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Alzheimer's Disease: Overview

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Introduction

The impact of dementia on the economic, social and health care needs of this country cannot be overemphasized and will continue to be an important issue as the demographics of our society continue to shift to reflect an aging population. Alzheimer's disease (AD) currently has been estimated to afflict 4 million Americans, a figure which is projected to reach 9 million by 2030. The prevalence of dementia is known to increase dramatically with age, doubling every 5 years after the age of 65 (4% at age 75, 16% at age 85, 32% at age 90) and affects all races.

AD places an enormous financial burden on the US healthcare system with annual treatment costs that ranges as high as $80 - $100 billion/year. Presently AD is the 3rd most expensive disease to treat in the US followed by cancer and heart disease. It is estimated that AD patients and their families will spend more than $200,000 in care over the remainder of the patient's lifetime with direct costs being estimated at $40,000 and indirect costs $174,000. Delaying the onset of symptoms by 5 years would reduce prevalence by 50% in one generation, and symptomatic treatment and delay of NH placement would reduce costs very significantly.

Many of the same barriers that limit access by ethnic population to medical care and long-term care services also affect their participation in basic, epidemiologic and clinical AD research. It has proven difficult for researchers to recruit ethnic population subjects in major clinical trials of pscyhopharmacological treatments for AD and related dementias. Restricting subject enrollment in several of the multicentered, randomized clinical trials may limit generalizability. Recently, Schneider et a1, published a paper that addressed this issue and found that from a sample of 3,470 subjects with possible or probable AD, only 4.4% or 7.9% respectively, would have been provisionally eligible for two typical clinical trials. In general these patients were younger, wealthier, better educated and more likely to be white than ineligible subjects (Schneider et al 1997). There is a strong need to encourage the recruitment of ethnic minorities in clinical research in AD, particularly in these clinical drug trials.

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Importance of Proper Diagnosis

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Our ability to diagnose AD clinically has improved greatly over the past several years with the use of specific diagnostic criteria. The criteria put forth jointly by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKahnn et al, 1984) is the most commonly used for research purposes and the accuracy of the diagnosis of probable AD using this criteria has been shown to exceed 85% in most autopsy series.

Diagnosis Of Dementia

Dementia is a syndrome characterized by a persistent decline in multiple areas of cognition. The essential features of dementia as defined in DSM-IV are:

> Impairment in short and long term memory plus additional decline in at least one other domain: aphasia (disturbance of language), apraxia (the inability to do on command an act that can be performed spontaneously), agnosia (disturbance of recognition and awareness), or a disturbance of executive functioning (ie. abstraction, judgment). The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning.

Alzheimer's disease is just one of many causes of dementia, albeit the most common accounting for 50%-60% of all cases of dementia. The differential diagnosis of dementia is extensive (see Table 1).

Table 1

Major Causes of Dementia

Cortical

- Alzheimer's Disease
- Frontotemporal Dementia (FTD)

Subcortical

- Vascular dementia (VaD)
- Extrapyramidal diseases
    - ie. Parkinson's disease
    - Progressive supranuclear palsy
    - Dementia with Lewy bodies (DLB)
- Depression
- Normal pressure hydrocephalus (NPH)
- HIV dementia
- Demyclinating disease

Mixed (Cortical/Subcortical)

- Vascular dementia
- Infection (ie, syphillis, slow virus)
- Miscellaneous:
    - post-anoxic
    - neoplastic
    - post-traumatic
    - metabolic disturbances (ie.thyroid, B_{12})

Research Criteria for a Diagnosis of Alzheimer's Disease

Definite AD

- Pathologic evidence of AD (autopsy or biopsy)
- A clinical diagnosis of probable AD

Probable AD

- Onset between ages 40-90
- Dementia established by clinical examination and documented by mental status questionnaire
- Dementia confirmed by neuropsychological testing
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Absence of systemic disorders or other brain diseases capable of producing a dementia syndrome

Possible AD

- Presence of a systemic disorder or other brain disease capable of producing dementia but not thought to be the cause of the dementia
- There is a gradually progressive decline in a single intellectual function in the absence of any other identifiable cause (i.e. memory loss or aphasia)

Unlikely AD

- Sudden onset
- Focal neurological signs
- Seizures or gait disturbance early in the course of the illness

Treatment Stategies

Symptomatic Treatments:

The Cholinergic Hypothesis

Researchers have found that concentrations of acetylcholine (ACh) decline to some extent in normal aging, but decrease by nearly 90% in patients with AD. Further scientific

evidence has implicated the decline in ACh concentrations with the cognitive impairment. Restoring cholinergic function in the brain may significantly reduce the severity of dementia. The current focus of AD therapy is the use of agents that inhibit the enzyme, acetylcholinesterase (AChE). Cholinesterase inhibitors act by increasing the availability of intrinsic ACh in the brain which is important in learning a memory processes. As the disease progresses and less ACh is made and cholinesterase inhibitors will become less effective. Cholinesterase inhibitors do not appear to slow the progression of AD, but can improve the symptoms in some patients. Loss of ACh in AD is only part of the problem and improving ACh function can reverse only that part of the illness due to the cholinergic defect. Other neurotransmitter are also diminish in AD and may be an additional target for specific symptomatic therapy in the future.

Tacrine (Cognex) was the first cholinesterase inhibitor to be approved and registered in the USA for AD. Mild improvement in cognitive function was seen in 25-40% of patients studied in clinical trials. Tacrine however has potential toxic side effects to the liver and requires biweekly blood tests to monitor liver enzymes and requires four times a day dosing.

Doncpezil (Aricept) is the second cholinesterase inhibitor approved for the treatment of AD by the US Food and Drug Administration (FDA) in 1997. Its chemical structure is different from Tacrine and thus it does not have the liver toxicity. In clinical trials, Aricept at doses of 5 and 10 mg were shown to be effective in improving cognitive and overall function in patients with mild-moderate AD. The drug was generally well tolerated. The main side effects involved the GI system (nausea, decreased appetite and diarrhea), but generalized fatigue and muscle cramps have also been reported. These effects tended to be mild and often resolved without discontinuation of the drug. This class of drugs can also slow the heart rate and should not be used in people with a condition known as "sick sinus syndrome" or who have very slow heart rates.

Several other cholinesterase inhibitors will soon become available, Rivastigmine (Exelon) was recently approved by the FDA and should be released on to the market soon. Another drug called, metrifonate (Promem) also applied to the FDA, but recently was rejected due to side effects. A third drug, galantamine is another cholinesterase inhibitor with additional action at the nicotinic receptor. It has been approved in Europe and an application has been filed with the FDA, but still awaits approval.

A number of other new drugs are also being actively investigated (see Table 4). As AD progresses and less ACh is synthesized, cholinesterase inhibitors will become less effective. There is however, recent evidence suggesting a potential affect of cholinesterase inhibitors on amyloid processing and deposition and thus may have a disease modifying effect.

Disease-Modifying Strategies:

Amyloidogenesis and processing

A key feature in the brains of patients with AD is the presence of a large number of amyloid-containing plaques and neurofibrillary tangles in the brain. Amyloid plaques are spherical, amorphous extracellular deposits of a protein known as β-amyloid with a

surrounding cluster of abnormal nerve processes. The abnormal amyloid is derived from a larger parent protein, known as amyloid precursor protein (APP).

The normal function of APP is not fully understood, but it is known that normal APP processing produces a soluble protein which appears to have important functions in normal cell function and survival. Abnormal APP processing leads to amyloid plaque formation which appears to be toxic to brain cells. Recently two key enzymes involved in abnormal processing of APP, called beta secretase and gamma secretase, have been discovered and are major targets for the development of new drugs. In addition, other therapeutic approaches to interfere with the accumulation of and the deposition of amyloid are under active investigation. Similarly, drugs such as protease inhibitors that may interfere with APP processing and important cell signalling pathways are also under investigation as potential targets for new treatment. In a recent publication in Nature, investigators discovered that they could reduce or plaque formation in mice that had been genetically altered to form plaques in the brain by giving them a vaccine against the material found in the plaque. This has led to the rapid development of this concept and clinical trials in humans are beginning.

Apo E

Apolipoprotein E (ApoE) is normal constituent of blood and is essential for the transporting lipids both between cells in different organs as well as among the cells within an organ. Everyone has some combination of E2, E3 or E4 type. It has been clearly shown that having the E4 type is associated with an increased risk for developing AD. It doesn't cause AD, but is merely associated with an increased risk and having an E4 type does not mean a patient will ever get AD. In addition to being a risk factor however, in 1991 it was found that ApoE could be found associated with the amyloid plaques in the brain and that the ApoE4 type appeared to bind much more tightly. Thus reducing the effects of ApoE4 may also be a potential target for therapy.

Antioxidants:

It has recently been shown in a large study of The Alzheimer's Disease Cooperative Study Consortium, that alpha-tocophcrol (vitamin E) given at doses of 2000 IU per day, or selegiline at 5mg twice a day was able to slow the progression of functional decline or time to institutionalization in patients with moderately severe AD when compared to placebo. Vitamin E is an antioxidant that may reduce nerve cell damage related to injury produced

NEW AGENTS for AD UNDER INVESTIGATIONS
Cholinesterase Inhibitors
Exclon (Novartis)
Metrifonatc (Bayer Corporation)
Galantamine (Jannsen)
Physostigmine SR (Forest Labs)
Linopiridine (Merck & Company)
Tacrine CR (Alza Corporation and Parke Davis)
Cholincrgic Agonists
Xanomeline (Eli Lilly)

Milameline (Hoechst Marion Roussel)
Memric (SmithKline Beecham)
Other Classes of Agents
Estrogens
Nonsteroidal Anti-inflammatory Drugs
NMDA channel blockers
Calcium channel blockers
Antioxidants
Growth Factors
Propentofylline
Dchydrocpiandrosterone
Gingko Biloba

by free radicals. (β-amyloid generates free radicals in cell culture and the toxicity of β-amyloid can be limited by antioxidants. There is a large number of other antioxidant medications currently under investigation. Potential therapeutic antioxidants include vitamin E, and C, co-enzyme Q-10, idebenone, selegiline and lazaroids. New generations of antioxidants that penetrate the CNS and concentrate within membranes may be particularly promising for treatment of AD.

Idebenone along with its parent compound co-enzyme Q-10, is an antioxidant shown to inhibit lipid peroxidation in cell cultures. Idebenone also stimulates synthesis of nerve growth factor and has been shown to protect against certain kinds of toxic neuronal damage. Clinical trials in dementia patients suggest mild benefit, but it remains experimental at this time.

Many different lines of evidence point to a potential instrument role of inflammatory mechanisms in AD. Epidemiological studies show an inverse relationship between AD and RA with one study demonstrating a prevalence rate of AD of 2% in patients with RA compared to approximately 13% of controls (Jenkinson 1989), A. co-twin study with 50 elderly twin pairs with onset of AD separated by 3 or more years also found the onsett of AD was inversely associated with prior use of corticosteroids or ACTH and to a lesser extent for history of arthritis and for prior daily use of NSAIDS.

A small clinical trial with 44 patients with early AD taking 100-150 mg/d of indomethacin maintained constant MMSE scores over the 6 month period of the trial while those taking placebo showed an expected 10-12% decline (Rogers 1993), suggesting that the use of NSAIDS may slow the progression of the disease, however 20% of patients on indocin developed sufficient drug-related AE's to withdraw from the trial.

NSAIDS are not yet to be considered as a preventative and/or therapeutic treatment for AD of gastrointestinal-sparing anti-inflammatory drugs (Elliot 1995; Vance 1995). Activation of inflammatory pathways may contribute to the neurodegencration in AD. Drugs such as indomethacin and ibuprofen have received a great deal of attention recently because it has been found that studies involving patient populations taking NSAIDs were less likely to develop AD prospective clinical trials are underway to further clarify the potential role of these agents in preventing or delaying disease onset or modifying the disease in some way.

Potential Role of Growth Factors

In the absence of neurotrophic factors for development and survival, programmed cell death (apoptosis) occurs. Cholinergic neurons of the basal forebrain express NGF receptors and NGF treatment promotes survival of these neurons in experimental animal models. Cognitive benefits of NGF treatment have been demonstrated in lesioned and aged rats. However, NGF administered systematically does not cross the blood-brain barrier. IVC administration requires surgical implantation of a device to administer the compound, which is not without risks. Gene therapy to administer genetically modified cells in the brain to chronically secrete NGF is under investigation.

AIT-082 an oral agent which crosses the BBB and stimulates the production of NGF and augments the effect of NGF on cells in culture. (Glasky 1994). (Middlemiss 1995). Sabeluzole: potentiates the action of NGF, accelerate axonal transport, promote ncurite outgrowth and prevent tangle formation. It is a new benzothiazole derivative. Clinical benefits on memory in patients with AAMI, well tolerated. 39 patients with Prob AD MMSE 23-12, double-blind placebo vs. two doses of sabeluzole bid for 48 wks. Did not decline on ADAS compared to controls no change in measurements.

Estrogen replacement:

Estrogen replacement therapy (ERT) in post-menopausal women may also have a protective effect against the development of AD. Several studies have shown a relationship between ERT and a reduced risk of AD by almost 50%. A recent study of estrogen replacement treatment in postmenopausal women who had had a hysterectomy in the past, showed no improvement or change in disease progression over one year. However, this study was done in a very select group of women who also were women already diagnosed with moderately severe AD and does not answer the question of whether ERT may help in disease prevention or if it is useful earlier in the course. A current prospective study with the Women's Health Initiative is underway to address the question of possible prevention.

Treatment of Neuropsychiatric Symptoms

Behavior problems arc common in AD and affect nearly all patients. These behavioral manifestations have effects on the course of the illness and represent a principle source of morbidity. Treatment of the neuropsychiatric manifestations of this disease involves both the use of non-pharmacological approaches as well as pharmacotherapy in many cases. The choice of agent selected depends on the specific behavioral symptom encountered and the medical history and medication profile of the individual patient, Antidepressant drugs with fewer anticholinergic properties may be useful, antipsychotic agents, anticonvulsants and anxiolytics also have a role in behavioral management: There is some evidence to suggest that the cholinersterase inhibitors may be beneficial for the behavioral symptoms as well as the cognitive changes.

Importance of Caring for the Caregiver:

Approximately 80% of the care provided to patients with AD in the community are by family members who spend on average 60 hours per week on caregiving duties. A number

of studies of caregiver burden and distress have been conducted and reports suggest that 30 - 50% of AD caregivers experience clinically significant depression. There are a number of services in the community that can be helpful to your patient's caregiver such as adult day care centers, support groups, community seminars, The local Alzheimer's Association chapter can be of enormous help. In addition, Pfizer pharmaceutical company has sponsored a support line to answer questions and also provides educational materials and assistance to contacting local support.

ALZHEIMER'S ASSOCIATION

Local Chapter

National Institute on Aging
National Institute of Health
ADEAR Center PO Box 8250
Silver Spring, MD 20907-8250
Adear@alzheimers.org
www.alzheimers.org

TriAD Assistance Program
1-888-TriADHELP
(sponsored by Pfizer Pharmaceutical)

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