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ALZHEIMER'S DISEASE: CURRENT AND FUTURE THERAPEUTIC PERSPECTIVES

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Abstract

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1. A better understanding of the pathophysiology of AD has been made possible through population-based epidemiological studies, human genetic and post-mortem studies, leading to a number of testable hypothesis towards delaying progression.
2. A number of disease milestones have been identified as therapeutic targets, such as conversion from MCI to diagnosable dementia.
3. Clinicians caring for patients with AD have currently available a number of symptomatic drugs, and will have in the future the ability to predict the risk for asymptomatic individuals to develop AD, and provide advice towards prevention.

Keywords: Alzheimer's disease, assessment of therapeutic response, prevention, symptomatic therapy

Abbreviations: activities of daily living (ADL), Alzheimer's disease (AD), Alzheimer Disease Assessment Scale cognitive section (ADAS-cog), cholinesterase inhibitors (CI), Clinical Dementia Rating (CDR), Disability Assessment in Dementia (DAD), mild cognitive impairment (MCI), Mini Mental State Examination (MMSE), Non Steroidal AntiInflammatory Drugs (NSAIDS), randomised clinical trials (RCT)

1. Introduction

There has been a renewed interest in AD since the discovery in the late 1970's of a reduction in brain cholinergic activity, leading to the 'cholinergic hypothesis' for symptomatic therapy. This critical review will summarize the RCT necessary to prove the efficacy and safety of a variety of cholinergic drugs, suggest how to use them, and will provide a description of trial designs required to demonstrate disease modification. A number of etiology-based hypothesis are available for testing in large human cohorts, and the results of these studies will greatly modify clinical practice in a not to distant future.

2. The Cholinergic Hypothesis and Related Drugs

The symptomatic treatment of AD is currently based on the cholinergic hypothesis, which states that many of the cognitive, functional and behavioral symptoms derive from a reduction in brain acetylcholine activity secondary to the loss of cholinergic neurons in the Nucleus Basalis of Maynert and other nuclei projecting to the hippocampus and mesial temporal region (Cummings et al, 1998a; Geula, 1998). The class of cholinergic drugs that has been most effective so far for the symptomatic treatment of AD are the CI (Table 1).

Table 1

Cholinergic Drugs Based on Their Modes of Action

* Precursor loading	ex. choline, lecithin
* Stimulation of transmitter release	ex. linopirdine
* Slowing of transmitter degradation (cholinesterase inhibitors)	ex. tacrine, donepezil, rivastigmine, metrifonate, galantamine
* Selective muscarinic agonists	ex. xanomeline, milameline, SB 202026, talsaclidine

The history of cholinergic pharmacotherapy for AD was recently reviewed (Giacobini, 2000) and is characterized by the failure of acetylcholine precursors, releasing agents and selective muscarinic agonists, but positive results with CI. These drugs have been studied individually and the value of combination therapy, looking for pharmacological synergism as in dopamine enhancement for Parkinson's disease, remains largely untested. Most of the data from the published literature on CI are derived from RCT of three to six months duration, in mild to moderate stages of 'probable AD' (McKahn et al, 1984), operationally defined as 10 to 26 on the MMSE (Folstein et al 1975), corresponding to the stages 3 to 5 on the Global Deterioration Scale (Sclan and Reisberg, 1992). More recent RCT have lasted

12 months under double-blind placebo-controlled conditions and have explored the response to treatment in moderate to severe stages.

Tacrine was the first tested and clinically used CI in many countries. Despite the practical issues of short half-life requiring four times a day schedule, gastro-intestinal side-effects requiring a slow titration towards the therapeutic doses of 120 to 160mg per day and the reversible elevation in liver transaminases levels, many important facts were learned from this drug, particularly for long term use. Thus patients treated with tacrine at therapeutic doses for extended periods (two years or more) needed nursing home care later than patients tolerating only a lower dose (Knopman et al, 1996). A retrospective analysis of responder profiles suggested that apolipoprotein E4 (apoE4) carriers have a lesser chance to improve on tacrine (Poirier et al, 1995). The proposed explanation was that apoE mutation is associated with a marked reduction in cholinergic activity and thus lessens response to a CI. Another analysis in a large number of patients treated with tacrine suggested that this pharmacogenetic effect is seen only in women (Farlow et al, 1998a). A post-hoc analysis of efficacy data based on the ADAS-cog (Rosen et al, 1984) has shown that a delay of six weeks is required for the maximal cognitive improvement at the highest dose tolerated (Sands et al, 1999). A meta-analysis of twelve RCT confirmed a measurable benefit detected by the MMSE and the clinical impression of change, with no influence of age or disease severity on therapeutic response (Qizilbash et al, 1998). An open label study (Kaufer et al, 1996) and a post-hoc analysis (Raskind et al, 1997) suggest a positive effect on behavior.

Donepezil was the second available CI and its use is facilitated by a long half-life allowing daily dosing, good gastro-intestinal tolerance using a two step titration spaced 4 to 8 weeks apart, and absence of hepatotoxicity. RCT of six months duration (Rogers et al, 1998; Burns et al, 1999) have demonstrated that both 5 and 10mg doses daily are effective in improving cognitive and global functioning. The latter study also showed a statistically significant reduction in the rate of loss for instrumental ADL at the 10mg dose. All beneficial effects were reversible after a six week wash-out. The long term follow-up of patients treated with donepezil suggest a sustained therapeutic benefit with a decline in ADAS-cog and CDR (Morris, 1993) parallel to groups of patients with no specific pharmacotherapy (Rogers and Friedhoff, 1998). Twelve months-long RCT have demonstrated a sustained improvement for the MMSE above baseline for 9 months (Winblad et al, 1999a), and a slowing down of functional decline (Winblad et al, 1999a, Mohs et al, 1999). A 6-month RCT at more severe stages of AD, operationally defined as MMSE 5 to 17, demonstrated an improvement in all outcomes, including behavior and ADL (Feldman et al, 2000). There is no evidence that certain types of patients are less likely to benefit from donepezil.

Rivastigmine was the third widely available CI. RCT using the Progressive Deterioration Scale (DeJong et al, 1989) were able to establish stabilisation of ADL at 6 to 12mg/day with BID dosing (Corey-Bloom et al, 1998; Rösler et al, 1999). Furthermore there is a clear dose-effect relationship for

cognition, global impression of change and ADL (Schneider et al, 1998). An open-label study in a nursing home setting demonstrated a positive effect on behavior (Anand et al, 2000). The use of rivastigmine requires good collaboration between carers and clinicians, in order to find best tolerated and effective dose for each individual patient. The recommended monthly titration may facilitate the detection of clinical response by carers and clinicians. As for donepezil, there is no evidence that certain types of patients are less likely to benefit from this drug. The BID dosing requires more supervision for compliance, particularly in patients living alone.

Metrifonate is the CI with the longest duration of action through its active metabolite dichlorvos (Schmidt et Heining, 1998). It can thus be administered once daily, with a good gastro-intestinal tolerance. Unfortunately a reversible but clinically significant proximal weakness of limbs has been noted in some individuals at high doses, leading to its withdrawal for clinical use, despite positive results from RCT for cognition (Cyrus et al, 1998), global impression (Morris et al, 1998), ADL (Gélinas et al, 1998) and behavior (Cummings et al, 1998b). The efficacy of metrifonate did not depend on apoE4 genotype, at least in the short term (Farlow et al, 1998b).

Galantamine is now available as the CI with intrinsic nicotinic activity (Pontecorvo 1998). RCT have shown efficacy on global impression, cognition, ADL and behavior (Raskind et al 2000, Tariot et al 2000). Furthermore the follow-up of patients treated for 12 months at 24mg/day without interruption demonstrated no decline from baseline for cognition using the ADAS-cog, and for ADL using the DAD (Gélinas et al, 1999). The therapeutic doses are 16 and 24mg/day with BID dosing. It is as yet unclear if galantamine's dual acetylcholinesterase inhibition and nicotinic actions will translate into higher or more sustained symptomatic benefit than other CI in clinical practice.

There are certain common characteristics among CI. In terms of efficacy:

- The measurable short term (6 months) improvement in cognition and global functioning is comparable between CI.
- The measurable benefit on ADL has been demonstrated for all CI and best described as a slowing of decline rather than an actual improvement of specific ADL.
- An improvement of some neuropsychiatric symptoms has been shown with all CI; the pattern is primarily an improvement in apathy and most likely a delay in emergence of symptoms. There are variable patterns of impairment for anxiety, depression and hallucinations, which are not of the magnitude seen with atypical neuroleptics.
- Age, gender and apoE genotype do not seem to be determinant factors in response to therapy, nor is the disease stage within the mild to moderately severe range (although the difference between placebo and treated patients is larger in the moderate to severe stages of AD because of faster decline in the placebo-treated group).

- The clinical relevance of pharmacological characteristics such as selectivity for acetylcholinesterase versus butyrylcholinesterase and reversibility versus pseudo-irreversibility of enzyme inhibition has not been established.

Table 2

Therapeutic Doses of Cholinesterase Inhibitors in Clinical Use

Tacrine (Cognex)	80 to 120 mg/day	QID
Donepezil (Aricept)	5 to 10 mg/day	QD
Rivastigmine (Exelon)	6 to 12 mg/day	BID
Galantamine (Reminyl)	16 to 24 mg/day	BID

In terms of safety:

- Gastro-intestinal side-effects (nausea, vomiting, diarrhea, anorexia) are dose-related and transient, avoidable to a great extent by a slower titration up to therapeutic doses (Table 2). These side-effects may be a limiting factor for the use of CI in patients of small body weight.
- Cardiovascular side-effects (symptomatic bradycardia, syncope) are not frequent, if one is cautious in persons with sick sinus syndrome or other supraventricular conduction defects. Syncope can occur even in the absence of pre-existing cardiac history or electrocardiographic abnormalities.
- Muscle cramps in the lower limbs can occur from cholinergic stimulation at the neuromuscular junction. These cramps are dose-related and usually transient.
- Less common central side-effects are insomnia and exaggeration of depressive symptoms, which can be avoided by ingestion in the morning with donepezil, and treatment of depression prior to initiating CI therapy.
- The presence or absence of hepatic P450 metabolism of CI seem to have little importance with other drugs commonly used in the management of AD (such as antidepressants and antiepileptics), although pharmaco-vigilance is important to document the possibility of drug interactions at the liver and neuromuscular junction.

The following responses to CI can be observed in clinical practice:

- obvious with return to hobbies and social activities, with or without improvement on MMSE scores; this 'awakening' may last six to twelve months, followed by a slower decline than anticipated for age of onset and severity of dementia at onset on therapy
- modest with a transient reduction in apathy and increase participation in conversation
- absent with clinical decline despite therapeutic doses, or failure to tolerate minimally effective doses.

If there is no clinically detectable improvement despite the maximal dose recommended or tolerated of a given CI, or if the patient has progressed to a severe stage of AD, the decision to withdraw treatment must be taken after discussion with the patient and his caregivers. In case of rapid deterioration off the drug, it is possible to restart the same or another CI. It is also possible for interested patients and caregivers to participate in a number of RCT with novel symptomatic or disease modifying drugs.

3. Trial Designs Relevant to Disease Modification

The first steps in attempts at modification of AD progression have been to understand its natural history, and develop outcomes appropriate to the stage of disease that is targeted for therapy. Most recently, brain imaging has been added as a valuable surrogate outcome.

The study of the natural history of AD has been facilitated by diagnostic research criteria (American Psychiatric Association, 1994; McKhann et al, 1984). A number of longitudinal studies spanning from one to seven years have looked at annual changes in cognition and functional autonomy (Katzman et al, 1988; Mortimer et al, 1992; Lucca et al, 1993; Morris et al, 1993) or at cumulative rates of nursing home placement and death (Berg et al, 1988; Bracco et al, 1994; Heyman et al, 1996; Heyman et al, 1997; Stern et al, 1997). A number of clinical milestones have been described in AD (Table 3), some potentially useful as endpoint for RCT (Galasko et al, 1995).

Table 3

Clinical Milestones in Alzheimer's Disease

-
- conversion from MCI to dementia
 - loss of selected instrumental ADL
 - emergence of neuropsychiatric symptoms
 - nursing home placement
 - loss of self-care ADL
 - death
-

In clinical practice, patients with typical AD followed over the expected survival time of eight years (Barclay et al, 1985) will often show anxiety and depression early in their evolution, and neuropsychiatric manifestations will emerge at the intermediate stage, to abate in the late stage where motor signs become prominent (Sclan et al, 1996). Cognitive and functional decline tend to be linear over time, whereas caregiver burden peaks and decreases in parallel to the neuropsychiatric symptoms (Zarit et al, 1986).

Table 4

Trial Designs For Disease Modification Studies

-
- parallel groups
 - survival to a clinical milestone
 - staggered start and withdrawal
 - single or double-blind active drug withdrawal
 - open labeled extended follow-up
-

Study designs to prove delay in progression have been reviewed critically (Gauthier et al, 1996; The Disease Progression Sub-Group, 1997; Whitehouse et al, 1998; Gauthier, 1998)(Table 4). The one year parallel groups design has been used more widely so far, with negative results using prednisone (Aisen et al, 2000), estrogens (Henderson et al, 2000) and celecoxib (Sainati et al, 2000) versus placebo in mild to moderate AD, but there is considerable interest in the survival to a clinical milestone design, as demonstrated by the very high clinical impact of the Sano et al study comparing tocopherol to selegiline and placebo in moderate to severe AD (1997). The staggered-start/withdrawal design had originally been suggested by Leber (1997) but has proven to be difficult to apply, because of the high attrition of patients over time, and lack of regulatory acceptance outside the USA. A single-blind drug washout component to RCT has been useful to demonstrate the reversibility of donepezil action over six weeks (Doody and Pratt, 1999), and it is postulated that agents slowing disease progression will show a lack of reversibility during such washout periods. Data from open label extensions of RCT with CI such as donepezil (Rogers and Friedhoff, 1998) or galantamine (Raskind et al, 2000) suggest a sustained 'shift to the right' or sustained therapeutic benefit over many months, but lack a control group.

The decision to study a disease modification effect on patients at a given stage (from mild to severe AD) will influence the choice of primary and secondary outcome variables, the trial design itself and its duration. For instance in the mild stage of AD, there is relatively little cognitive loss over one year, some loss of instrumental ADL but no loss in self-care ADL, and few neuropsychiatric symptoms will emerge. In moderate stage there will be a more rapid decline in cognition, in instrumental ADL and self-care ADL, and neuropsychiatric symptoms will emerge. In severe stages cognitive instruments such as Severe Impairment Battery (Panisset et al, 1994) will be more sensitive to change than the ADAS-cog and the MMSE, the decline on the DAD is quite fast even over period as short as 6 months, and behavior can be measured with scales such as the Neuropsychiatric Inventory. In fact, considering the high societal and human costs of AD in its severe stages (Winblad et al, 1999b) and recent positive results for symptomatic improvement at those stages using the CI donepezil (Feldman et al, 2000) or the NMDA antagonist memantine (Winblad and Porotis, 1999), RCT should be considered as not only feasible but desirable in

later stages of AD, although with very high sensitivity to ethical and legal considerations, since patients have lost competence to give fully informed consent (Young and Gauthier, 2000).

Considering the symptomatic benefit of CI in many patients, the issue of whether placebo-controlled RCT are still possible in mild to moderate stages of AD has arisen, with arguments for (Karlavish and Whitehouse, 1998; Farlow, 1998) and against (Knopman et al, 1998). At this point in time there are no ethical restrictions against placebo studies in AD (Post, 1998), but there may well be practical ones. The enrollment of 'non-responders' to CI may become necessary in RCT aiming at delaying progression. Alternatively all patients will be treated as 'usual care' that would include a CI and possibly vitamin E.

A novel design has been proposed by Petersen et al (1999) and consist of delaying the conversion from MCI (Table 5) to diagnosable AD over 3 years, with an expected rate of conversion of 15% per year in the placebo-treated group. There are currently a number of RCT looking at the potential preventive effects of COX-2 selective inhibitors, alpha-tocopherol, and CI such as donepezil, rivastigmine and galantamine, versus placebo (Sherwin, 2000). The validity of these studies may be enhanced by the addition of brain volumetric measurements on MRI scans (Rombouts et al, 2000), which would show a slower rate of atrophy for the whole brain or selected regions such as the mesial temporal lobe, in patients who are on active treatment versus those on placebo.

Table 5

Operational Definition of MCI

-
- subjective memory complaints
 - normal ADL
 - normal general cognitive performance
 - abnormal memory for age and education level
 - not demented clinically
-

4. Pathophysiology of AD and Testable Hypothesis

Epidemiological studies have established the high prevalence and incidence figures of AD in different countries, with projected increases as populations are aging. A number of risk and protective factors have been found, some leading to testable hypothesis towards delaying the onset of symptoms of AD in asymptomatic individuals at risk because of genetic background or simply from advancing age (Table 6).

Post-mortem and human genetic studies have also added a number of testable hypothesis (Table7). Animal models such as transgenic mice may offer some validation of treatments prior to human studies (Rosenberg, 2000). For instance transgenic mice overexpressing mutant human amyloid precursor

protein immunized with abeta42 show improvement of neuropathologic features (Schenk et al, 1999). These models are important requirements for the decision to commit large human and financial resources to test one of the etiology-driven hypothesis. Other requirements are supporting epidemiological or observational data, and adequate information on dosing and safety (Thal et al, 1997).

Table 6

Examples of Epidemiology Derived Factors Leading to Testable Hypothesis to Delay Onset of AD

Factor	Risk of AD	Potential Intervention
ApoE4	increased	induction of ApoE secretion (Poirier and Panisset, 2000)
Systolic hypertension	increased	calcium-channel blockers (Forette et al, 1998)
NSAIDS	decreased	NSAIDS or COX-2 selective drugs (Aisen, 2000)
Estrogens	decreased	conjugated estrogens replacement (Marder and Sano, 2000)

Table 7

Examples of Basic Science Data Leading to Testable Hypothesis to Delay Onset of AD

Factor	Potential Intervention
Excessive beta-amyloid deposition	beta or gamma secretase inhibition, amyloid 'vaccination' (Wolozin and Behl, 2000a)
Apoptosis	antioxidants (Wolozin and Behl, 2000b)
Excitotoxic amino acids	NMDA antagonists (Emilien et al, 2000)
Decrease levels of neurotrophic	neurotrophic factors enhancement factors (Wieland et al, 2000)

5. The Future of AD Therapy

There is a genuine interest among primary care practitioners, neurologists, geriatricians and psychogeriatricians for an accurate diagnosis of AD, which is moving towards very early symptomatic stages. The global management of this condition includes the treatment of concomitant disorders such as depression, disease-specific drugs such as CI, and atypical neuroleptics when necessary (Gauthier, 2000). Since comprehensive support and counselling programs have been shown to increase the time spouse-caregivers are able to care for AD patients at home (Mittelman et al, 1996), a judicious combination of support programs from community and lay associations to disease-specific pharmacotherapy is currently the best therapeutic approach in the mild to moderately severe stages of dementia.

In the near future (3 to 5 years), RCT with MCI populations will have hopefully confirmed one or the other etiology-driven hypothesis, which will bring to the attention of clinicians a large number of persons with memory complaints. New diagnostic strategies will be needed to cope with these mildly symptomatic individuals. Careful examination of the natural history of such complaints through population-based studies are suggesting a number of leads as to which simple clinical assessments are most sensitive to predict who will progress towards AD (Table 8). Those individuals estimated at risk of conversion from mild cognitive complaints to AD would be offered 'preventive' therapy. The availability of biological markers may increase the validity of the clinical prediction. Candidate markers include ApoE genotype and cerebro-spinal fluid levels of amyloid fragments and tau (Kanai et al, 1998).

Table 8

Examples of Predictors for Progression From Mild Cognitive Complaints to AD

- MMSE, age, informant identification of memory difficulties (Hogan and Ebly, 2000)
 - Impairment in instrumental ADL such as use of phone, transportation, medication, money (Barberger-Gateau et al, 1999)
 - Sum of CDR categories (Daly et al, 2000)
 -
-

At a population level, delaying onset of AD by 5 to 10 years would greatly reduce its prevalence within one generation (Khachaturian, 1992). RCT of at least 5 years duration will be required to prove that an intervention will reduce the incidence of MCI or of AD in an aging population. If positive, these approaches will be promoted at the public health level. Already, it is appropriate to state that control of systolic hypertension will reduce the incidence of strokes, large and small, and thus reduce the incidence of dementia (Snowdon et al, 1997). It is hoped that in 5 to 10 years, primary care clinicians and specialists will be using an evidence-based approach to AD prevention, offering recommendations commensurate to the individual risk (Table 9), as is currently done for the prevention of atherosclerotic cardio-vascular diseases.

6. Conclusions

Much has been learned in the past 25 years on the natural history of AD and its global management, which includes symptomatic drugs targeting a specific neurotransmitter deficiency. We now have the opportunity to test a number of etiology-driven hypothesis that may modify disease progression, using appropriate RCT designs and outcomes. Success in this enterprise will change our approach to AD from palliative care to prevention.

Table 9

Possible Preventive Approaches in AD

Risk	Recommendations
Low average	Healthy diet; physical and mental exercises
Positive family history	Antioxidants; estrogens after menopause
MCI	NSAIDS
Carrier of presenilin or amyloid precursor protein mutation	Suppressors of amyloid aggregation

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