be severely disruptive to patients as well as their caregivers are urinary incontinence, sleep/wake cycle disruption, and rejection of oral nutrition and hydration. These late complications are very common. They must be anticipated, and treatment options should be discussed early. Urinary incontinence is often cited as the trigger for nursing home placement [54]. Feeding tubes in their various forms might improve the hematoletic parameters of malnutrition, but rarely improve prognosis or outcome. Similarly, the use of medications to correct sleep disturbances rarely achieve the intended purpose and are associated with serious complications. In terminal cases of dementia, palliative care is warranted, including caregiver support.

TREATMENT

Advances in the understanding of the pathophysiology of dementing illnesses have changed the management of patients with these disorders from a conservative, supportive approach to a more specific biological and physiological one. The goal of current therapies is to delay the pro-
progression of the disease rather than reverse existing cognitive deficits. The mainstay of management, as the disease progresses, remains symptomatic: treatment of behavioral disturbances, environmental manipulations to support function, and counseling with respect to safety issues. The future promises disease-specific interventions and, hopefully, disease-modifying treatments. Although the exact pathogenesis of neuronal degeneration and cognitive impairment in AD remains unclear, a consistent pharmacological and neurochemical finding is the loss of centrally acting cholinergic neurons and a subsequent deficit in cholinergic neurotransmission. It has been known for some time that the activity of choline acetyltransferase, which synthesizes acetylcholine, is markedly reduced in the cortex and hippocampus of patients with Alzheimer’s disease, and depletion of choline acetyltransferase correlates with the severity of cognitive disturbance [55]. It is not surprising, hence, that research on drugs for AD have centered on preserving neurotransmitter function. This final section will only discuss disease-specific medications. Management of the various aspects of BPSD is beyond the scope of this text and can be found elsewhere.

The United States Food and Drug Administration (USFDA) has approved two classes of medications for the treatment of Alzheimer’s disease. These drugs target two different neurotransmitters. The primary options for the treatment of Alzheimer’s disease are the cholinesterase inhibitors (ChEIs) such as tacrine, donepezil, rivastigmine, and galantamine. These drugs decrease the degradation of acetylcholine in the synaptic cleft and maintain the fidelity of synaptic transmission [56]. The other class of drugs works on the glutamatergic system by blocking the N-methyl d-aspartate (NMDA) receptor. In this category, memantine is the only drug approved by the FDA for the treatment of AD. In both classes of medications effective adherence to therapy is essential to moderate disease progression and improve long-term quality of functioning. Patient or caregiver education about treatment expectations is essential for compliance with these costly medications. Some studies have shown an improvement in the MMSE score of up to two points with treatment, while others have not replicated these results. The intended goal of treatment is to delay disease progression. In individual cases, any observed improvement (or deterioration) in cognition or behavior may be due to normal disease fluctuation or selective (biased) recall. If well-tolerated, medications should be continued even if no significant benefit is initially apparent.

**Acetylcholine esterase inhibitors**

Tacrine was the first agent approved for use in Alzheimer’s disease, but it can cause hepatotoxicity and is rarely used today. Among the other three drugs available in this class, efficacy is similar; therefore the choice is largely based upon cost, individual patient tolerability and physician preference [57]. FDA-approved regimens and delivery systems for the treatment of patients with Alzheimer’s disease include once-daily donepezil, once-daily extended release galantamine, and the rivastigmine transdermal patch.

**Donepezil**

Donepezil (Aricept) is a reversible and noncompetitive ChEI, which produces definite and long-lasting inhibition of brain cholinesterase with minimal effect on peripheral tissues. It is FDA-approved for the treatment of mild, moderate, and severe forms of the disease [58]. Low peripheral anticholinesterase activity, along with once-daily administration, has made donepezil one of the most commonly used drugs for Alzheimer’s disease. The recommended dose for donepezil is 5 mg/day for four weeks, then 10 mg/day. After a minimum of three months on 10 mg, a dose of 23 mg may be prescribed, but most patients remain on the 10 mg dose. Donepezil may produce gastrointestinal adverse effects such as diarrhea, nausea, and anorexia. Muscle cramping and sleep disturbance have also been reported in some patients. Since the patent for donepezil expired in November 2010, less costly generic preparations have become available.

**Rivastigmine**

The ChEI rivastigmine (Exelon) has been available since 1997 and was approved for use by the FDA in 2006 in capsule and liquid form. It is available in many countries for the symptomatic treatment of mild to moderate Alzheimer’s disease and, more recently, was approved for mild to moderate dementia associated with Parkinson’s disease [59]. Rivastigmine is a dual inhibitor of acetylcholinesterase and butyrylcholinesterase. The efficacy of rivastigmine in AD is dose related. Total daily doses ranging from 6 mg/day to 12 mg are associated with greater efficacy. The starting dose is 1.5 mg twice a day with food; if well tolerated this should be titrated in 3 mg/day increments every 2–4 weeks. Transdermal rivastigmine is also FDA approved, and provides continuous drug delivery thereby preventing fluctuations in drug serum concentration as seen with oral therapy [60]. This minimizes side effects and increases adherence to the drug. The most common side effects include nausea and vomiting, particularly during the titration phase. When switching from oral preparation to patch, a total daily dose of less than 6 mg can be switched to the 4.6 mg/24 hours patch; if total daily dose is 6-12 mg, the 9.5 mg/24 hours patch is recommended.

**Galantamine**

Galantamine (Razadyne; marketed as Reminyl in some countries) is FDA approved for the treatment of patients with mild to moderate Alzheimer’s disease. Treatment with galantamine (maintenance dosage 16 or 24 mg/day) slows the decline in both cognition and activities of daily living (ADL) compared with placebo in patients with early Alzheimer’s disease [61]. Galantamine inhibits acetylcholinesterase, and may also modulate presynaptic nicotinic receptor activation, thereby increasing neurotransmitter concentrations in the synaptic cleft [62]. Galantamine-ER (ex-tended release) requires once daily dosing and has been approved in several countries, including the US, for the treatment of mild to moderate dementia of the Alzheimer’s type.
NMDA receptor inhibitors

**Memantine**

Excessive NMDA receptor activation can lead to excitatory toxicity and neuronal death. This suggests that agents that block pathological stimulation of NMDA receptors may protect against further tissue damage in patients with vascular dementia and possibly Alzheimer’s disease [63]. Memantine (Namenda) is a moderate affinity, noncompetitive, NMDA receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics that allow it to be used in humans with an excellent safety and tolerability profile [64]. It is approved by the FDA for the treatment of moderate to severe stages of Alzheimer’s disease. Memantine is generally well tolerated. Dizziness is the most common adverse effect. Increased agitation and delusional behavior has been reported in some patients. Currently, the recommended daily dose of memantine is 10 mg twice daily, achieved by a 3-week, three-step, titration schedule starting with 5 mg daily. A 20 mg once daily preparation has recently been introduced.

**FINAL COMMENT**

The natural course of AD spans approximately ten years. It steadily evolves and progresses during this timeframe, much to the dismay of the patients, caregiver, and treating physician. Late-stage dementia, with its behavioral disturbance, is a very different condition than the early cognitive deficits that most people are familiar with. Moderate-severe stages can take its toll on the patient, but also on family members. Caregiver burnout becomes a serious complication of the disease with tangible health ramifications for the patient and caregiver. In a forthcoming issue of the LMJ, Hajjar and his team will discuss support options for caregivers during this difficult stage.

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