In Review

Pharmacological Treatment of Alzheimer Disease

Fadi Massoud, MD, CSPQ, FRCPC[1]; Gabriel C Léger, MD, CSPQ, FRCPC[2]

Objective: To review the different pharmacological approaches to the cognitive, functional, and behavioural manifestations of Alzheimer disease (AD).

Methods: We searched and critically analyzed the most recent relevant literature on pharmacological treatment of AD.

Results: The current pharmacological approach to AD treatment is based on vascular prevention and symptomatic therapy with cholinesterase inhibitors (ChEIs) and memantine, an *N*-methyl-D-aspartic acid antagonist. Clinical trials of 6- to 12-month duration have shown statistically significant benefits with ChEIs and memantine on cognitive, global, functional, and behavioural outcome measures. In general, these benefits are modest. However, they are dose-dependent and reproducible across studies. Most importantly, these benefits are symptomatic as they do not alter disease course. According to the third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, these agents are considered standard treatment options in AD. We will discuss practical issues related to current pharmacological management, such as setting realistic expectations, management of side effects, switching ChEIs, and the decision to discontinue treatment. The results of clinical trials studying potentially disease-modifying approaches in AD will also be reviewed. Unfortunately, although there remains much promise and enthusiasm, none of these agents has shown consistent benefits, and none are available for use in clinical practice.

Conclusion: Pharmacological options are presently available for the symptomatic treatment of AD. These treatments provide mild but sustained benefits. Before disease-modifying approaches become available, optimizing the use of the available treatment options is crucial.

Can J Psychiatry. 2011;56(10):579–588.

Clinical Implications

- AD is the most common neurodegenerative disorder.
- Symptomatic treatments are currently available, and they provide mild and reproducible benefits across studies.
- Several clinical trials of potentially disease-modifying treatments are ongoing.

Limitations

- Most clinical trials evaluating symptomatic pharmacological treatments in AD exclude patients with medical comorbidities.
- There are no randomized controlled trials exceeding 1-year duration.
- Few clinical trials have evaluated combinations of pharmacological treatments.

Key Words: *Alzheimer, dementia, pharmacotherapy, cholinesterase inhibitors, memantine, amyloid*

AD is the most common neurodegenerative disorder. The World Alzheimer Report published in 2009 estimated that 35.6 million people will be living with dementia, worldwide, in 2010.[1] This figure will increase to 65.7 million by 2030 and to 115.4 million by 2050. The World Alzheimer Report published on Alzheimer's Day in September 2010 estimates the cost of dementia at $604 billion, globally, which is equivalent to 1% of the world's gross domestic product.[2] As are most aging industrialized countries, Canada is not spared by this disease. A report commissioned by the Alzheimer Society published in 2009 and entitled *Rising Tide: The Impact of Dementia in Canada* drew alarming conclusions.[3] According to this report, more than 480 000 Canadians (1.5% of Canada's population) were affected by dementia in 2008. This figure will more than double by 2038, reaching 1 125 200 people (2.8% of Canada's population). The cost of dementia in Canada will double every decade and increase from $15 billion in 2008 to $153 billion in 2038. The Rising Tide report[3] concluded by making 5 general recommendations, which include recognizing the importance of prevention and early intervention. This review will critically discuss the roles of vascular prevention, ChEIs, and memantine, an NMDA antagonist, in the pharmacological management of AD. The results of clinical trials studying potentially disease-modifying approaches in AD will also be discussed.

Abbreviations

Aβ	beta-amyloid
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer disease
APP	amyloid precursor protein
BACE1	beta-site amyloid precursor protein-cleaving enzyme 1
BuChE	butyrylcholinesterase
CCCDTD	Canadian Consensus Conference on Diagnosis and Treatment of Dementia
ChEI	cholinesterase inhibitor
CIBIC	Clinician Interview-Based Impression of Change
GSK3	glycogen-synthase-kinase-3
HYVET	Hypertension in the Very Elderly Trial
NFT	neurofibrillary tangle
NMDA	*N*-methyl-D-aspartic acid
PPARγ	peroxisome proliferator-activated receptor gamma
RCT	randomized controlled trial
tau	tubulin-associated unit

Mechanisms of Disease

A brief description of the mechanisms of disease involved in AD facilitates the understanding of current and future pharmacological interventions. Although the pathophysiology of AD is largely unknown, the amyloid cascade hypothesis is the main one proposed to explain the disease process.[4–6] According to this hypothesis, abnormal production or insufficient clearance of the Aβ protein is thought to result in extracellular amyloid plaque deposition, which in turn leads to secondary events, such as hyperphosphorylation of the protein tau and generation of NFTs, inflammation, excitotoxicity, and, eventually, cell death through activation of the apoptotic pathway.[7–9] These events cause deficits in neurotransmitters (especially ACh), which are thought to be responsible for the clinical manifestations of the disease.[10] The APP undergoes cleavage by 2 pathways (Figure 1). The sequential cleavage of APP by alpha-secretase and gamma-secretase leads to the formation of a soluble particle (p3 protein) that does not deposit abnormally. However, the sequential cleavage of APP by beta-secretase and gamma-secretase leads to the formation of insoluble Aβ that eventually deposits into amyloid plaques leading to the pathological process. Recent data suggest that soluble Aβ may be toxic before it actually deposits into plaques.[11,12]

An alternate hypothesis considers NFTs at the centre of the pathophysiological process. NFTs are produced by hyperphosphorylation of the protein tau, which is usually responsible of stabilizing the axonal cytosqueletton.[13–15] They lead to disruption in axonal transport and eventually to cell death.

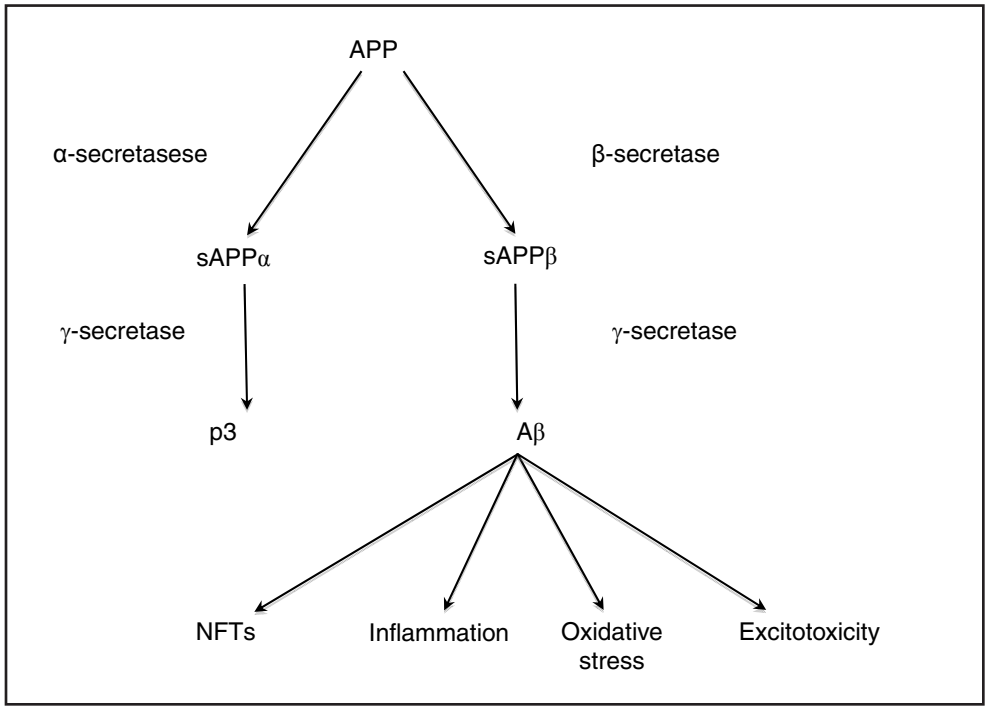
In recent years, increased emphasis has been put on the vascular contribution to AD's pathophysiology. Most vascular risk factors are also risk factors for AD.[16] In the Nun Study, a longitudinal clinico-pathological study, the coexistence of ischemic lesions with plaques and tangles in the brains of participants increased the risk of clinical expression of dementia by a factor of 20.[17] A recent study shows that as people suffering from dementia get older, the neuropathological contribution of typical AD stigmata decreases, suggesting an incremental role for vascular contribution.[18–20]

Approved Pharmacological Treatment

Vascular Prevention

The 2 vascular risk factors mostly studied with respect to cognitive outcomes are hypertension and dyslipidemia. Three RCTs have shown that optimal treatment of high blood pressure in people with or without cerebrovascular disease was associated with better cognitive outcomes.[21–23] HYVET evaluated the impact of treating hypertension on incidence of dementia in people aged 80 years and older.[24,25] The treatment group in this study showed statistically significant benefits on cardiovascular and cerebrovascular outcomes. However, treatment of hypertension did not result in a reduction of

Figure 1 Amyloid cascade hypothesis in AD



dementia incidence. The results of HYVET were included in a metanalysis of all 4 primary prevention studies in hypertension evaluating incident dementia. The pooled relative risk calculated from this meta-analysis is borderline significant (RR 0.87; 95% CI 0.76 to 1.00, $P = 0.04$). The CCCDTD gave treatment of hypertension a grade B, level I recommendation as an option in primary prevention of cognitive decline.[26] Two major primary prevention RCTs evaluating the benefits of cholesterol-lowering medications showed statistically significant benefits on cardiovascular and cerebrovascular outcomes in treated people.[27,28] However, there were no benefits on cognitive outcome measures used in these RCTs. These counterintuitive results can be explained, at least in part, by the relatively crude cognitive measures used and by the short duration of follow-up. A longitudinal observational study in a tertiary memory clinic showed that treatment of vascular risk factors is associated with a slower decline on cognitive measures in people with AD.[29]

Cholinesterase Inhibitors

There are 3 ChEIs available on the Canadian market: donepezil, rivastigmine, and galantamine. Use of these agents is based on studies showing that people with AD have deficits in ACh production leading to cortical cholinergic dysfunction.[30] Cholinesterase, which exists in 2 forms, BuChE and AChE, degrades ACh in the synaptic cleft. ChEIs act by inhibiting this action and optimize the levels of ACh available for postsynaptic stimulation.[31] ChEIs improve symptoms of AD, but they do not alter its natural clinical course. Hence they are considered symptomatic treatments for AD (Tables 1 and 2).

Donepezil. Donepezil is a piperidine derivative that inhibits AChE.[32] A Cochrane review[33] evaluated the benefits of donepezil and included 24 trials and 5796 people with mild-to-severe AD. Pooled analyses showed statistically significant benefits on cognitive, global (clinician's or caregiver's impression of response to treatment), functional, and behavioural outcome measures (Table 2). In general, both the doses of 5 and 10 mg daily were effective, with marginal incremental benefit at the higher dose. There were more dose-dependent side effects in donepezil-treated patients, the most common of which are nausea, vomiting, diarrhea, muscle cramps, dizziness, fatigue, and anorexia.

Rivastigmine. Rivastigmine is a carbamate derivative that reversibly inhibits both AChE and BuChE.[34] The clinical relevance of this dual inhibition is unclear.[35] A transdermal formulation of rivastigmine is currently available on the Canadian market, which aims at minimizing cholinergic side effects while allowing titration to the highest (and most effective) doses of the medication.[36,37] A Cochrane review[38] including 9 trials and 4775 patients evaluated the benefits of rivastigmine in mild-to-moderate AD. Pooled analyses showed benefits on cognitive, global, and functional outcome measures (Table 2). There were no statistically significant benefits on behavioural outcomes. The benefits were observed mostly in people on the highest doses of the medication (6 to 12 mg daily). Side effects include nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain, and dizziness. The Investigation of transDermal Exelon in ALzheimer's disease (commonly referred to as IDEAL) study compared transdermal rivastigmine to oral rivastigmine.[37] The highest available transdermal dose (10 cm^2) was as effective as the oral maximal dose

Table 1 Pharmacological properties of ChEIs and memantine

Name	Metabolism	Starting dose	Minimal effective dose	Maximal dose
Donepezil	Hepatic CYP, CYP2D6, CYP3A4	5 mg/sid	5 mg/sid	10 mg/sid
Rivastigmine (Oral)	Renal	1.5 mg/bid	3 mg/bid	6 mg/bid
Rivastigmine (Transdermal)	Renal	5 cm^2/sid	10 cm^2/sid	10 cm^2/sid
Galantamine ER	Hepatic CYP, CYP2D6, CYP3A4	8 mg/sid	16 mg/sid	24 mg/sid
Memantine	Renal	5 mg in 1 or 2 daily doses	10 mg in 1 or 2 daily doses	20 mg in 1 or 2 daily doses[a]

[a] In people with significant renal impairment (creatinine clearance of ≤30 mL/min), the maximal daily dose should not exceed 10 mg.

bid = twice daily; CYP = cytochrome P450; ER = extended release; sid = once daily

(12 mg daily) on cognitive, global, and functional outcome measures. However, it was associated with almost 3 times less gastrointestinal cholinergic side effects.

Galantamine. Galantamine is a tertiary alkaloid that reversibly inhibits AChE and allosterically binds to nicotinic receptors enhancing cholinergic transmission.[39] The clinical relevance of this unique additional property is unclear. A Cochrane review[40] including 10 clinical trials and 6805 patients with AD and mild cognitive impairment showed statistically significant treatment effects on cognitive, global, functional, and behavioural outcome measures (Table 2). Unlike trials with other ChEIs, dose-response was inconsistent with galantamine, especially on measures of global rating. An RCT that studied patients with mixed AD with cerebrovascular disease and vascular dementia showed statistically significant treatment benefits at 24 weeks for doses of 16 to 24 mg daily on the Alzheimer's Disease Assessment Scale—Cognition (commonly referred to as ADAS-Cog), the CIBIC, the Disability Assessment for Dementia (commonly referred to as DAD) scale, and the Neuropsychiatric Inventory (commonly referred to as NPI).[41] Typical cholinergic side effects were more commonly reported in patients on galantamine, compared with placebo.

Memantine

Memantine is an NMDA noncompetitive glutamate receptor antagonist.[42] Its use in AD is based on studies showing that glutamate-related excitotoxicity is involved in the pathophysiology of the disease.[43] A Cochrane review[44] of memantine showed statistically significant treatment benefits at 24 weeks on measures of cognition, function, and global measures in pooled analyses of the 3 RCTs in moderate-to-severe AD. Analyses of the 3 unpublished trials in mild-to-moderate AD showed statistically significant treatment benefits on measures of cognition only. One study in moderate-to-severe AD showed that combining memantine to a stable dose of donepezil led to statistically significant additional benefits on measures of cognition (Severe Impairment Battery), function (Alzheimer's Disease Cooperative Study—Activities of Daily Living), and global assessment CIBIC.[45] Memantine is usually well tolerated. Dose-limiting side effects are rare and they consist of dizziness, headache, somnolence, and confusion. In Canada, memantine is approved for the treatment of moderate-to-severe AD.

Practical Issues in Current Pharmacological Management

Four clinical issues need to be considered when prescribing ChEIs and memantine for AD: treatment expectations, management of side effects, switching agents, and discontinuation of therapy.

Treatment Expectations. As mentioned previously, all available pharmacological treatments are symptomatic, and they do not alter progression of an otherwise neurodegenerative process. Treatment expectations need to be adjusted accordingly. It is challenging to translate the results of RCTs of several hundred patients to an individual patient with no placebo comparator.[46] In clinical practice, the individual patient, before treatment is started, serves as their own comparator, once treatment is instituted. Overall, in mild-to-moderate AD, patients tend to show improvement on cognitive measures that reach their peak at 6 months, and cross baseline at 9 to 12 months. On global measures, maximal benefit is usually observed at 3 months, and patients tend to cross baseline performance at 6 months. Patients do not typically show improvement on functional measures but rather a stabilization that lasts for an average of 6 months. Hence functions lost, such as managing one's finances or driving, should not be expected to significantly improve with treatment. Regarding behaviour, treatment with ChEIs usually prevents new neuropsychiatric symptoms in mild-to-moderate AD, and may help alleviate some of these symptoms in moderate-to-severe AD (such as depression, apathy, and anxiety). In moderate-to-severe AD, memantine

Table 2 Summary of statistically significant benefits in recent cochrane reviews with ChEIs in AD

Measure	Donepezil, weeks (mg/day)	Rivastigmine, weeks (mg/day)	Galantamine, weeks (mg/day)
Cognitive outcome measures			
Alzheimer's Disease Assessment Scale—Cognition	24 (5 and 10)	26 (1–4 and 6–12) and 52 (6–12)	12 (18–36) 24 (8–32)
Severe Impairment Battery	24 (10)	26 (6–12)	
Mini mental status examination	24 (5 and 10) and 52 (10)	26 (1–4 and 6–12) and 52 (6–12)	
Functional outcome measures			
Disability Assessment for Dementia Scale	24 (10)		12 and 24 (24–32[a])
ADCS-ADL	24 (10)	24 (6–12)	24 (16–24[a])
Progressive Deterioration Scale	52 (10)	26 and 52 (6–12)	
Global outcome measures			
CIBIC-Plus	24 (5 and 10)	26 and 52 (1–4 and 6–12)	
Global ratings			12 (18 and 36) and 24 (16, 24, and 32)
ADCS-CGIC		26 and 52 (1–4 and 6–12)	
Behavioural outcome measures			
Neuropsychiatric Inventory	24 (10)	Nonsignificant	24 (16 and 24)

[a] One trial

The table describes the doses (mg/day) and duration (weeks) of trials at which treatment differences were statistically significant for various outcome measures.

ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living inventory; ADCS-CGIC: ADCS Clinical Global Impression of Change; CIBIC-Plus = CIBIC with Caregiver Input

tends to stabilize cognitive and functional manifestations of the disease for an average of 6 months. Most,[47–52] but not all,[53,54] published guidelines agree that a standard pharmacological approach to AD should be to offer patients at least a trial of ChEI and (or) memantine. On that issue, the CCCDTD concludes: "all three cholinesterase inhibitors available in Canada are modestly efficacious for mild to moderate AD. They are all viable options for most patients with mild to moderate AD."[50, p 362]

Management of Side Effects. ChEIs are associated with cholinergic side effects, which include anorexia, nausea, vomiting, diarrhea, abdominal discomfort, dizziness, fatigue, and muscle cramps. These symptoms are observed with the 3 available ChEIs and are clearly dose-dependent. Starting these agents at the lowest dose, and slowly titrating by no less than 4-week intervals to the minimally effective dose, helps to minimize these side effects. The transdermal formulation of rivastigmine is associated with considerably less gastrointestinal cholinergic side effects, but may be associated with skin intolerance in a minority of patients.

RCTs have excluded many subgroups of patients with common comorbidities. In the absence of clear guidelines regarding the treatment of patients with AD suffering from other serious medical comorbidities, we can only recommend prudence and an individualized approach based on clinicians' judgment.

Switching Agents. Even though ChEIs belong to the same general class, their individual pharmacological properties make switching a feasible option for intolerance or for lack of clinical response.[55] In the case of intolerance, we recommend clinicians wait for complete resolution of side effects of the initial agent before switching to the second agent, which can then be titrated according to the usual recommendations. In the case of lack of clinical response, which we define empirically as significant deterioration despite the use of a symptomatic medication at an effective dose for at least 6 months, switching to the second agent can be done overnight, with quicker titration (in 2-week intervals) until the minimal effective dose is reached. We do not recommend switching for loss of response after several years of treatment with a ChEI as this usually indicates natural progression to a more severe stage of the disease. In our experience, these people benefit from the addition of memantine rather than from switching to a second ChEI. Unfortunately, memantine is only reimbursed as monotherapy and in only one Canadian province.

Discontinuation of Therapy. Discontinuing therapy with ChEIs or memantine is both scientifically and emotionally challenging, and no clinical trial satisfyingly guides the clinicians confronted with this difficult decision. The CCCDTD has identified some indications for discontinuation of treatment in AD[50] (Table 3).

Table 3 Indications for discontinuation of therapy in AD (adapted from Hogan et al[50])
1. The patient and (or) their proxy decision maker decide to stop
2. Refusal to take the medication
3. Nonadherence to the medication
4. No response to therapy after a reasonable trial
5. Intolerable side effects
6. Comorbidities making continued use of the agent risky or futile
7. Progression to a stage of the disease where there is no significant benefit from continued therapy

Some of these recommendations are very clear in their indication (Criteria 1, 2, 3, and 5), while others are open to interpretation (Criteria 4, 6, and 7) and should be guided by individualized clinical judgment.

Emerging Treatments

Ever since Selkoe's proposal of the amyloid hypothesis[8,56] some 20 years ago, and as a result of our growing understanding of the multiple genes and proteins involved in the complex pathogenesis of AD, most pharmaceuticals in the development pipeline are created to act on individual protein targets in the hope of slowing or halting disease progression (and thus are potentially disease-modifying). In the discussion that follows, we attempt to place new drugs within this molecular framework and offer a road map to the mechanistic underpinnings of the categories of drugs in question. For more details, an authoritative review of the current state of phase II and III trials has recently been published.[57]

Amyloid-Based Therapies

The amyloid cascade hypothesis[56] suggests that the accumulation of Aβ is the initial trigger to the AD pathophysiological process, and that all downstream events, potentially as, or possibly even more, devastating to neuronal integrity are simply consequential. Preventing the production, increasing or promoting the removal, and reducing the effective putative toxicity of Aβ are obvious goals.

Reducing Aβ Production.

BACE1. Shifting of APP processing away from the amyloidogenic β-secretase (also called the β-site APP-cleaving enzyme 1 or BACE1) toward the nonamyloidogenic α-secretase pathway can be achieved by blocking BACE1. Inhibiting this enzyme directly may be problematic because it also cleaves numerous other substrates, including one involved in myelination, but an early candidate has completed a phase I trial.[58]

Indirect modulation of BACE1 activity is possible through complex mechanisms involving the PPARγ.[59] When stimulated, this factor reduces expression of BACE1[60] and leads to reductions in APP concentrations.[61] Because of its actions on glucose and lipids, PPARγ is an important target in type II diabetes. Known PPARγ ligands include the diabetic drugs rosiglitazone and pioglitazone. Although most RCTs of these drugs in AD are still ongoing, initial reports are not encouraging.[62,63]

γ-Secretase. As depicted in Figure 1, γ-secretase cleaves both sAPPα and, completing the amyloidogenic pathway, sAPPβ. It is also involved in numerous other processes, including the notch-signalling pathway critical to cell differentiation.[64] Numerous candidate drugs are in various trial phases. Despite promising phase II results, negative outcomes have led Eli Lilly to stop development of their inhibitor semagacestat[65] after completing 2 phase III trials.[66]

Not all Aβs are created equal. The amyloidogenic pathway can produce Aβ peptides of sizes varying from 37 to 42 amino acids. The longer Aβ42 species is thought to be critical to the aggregation process.[67] Certain chemicals, including some nonsteroidal antiinflammatroy drugs (commonly referred to as NSAIDS), collectively known as selective Aβ42 lowering agents (commonly referred to as SALAs), can modulate γ-secretase to shift Aβ production toward the shorter form.[68] The first of these agents to clinical trials was tarenflurbil (R-flurbiprofen). Initial phase II results were encouraging,[69] but phase III RCTs failed to show beneficial effects.[70]

α-Secretase. Shunting of APP toward nonamyloidogenesis could be achieved by stimulating α-secretase. Through a myriad of complex mechanisms, numerous agents appear to do just that, but their role in the treatment of AD is not established.[71] Candidates are in phase I or II studies, including exebryl-1, which potentially increases α-secretase activity, decreases β-secretase activity, and may even reduce tau aggregation.[72]

Preventing Aβ Accumulation and Promoting Clearance.

Regardless of any remaining controversy concerning which of the Aβ species is most responsible for its ascribed neurotoxicity,[73] removal of all of its forms is a legitimate objective. Numerous agents able to prevent its self-association and downstream aggregation or even promote disaggregation are under investigation.[74]

Preventing Aggregation. Alzhemed (tramiprosate or homotaurine) is a chemically produced agent naturally found in seaweed. As an early antiaggregant involved in human studies, it showed encouraging phase II trials.[75] Results from the subsequent phase III trial proved disappointing, perhaps as a consequence of an unusually high placebo response.[76] Post hoc analysis using volumetric magnetic resonance imaging showed possible slowing of

hippocampal atrophy.[77] The product has since been marketed as a memory loss–preventing neutraceutical (Vivimind) and generated much controversy. Caution is warranted as some data also suggest the drug may promote tau aggregation.[78]

Aβ aggregation, as well as numerous other pathological processes involved in AD, is promoted by the presence of certain metals, such as copper or zinc.[79] Small agents, such as quinolone analogues, are able to interfere with this interaction and produce positive effects in murine models[80] and in human phase II trials,[81,82] but phase III trials have not yet been undertaken.

Other antiaggregants also showing promise that are currently in phase II trials include a polyphenol derived from green tea (epigallocatechin-3-gallate)[83] and an uncommon stereoisomer of the carbohydrate inositol (scyllo-inositol).[84]

Promoting Clearance. Approaches to enhancing clearance include both passive and active immunization. Passive immunization includes monoclonal humanized antibodies (ending with the suffix -zumab). At least 6 candidates are presently under active phase II or III investigations, and results, although not spectacular, are promising.[57] Healthy donor-derived intravenous immunoglobulin can be used as a form of passive immunization. It contains naturally occurring anti-Aβ antibodies, which are reduced in patients with AD. Although this agent is polyclonal and less specific, phase II trials have showed favourable outcomes,[85,86] and phase III trials are ongoing.[87]

As for active immunization, the phase I study involving AN172 (the first vaccine used in humans) had to be prematurely terminated because of the development of aseptic meningitis in 18 patients (of 300, or 6%).[88] This aggressive autoimmunity was attributed in part to the sensitization of cytotoxic T-cells.[89] One patient who died of the encephalitis showed significant clearing of Aβ plaques.[90] Surviving patients who developed antibodies showed less functional decline,[91] but long-term postmortem analysis showed, despite documented reductions in Aβ load, continued progression of other markers of neurodegeneration.[92] Numerous new vaccines are entering phase I trials and appear to reduce Aβ load without producing encephalitis.[93]

Although numerous stage II trials mentioned above have been promising, it should be noted that none of the completed phase III trials have yet to report positive results. There are surely several important factors that may explain these negative results,[94] but many are turning back and re-examining the hypothesis, including one of its creators.[95]

Nonamyloid Strategies

The most salient neuropathological features present in brains of patients with AD are Aβ plaques and, as the amyloid cascade hypothesis would have it, secondary hyperphosphorylated tau-based NFTs. Other downstream findings include inflammation, oxidative stress, and excitotoxicity (Figure 1). Irrespective of the validity of the hypothesis or the actual sequence of events, any implicated process amenable to pharmacological modulation represents a viable target.

Tau-Targeted Therapies. Regardless of the inaugural event in AD,[96] because clinical severity is anatomically more closely related to tau pathology staging[97] than to Aβ accumulations[98–100] it justifies targeting tau. Hyperphosphorylation of the tau leads to formation of NFTs. A key phosphorylation enzyme (a kinase) in this process is GSK3, while protein phosphatase 2A is responsible for dephosphorylation.[101]

Two well-known drugs, the mood stabilizers valproic acid (also an antiepileptic) and lithium, demonstrate some degree of GSK3 inhibition. For these drugs, analysis of available data and results from a phase II trial are not encouraging enough to justify proceeding to phase III studies,[102] possibly because brain concentrations high enough to inhibit GSK3 cannot be reached without untoward side effects. At least 5 other candidates have undergone encouraging phase II studies and are awaiting phase III conformation,[57] including vitamin B_3 (nicotinamide)[103] and methylene blue (Rember).[104]

Other Downstream Processes to Target. More generalized targets, such as inflammation, oxidative stress (most often impacting mitochondria), and excitotoxicity, are also being actively explored,[57] but no convincing benefits have been demonstrated. Mitochondrial dysfunction is an emerging target.[105,106] Mitochondrial stabilization was latrepirdine's (dimebon) main putative mode of action. Despite spectacular results from a phase II study in Russia,[107] a recent phase III study conducted in North America was negative.

Final Remarks

Pharmacological options are presently available for symptomatic treatment of AD. These treatments provide mild but sustained benefits. Before disease-modifying approaches become available, optimizing the use of the available treatment options is crucial. This is particularly important, because, although our growing understanding of the amyloid hypothesis and drug discovery targeting single steps in the hypothesized pathophysiological process have generated much enthusiasm, results of phase III trials have been relentlessly negative. The amyloid cascade hypothesis, the validity of our animal models, and even our ability to conduct clinical trials that will detect disease modification in patients with already diagnosed AD or even mild cognitive impairment (commonly referred to as MCI) are being questioned.[108] The amyloid cascade hypothesis remains, but more attention is directed at the role of other disease mechanisms.[109,110]

Acknowledgements

Dr Massoud and Dr Léger have both received speaker's honoraria, consultant fees, and research support from Pfizer, Janssen Ortho Inc, Novartis, and Lundbeck.

The Canadian Psychiatric Association proudly supports the In Review series by providing an honorarium to the authors.

References

1. Alzheimer's Disease International. World Alzheimer report 2009 [Internet]. London (GB): Alzheimer's Disease International; 2009 [cited 2010 Oct 22]. Available from: http://www.alz.co.uk/research/worldreport.
2. Alzheimer's Disease International. World Alzheimer report 2010 [Internet]. London (GB): Alzheimer's Disease International; 2010 [cited 2010 Oct 22]. Available from: http://www.alz.co.uk/research/worldreport.
3. Alzheimer Society. Rising tide: the impact of dementia on Canadian society [Internet]. Toronto (ON): Alzheimer Society; 2010 [cited 2010 Oct 25]. Available from: http://www.alzheimer.ca/english/rising_tide/rising_tide_report.htm.
4. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329–344.
5. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001;81:741–766.
6. Selkoe DJ, American College of Physicians, American Physiological Society. Alzheimer disease: mechanistic understanding predicts novel therapies. Ann Intern Med. 2004;140(8):627–638.
7. Cummings JL. Alzheimer's disease. N Engl J Med. 2004;351:56–67.
8. Harris ME, Hensley K, Butterfield DA, et al. Direct evidence of oxidative injury produced by the Alzheimer's beta-amyloid peptide (1–40) in cultured hippocampal neurons. Exp Neurol. 1995;131:193–202.
9. Mattson MP, Cheng B, Davis D, et al. beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci. 1992;12:376–389.
10. Francis PT, Palmer AM, Snape M, et al. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatr. 1999;66:137–147.
11. Lue LF, Kuo YM, Roher AE, et al. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am J Pathol. 1999;155:853–862.
12. McLean CA, Cherny RA, Fraser FW, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999;46:860–866.
13. Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci. 1993;16:460–465.
14. Lee VM. Disruption of the cytoskeleton in Alzheimer's disease. Curr Opin Neurobiol. 1995;5:663–668.
15. Trojanowski JQ, Lee VM. Phosphorylation of paired helical filament tau in Alzheimer's disease neurofibrillary lesions: focusing on phosphatases. FASEB J. 1995;9:1570–1576.
16. Kivipelto M, Ngandu T, Laatikainen T, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 2006;5:735–741.
17. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277:813–817.
18. Ewbank DC, Arnold SE. Cool with plaques and tangles. N Engl J Med. 2009;360:2357–2359.
19. Savva GM, Wharton SB, Ince PG, et al. Age, neuropathology, and dementia. N Engl J Med. 2009;360:2302–2309.
20. Troncoso JC, Zonderman AB, Resnick SM, et al. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol. 2008;64:168–176.
21. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998;352:1347–1351.
22. Tedesco MA, Ratti G, Mennella S, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. Am J Hypertens. 1999;12:1130–1134.
23. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163:1069–1075.
24. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–1898.
25. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683–689.
26. Bocti C, Black S, Frank C. Management of dementia with a cerebrovascular component. Alzheimers Dement. 2007;3:398–403.
27. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363:757–767.
28. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623–1630.
29. Deschaintre Y, Richard F, Leys D, et al. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology. 2009;73:674–680.
30. Whitehouse PJ, Price DL, Struble RG, et al. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science. 1982;215:1237–1239.
31. Bentley P, Driver J, Dolan RJ. Modulation of fusiform cortex activity by cholinesterase inhibition predicts effects on subsequent memory. Brain. 2009;132:2356–2371.
32. Seltzer B. Donepezil: an update. Expert Opin Pharmacother. 2007;8:1011–1023.
33. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006:CD001190.
34. Onor ML, Trevisiol M, Aguglia E. Rivastigmine in the treatment of Alzheimer's disease: an update. Clin Interv Aging. 2007;2:17–32.
35. Darvesh S, Hopkins DA, Geula C. Neurobiology of butyrylcholinesterase. Nat Rev Neurosci. 2003;4:131–138.
36. Blesa R, Ballard C, Orgogozo JM, et al. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. Neurology. 2007;69:S23–S28.
37. Winblad B, Grossberg G, Frolich L, et al. IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69:S14–S22.
38. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2009:CD001191.
39. Robinson DM, Plosker GL. Galantamine extended release in Alzheimer's disease: profile report. Drugs Aging. 2006;23:839–842.
40. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006:CD001747.
41. Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet. 2002;359:1283–1290.
42. Kavirajan H. Memantine: a comprehensive review of safety and efficacy. Expert Opin Drug Saf. 2009;8:89–109.
43. Sucher NJ, Awobuluyi M, Choi YB, et al. NMDA receptors: from genes to channels. Trends Pharmacol Sci. 1996;17:348–355.
44. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006:CD003154.
45. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291:317–324.
46. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. Curr Neuropharmacol. 2010;8:69–80.
47. Burns A, O'Brien J, BAP Dementia Consensus, et al. Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. J Psychopharmacol. 2006;20(6):732–755.

48. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56:1154–1166.
49. Fillit HM, Doody RS, Binaso K, et al. Recommendations for best practices in the treatment of Alzheimer's disease in managed care. Am J Geriatr Pharmacotherapy. 2006;4(Suppl A):S9–S24.
50. Hogan DB, Bailey P, Carswell A, et al. Management of mild to moderate Alzheimer's disease and dementia. Alzheimers Dement. 2007;3:355–384.
51. Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. Am J Geriatr Psychiatry. 2006;14:561–572.
52. National Institute for Health and Clinical Excellence (NICE). Alzheimer's disease—donepezil, rivastigmine, galantamine and memantine (review)—final appraisal [Internet]. London (GB): NICE; 2011 [cited 2011 Jul 7]. Available from: http://www.nice.org.uk/page.aspx?o=322952.
53. Qaseem A, Snow V, Cross JT, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2008;148:370–378.
54. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148:379–397.
55. Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. Int Psychogeriatr. 2011;23(3):372–378.
56. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron. 1991;6:487–498.
57. Mangialasche F, Solomon A, Winblad B, et al. Alzheimer's disease: clinical trials and drug development. Lancet Neurol. 2010;9:702–716.
58. Tang J. Beta-secretase as target for amyloid-reduction therapy. Alzheimers Dement. 2009;5:P74–P74.
59. Landreth G, Jiang Q, Mandrekar S, et al. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. Neurotherapeutics. 2008;5:481–489.
60. Sastre M, Dewachter I, Rossner S, et al. Nonsteroidal anti-inflammatory drugs repress beta-secretase gene promoter activity by the activation of PPARgamma. Proc Natl Acad Sci U S A. 2006;103:443–448.
61. d'Abramo C, Massone S, Zingg J-M, et al. Role of peroxisome proliferator-activated receptor gamma in amyloid precursor protein processing and amyloid beta-mediated cell death. Biochem J. 2005;391:693–698.
62. Risner ME, Saunders AM, Altman JFB, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J. 2006;6:246–254.
63. Gold M, Alderton C, Zvartau-Hind M, et al. Effects of rosiglitazone as monotherapy in APOE4-stratified subjects with mild-to-moderate Alzheimer's disease. Alzheimers Dement. 2009;5:P86–P86.
64. Tomita T. Secretase inhibitors and modulators for Alzheimer's disease treatment. Expert Rev Neurother. 2009;9:661–679.
65. Henley D, May P, Dean R, et al. Development of semagacestat (LY450139), a functional γ-secretase inhibitor, for the treatment of Alzheimer's disease. Expert Opin Pharmacother. 2009;10:1657–1664.
66. Eli Lilly. Lilly halts development of semagacestat for Alzheimer's disease based on preliminary results of phase III clinical trials [Internet]. Indianapolis (IN): Eli Lilly; 2010 [cited 2011 Jan 15]. Available from: http://newsroom.lilly.com/releasedetail.cfm?releaseid=499794.
67. McGowan E, Pickford F, Kim J, et al. Abeta42 is essential for parenchymal and vascular amyloid deposition in mice. Neuron. 2005;47:191–199.
68. Eriksen JL, Sagi SA, Smith TE, et al. NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo. J Clin Invest. 2003;112:440–449.
69. Wilcock GK, Black SE, Hendrix SB, et al. Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial. Lancet Neurol. 2008;7:483–493.
70. Green RC, Schneider LS, Amato DA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA. 2009;302:2557–2564.
71. Hooper NM, Turner AJ. The search for alpha-secretase and its potential as a therapeutic approach to Alzheimer s disease. Curr Med Chem. 2002;9:1107–1119.
72. Snow A, Cummings J, Lake T, et al. Exebryl-1: a novel small molecule currently in human clinical trials as a disease-modifying drug for the treatment of Alzheimer's disease. Alzheimers Dement. 2009;5:P418–P418.
73. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol. 2007;8:101–112.
74. Amijee H, Scopes DIC. The quest for small molecules as amyloid inhibiting therapies for Alzheimer's disease. J Alzheimers Dis. 2009;17:33–47.
75. Aisen PS, Saumier D, Briand R, et al. A Phase II study targeting amyloid-beta with 3APS in mild-to-moderate Alzheimer disease. Neurology. 2006;67:1757–1763.
76. Sabbagh M. Drug development for Alzheimer's disease: where are we now and where are we headed? Am J Geriatr Pharmacother. 2009;7:167–185.
77. Gauthier S, Aisen PS, Ferris SH, et al. Effect of tramiprosate in patients with mild-to-moderate Alzheimer's disease: exploratory analyses of the MRI sub-group of the Alphase study. J Nutr Health Aging. 2009;13:550–557.
78. Santa-Maria I, Hernández F, Del Rio J, et al. Tramiprosate, a drug of potential interest for the treatment of Alzheimer's disease, promotes an abnormal aggregation of tau. Mol Neurodegener. 2007;2:17.
79. Adlard PA, Bush AI. Metals and Alzheimer's disease. J Alzheimers Dis. 2006;10:145–163.
80. Adlard PA, Cherny RA, Finkelstein DI, et al. Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. Neuron. 2008;59:43–55.
81. Faux NG, Ritchie CW, Gunn A, et al. PBT2 rapidly improves cognition in Alzheimer's disease: additional phase II analyses. J Alzheimers Dis. 2010;20:509–516.
82. Lannfelt L, Blennow K, Zetterberg H, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2008;7:779–786.
83. Mandel SA, Amit T, Kalfon L, et al. Cell signaling pathways and iron chelation in the neurorestorative activity of green tea polyphenols: special reference to epigallocatechin gallate (EGCG). J Alzheimers Dis. 2008;15:211–222.
84. Fenili D, Brown M, Rappaport R, et al. Properties of scyllo-inositol as a therapeutic treatment of AD-like pathology. J Mol Med. 2007;85:603–611.
85. Dodel RC, Du Y, Depboylu C, et al. Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. J Neurol Neurosurg Psychiatr. 2004;75:1472–1474.
86. Relkin NR, Szabo P, Adamiak B, et al. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging. 2009;30:1728–1736.
87. Dodel R, Neff F, Noelker C, et al. Intravenous immunoglobulins as a treatment for Alzheimer's disease: rationale and current evidence. Drugs. 2010;70:513–528.

88. Gilman S, Koller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology. 2005;64:1553–1562.
89. Orgogozo J-M, Gilman S, Dartigues J-F, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology. 2003;61:46–54.
90. Nicoll JAR, Wilkinson D, Holmes C, et al. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. Nat Med. 2003;9:448–452.
91. Vellas B, Black R, Thal LJ, et al. Long-term follow-up of patients immunized with AN1792: reduced functional decline in antibody responders. Curr Alzheimer Res. 2009;6:144–151.
92. Holmes C, Boche D, Wilkinson D, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet. 2008;372:216–223.
93. Chackerian B. Virus-like particle based vaccines for Alzheimer disease. Hum Vaccin. 2010;6(11):926–930.
94. Why are drug trials in Alzheimer's disease failing? Lancet. 2010;376:658.
95. Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. J Neurochem. 2009;110:1129–1134.
96. Mudher A, Lovestone S. Alzheimer's disease—do tauists and baptists finally shake hands? Trends Neurosci. 2002;25:22–26.
97. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82:239–259.
98. Giannakopoulos P, Herrmann F, Bussière T, et al. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology. 2003;60:1495–1500.
99. Grober E, Dickson D, Sliwinski MJ, et al. Memory and mental status correlates of modified Braak staging. Neurobiol Aging. 1999;20:573–579.
100. Nagy Z, Esiri MM, Jobst KA, et al. Relative roles of plaques and tangles in the dementia of Alzheimer's disease: correlations using three sets of neuropathological criteria. Dementia. 1995;6:21–31.
101. Pei J-J, Sjögren M, Winblad B. Neurofibrillary degeneration in Alzheimer's disease: from molecular mechanisms to identification of drug targets. Curr Opin Psychiatry. 2008;21:555–561.
102. Tariot PN, Aisen PS. Can lithium or valproate untie tangles in Alzheimer's disease? J Clin Psychiatry. 2009;70:919–921.
103. Green KN, Steffan JS, Martinez-Coria H, et al. Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. J Neurosci. 2008;28:11500–11510.
104. Atamna H, Nguyen A, Schultz C, et al. Methylene blue delays cellular senescence and enhances key mitochondrial biochemical pathways. FASEB J. 2008;22:703–712.
105. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med. 2008;14:45–53.
106. Swerdlow RH. The neurodegenerative mitochondriopathies. J Alzheimers Dis. 2009;17:737–751.
107. Doody RS, Gavrilova SI, Sano M, et al. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet. 2008;372:207–215.
108. Becker RE, Greig NH, Giacobini E. Why do so many drugs for Alzheimer's disease fail in development? Time for new methods and new practices? J Alzheimers Dis. 2008;15:303–325.
109. Pimplikar SW. Reassessing the amyloid cascade hypothesis of Alzheimer's disease. Int J Biochem Cell Biol. 2009;41:1261–1268.
110. Pimplikar SW, Nixon RA, Robakis NK, et al. Amyloid-independent mechanisms in Alzheimer's disease pathogenesis. J Neurosci. 2010;30:14946–14954.

Manuscript received, revised, and accepted February 2011.

[1] Internist-Geriatrician, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montreal, Quebec; Associate Professor of Medicine, Department of Medicine, University of Montreal, Hôpital Notre-Dame, Service de Gériatrie, Montreal, Quebec.
[2] Neurologist, Neurology Service, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montreal, Quebec; Clinical Assistant Professor and Director, Neurology Program, Université de Montréal, Hôpital Notre-Dame, Service de Neurologie, Montreal, Quebec.
Address for correspondence: Dr F Massoud, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Service de Gériatrie, 1560 Sherbrooke Est, Montreal, QC H2L 4M1; fadi.massoud.chum@ssss.gouv.qc.ca.

Résumé : Traitement pharmacologique de la maladie d'Alzheimer

Objectif : Examiner les différentes approches pharmacologiques des manifestations cognitives, fonctionnelles et comportementales de la maladie d'Alzheimer (MA).

Méthodes : Nous avons recherché la littérature pertinente la plus récente sur le traitement pharmacologique de la MA et en avons fait une analyse critique.

Résultats : L'approche pharmacologique actuelle du traitement de la MA se fonde sur la prévention vasculaire et la thérapie symptomatique au moyen d'inhibiteurs de la cholinestérase (IdCh) et de la mémantine, un antagoniste de l'acide *N*-méthyl-D-aspartate. Des essais cliniques d'une durée de 6 à 12 mois ont démontré les bénéfices statistiquement significatifs des IdCh et de la mémantine sur les mesures des résultats cognitifs, globaux, fonctionnels, et comportementaux. En général, ces bénéfices sont modestes. Cependant, ils sont proportionnels à la dose administrée et reproductibles dans toutes les études. Surtout, ces bénéfices sont symptomatiques car ils ne changent pas le cours de la maladie. Selon la Troisième conférence canadienne de consensus sur le diagnostic et le traitement de la démence, ces agents sont considérés comme étant des options de traitement standards de la MA. Nous discuterons des questions pratiques liées à la prise en charge pharmacologique actuelle, comme la détermination d'attentes réalistes, la prise en charge des effets secondaires, le changement d'IdCh, et la décision de cesser le traitement. Les résultats des essais cliniques qui étudient les approches ayant le potentiel de modifier la maladie dans la MA seront aussi examinés. Malheureusement, bien que les promesses et l'enthousiasme subsistent, aucun de ces agents n'a démontré de bénéfices constants, et ces agents ne sont pas disponibles dans la pratique clinique.

Conclusion : Des options pharmacologiques sont présentement offertes pour le traitement symptomatique de la MA. Ces traitements procurent des bénéfices légers mais soutenus. Avant que des approches modifiant la maladie ne soient disponibles, l'optimisation de l'utilisation des options de traitement offertes est essentielle.