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Therapeutic Options

FOCUS ON ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of dementia, accounting for at least 60 per cent of cases in individuals over 65 years of age.[1,2] In developed countries, AD has reached epidemic proportions and its prevalence will continue to increase in coming years due to growth in aging populations, placing even greater demands on families, caregivers, and the healthcare system.[1,3]

Although there is no cure for this devastating, progressive disease, appropriate management can improve symptoms. This article provides a brief overview of AD, with a focus on the management of core symptoms using available pharmacotherapies.

PATHOGENESIS AND RISK FACTORS

The pathophysiologic mechanisms leading to AD are largely unknown; however, two pathological hallmarks have been identified: (1) amyloid plaques and (2) neurofibrillary tangles (NFTs).[4,5] The amyloid cascade hypothesis proposes that abnormal production or insufficient clearance of amyloid β protein leads to extracellular amyloid plaque deposition, in turn leading to secondary neurotoxic events such as hyperphosphorylation of the protein tau (and subsequent generation of NFTs), inflammation, excitotoxicity and, ultimately, cell death.[4] The end result is a deficit in neurotransmitters (particularly acetylcholine), which causes the clinical manifestations of AD.[4]

Alternative pathophysiologic hypotheses exist, including those that focus on tau-related NFTs, which appear to be more closely associated with dementia severity than amyloid plaques.[4,5] A multifactorial pathway for AD development is likely.[6]

Several risk factors for AD have been identified (see Box 1), although evidence is currently insufficient to prove that targeting any of the potentially modifiable factors has a substantial impact on disease development or progression.[7,8] Nonetheless, adhering to healthy lifestyle recommendations and achieving control of medical conditions that pose a potential risk is prudent.[8]

Box 1 – Risk factors for Alzheimer's disease[5,7,9]

Nonmodifiable risk factors

- Advanced age
- Genetic predisposition*
- Traumatic brain injury
- Trisomy 21 (Down syndrome)

Modifiable/potentially modifiable risk factors

- Hypertension
- Diabetes
- Hypercholesterolemia
- Elevated homocysteine levels
- Smoking
- Obesity

* Of all known risk factors, genetics confer the highest risk for developing Alzheimer's disease.[5]

SYMPTOMS AND DIAGNOSIS

Characteristic features of AD include

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progressive decline in memory and reasoning.[1] While the timing of symptom expression is highly variable between patients, minor problems recalling new information may be the first noticeable symptom.[1,8] Gradual deterioration in memory follows, along with impairment in spatial and temporal orientation and difficulties with language and activities of daily living (ADL).[1,8] Changes in personality, mood, and behaviour—collectively referred to as neuropsychiatric symptoms or behavioural and psychological symptoms of dementia (BPSD)*—are also common.[1,10] In late stages of AD, many patients lose basic functions such as motor control and become completely dependent on caregivers.[1]

A definitive diagnosis of AD can presently only be made upon autopsy.[5] Nevertheless, recommendations to aid clinicians in diagnosing AD clinically have recently been put forth by the National Institute on Aging and the Alzheimer's Association.[11] A discussion of these recommendations is beyond the scope of this article; however, they are available online for interested individuals to review (see References, below, for URL).

MANAGEMENT

Pharmacological interventions for core symptoms

The primary drug treatments for core symptoms of AD include the cholinesterase inhibitors (ChEIs)—donepezil, galantamine, and rivastigmine—and memantine. Dosing guidelines and other pertinent information about these medications are presented in Table 1. Further information is provided under the subheadings below. Overall, these agents have been shown to result in modest benefits in cognition, global status, and functional ability[1,4] and they are considered standard treatment options for most patients with AD according to clinical practice guidelines.[2,7,8,10,12,13]

Factors to consider when selecting among the available drugs include stage of disease, cost, adverse effects, convenience, medical comorbidities, and the potential for drug interactions.

Cholinesterase inhibitors

The clinical effects of the ChEIs in AD are believed to result from their ability to increase levels of acetylcholine and improve cholinergic transmission in relevant regions of the brain.[1,4]

All three ChEIs available in Canada have demonstrated modest but significant efficacy with respect to cognitive function, global outcome, and ADL in patients with mild to moderate AD.[7] Efficacy in patients with severe AD has also been demonstrated,[7] although only donepezil is currently approved for use in this population and some experts report that improvements with the ChEIs are more pronounced in mild disease than in severe disease.[1] Behavioural and psychological symptoms have been shown to improve modestly with the ChEIs, with beneficial effects on psychosis (e.g., delusions, hallucinations) and apathy consistently reported.[7]

It has been suggested that improvement in cognitive measures peaks at six months and that cognitive scores remain above pretreatment levels for up to nine months.[4,17] It has also been suggested that benefits on functional measures (e.g., managing finances) manifest as stabilization (rather than improvement) that lasts an average of six months.[4]

Robust data comparing the different ChEIs are lacking, but efficacy appears to be broadly similar for the three available agents.[7,8,17,18]

Memantine

Memantine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist.[1] Therapeutic effects in AD are believed to result from the drug's ability to block glutamate binding to NMDA receptors and attenuate glutamate-mediated excitoxicity.[9]

Efficacy of memantine has been shown in moderate to severe AD, with modest clinical benefit noted in cognitive and global function, ADL, and behaviour.[1] Agitation and delusions may respond better than other BPSD.[7] In mild to moderate AD, slight improvement in cognitive and global status has been reported, but the drug does not appear to ameliorate function or behaviour.[1]

It has been suggested that benefits of memantine in patients with moderate to severe AD are generally seen as stabilization of cognitive and functional measures for an average of six months.[4]

Other drugs

Several drugs other than the ChEIs and memantine have been suggested as potentially beneficial for AD, including statins, anti-inflammatories (e.g., acetylsalicylic acid [ASA], other nonsteroidal agents), Ginkgo biloba, vitamin E, nootropics (e.g., piracetam, nicergoline), selegiline, estrogens, androgens, pentoxifylline, and cerebrolysin.[7,8,10] However, there is presently insufficient evidence to support the use of these agents to treat AD, and there is strong evidence to recommend against using ASA or vitamin E based on lack of efficacy.[7,8,10]

Practical issues in drug therapy

Management of side effects

Appropriate dose titration (i.e., starting at the lowest dose and increasing gradually; see Table 1) with the ChEIs can minimize dose-dependent cholinergic side effects such as nausea, vomiting, anorexia, and dizziness.[4] For rivastigmine in particular, the transdermal formulation is associated with considerably fewer gastrointestinal side effects than the oral formulation.[4] For non-serious adverse effects with the ChEIs, dose reduction can be attempted, with an option to retry the higher dose after two to four weeks if the lower dose is well tolerated.[10]

Switching/combining agents

Switching from one ChEI to another is an option if the first agent is not tolerated or effective, although evidence for this approach is not based on double-blinded studies.[7,8] If switching because of intolerance, some experts advise that complete resolution of side effects occur before starting the new agent.[4] If switching as a result of lack of response, an overnight switch with quicker dose titration (e.g., 2-week intervals) has been recommended.[4] It is notable that loss of response after several years of therapy usually indicates natural disease progression, and switching from one ChEI to another would

* Such symptoms include agitation, aggression, disinhibition, apathy, depression, anxiety, delusions, hallucinations, and wandering.[2]

Table 1 – Available medications for core Alzheimer's disease symptoms[1,2,4,7,10,12,14-16]

Drug	Dosing*	Comments
Cholinesterase inhibitors		
Donepezil (Aricept, Aricept RDT)	ID: 5 mg/day x ≥4 weeks TD: 10 mg/day†	• All three ChEIs are approved for use in mild to moderate AD; donepezil is also approved for use in severe AD • ChEI therapy is an option for most AD patients (mild through severe) and should be considered at the time of diagnosis • Gastrointestinal adverse effects (e.g., nausea, vomiting, anorexia) are common with all ChEIs, but may occur less frequently with donepezil than with galantamine or rivastigmine; these adverse effects are generally transient and occur most frequently during dose titration • The patch formulation of rivastigmine appears to have efficacy equivalent to oral rivastigmine, but a lower incidence of side effects • Patients should be reassessed at least every six months
Galantamine (Reminyl ER, generics)	ID/T: 8 mg/day x ≥4 weeks, then 16 mg/day x ≥4 weeks TD: 24 mg/day†	
Rivastigmine (Exelon, generics; Exelon Patch)	Oral ID/T: 3 mg/day x ≥2 weeks, then 6 mg/day x ≥2 weeks, then 9 mg/day x ≥2 weeks TD: 12 mg/day† Patch ID: 4.6 mg/day x ≥4 weeks TD: 9.5 mg/day†	
NMDA receptor antagonist		
Memantine (Ebixa, generics)	ID/T: 5 mg/day x ≥1 week, then 10 mg/day x ≥1 week, then 15 mg/day x ≥1 week TD: 20 mg/day†	• Memantine is approved for use in patients with moderate to severe AD and should be considered for such patients • Memantine is usually well tolerated; dose-limiting side effects are rare, but include dizziness, headache, somnolence, and confusion • Results of a small (n=78) study suggest that once daily dosing results in efficacy and tolerability similar to twice daily dosing • Patients should be reassessed at least every six months

ChEI = cholinesterase inhibitor; ID = initial dose; ID/T = initial dose and titration; NMDA = N-methyl-D-aspartate; TD = target dose

* Refer to approved product monographs for dosing recommendations in special situations (e.g., low body weight, renal impairment).

† Side effects may prohibit use of target doses;[2] minimum therapeutic doses are: donepezil, 5 mg/day; galantamine, 16 mg/day; rivastigmine, 6 mg/day (oral).[14]

not usually be appropriate in such a scenario.[4]

The benefits of adding memantine to a ChEI are currently unclear as available evidence is conflicting.[7,8] Still, the combination may be considered for patients with moderate to severe AD.[4,10,12]

Discontinuing therapy

Other than when serious side effects occur, it is unclear when therapy with a ChEI or memantine should be withdrawn.[2,4,7,10] Generally speaking, treatment may be continued as long as it is considered to be having a worthwhile effect on cognitive, global, functional, or behavioural symptoms.[13] In any case, the decision to discontinue therapy should be made in conjunction with patients and/or relatives/caregivers/legal representatives.[2]

Interventions for behavioural and psychological symptoms

A detailed discussion regarding the management of behavioural and psychological symptoms associated with AD is beyond the scope of this article. Nonetheless, some important points warrant mentioning.

In some studies, BPSD were episodic in nature and did not show progressive worsening over time.[10] In addition, antipsychotic agents, which have commonly been used to treat BPSD, have been linked to serious adverse events such as increased risk of stroke and mortality.[7,12,13] As such, nonpharmacological interventions (e.g., education, exercise, aromatherapy, sensory stimulation, personalized music) should be the first line of therapy in managing BPSD in the majority of instances.[2,7,10,12] A careful search for

triggers and causative factors (e.g., physical illness, hunger or thirst, environmental factors) is essential.[2,7]

In situations where moderate to severe BPSD pose a risk of harm, or they are a source of significant distress and have not responded to nonpharmacological measures, drug therapy may be considered.[7,12] As noted above, ChEIs and memantine may improve BPSD and can be considered for such symptoms.[10]

Antipsychotic agents have demonstrated efficacy in treating agitation, aggression, and psychosis, and atypical agents (where indicated) have been specifically recommended in some guidelines.[7,10,12] Because of the potential for serious adverse effects, these drugs should only be used after a full discussion with the patient and/or caregivers about possible risks and benefits.[13] If utilized, antipsychotics should be initiated at the lowest possible doses and should be slowly titrated with close monitoring.[7,10,12] They should also be used for the shortest possible duration;[7] tapering and withdrawing therapy after three months of behavioural stability has been recommended.[10,12]

Antidepressant therapy may be useful for depression in people with dementia.[7] When necessary, medications without significant anticholinergic effects (e.g., selective serotonin reuptake inhibitors) should be used.[7,10,12]

PREVENTION

Unfortunately, there is presently no clear and consistent evidence from large, randomized trials that any intervention can prevent or delay the onset of AD.[2,7,8]

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