

Alzheimer Insights

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Butyrylcholinesterase: a new therapeutic target in AD treatment?

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Nigel Greig has held the position of Chief of the Drug Design and Development Section at the NIA since 1995. Dr Greig's research has evolved into his present interest, the design and development of drugs and diagnostics for the treatment of AD and other neurodegenerative diseases, and of type 2 diabetes.

Update on the cholinergic hypothesis

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease that is characterized symptomatically by progressive deteriorations of activities of daily living (ADL), behavioral disturbances and cognitive loss. The neurodegenerative features of AD include pathological changes in the brain, such as the formation of β -amyloid plaques and neurofibrillary tangles. Furthermore, AD is associated with substantial reductions in the activity of choline acetyltransferase (ChAT) and reduced levels of acetylcholine (ACh) in the brain as cholinergic neurons are lost and cholinergic neurotransmission declines. Cholinesterase (ChE) inhibitors retard the inactivation of ACh after synaptic release and represent the only approved treatment resulting in significant clinical benefit.

Two types of ChE enzymes are found in the CNS – acetylcholinesterase (AChE) and butyrylcholinesterase

(BuChE). Extraordinarily efficient, they are both able to cleave >10,000 molecules of ACh per second [1], at a rate that is limited more by the diffusion of ACh to the enzyme, rather than catalytic capacity. Until recently, the relative contribution of BuChE in the regulation of ACh levels had been largely ignored. However, there is growing evidence that AChE and BuChE both play important roles in the regulation of ACh levels and may also have an important role in the development and progression of AD.

Looking at BuChE

AChE and BuChE share 65% amino acid sequence homology despite being products of different genes on human chromosomes 7 (specifically 7q22) and 3 (specifically 3q26), respectively [2]. Both BuChE and AChE exist as separate molecular forms: a G4 form comprising

Table 1. A role for butyrylcholinesterase (BuChE) in AD

- BuChE may be increased 40–90% in the AD brain [3,4]
- Increases in BuChE activity occur mainly in the temporal cortex and hippocampus, those areas of the brain most affected by AD [3]
- In the human hippocampus and amygdala 10% of ChE-positive neurones contain BuChE [5]
- High levels of BuChE are found in neuronal plaques in AD [4]
- Both AChE and BuChE amplify the activity of the toxic β -amyloid peptide in tissue culture [6]
- BuChE may be involved in the transformation of diffuse β -amyloid into compact, neuritic plaques [7]
- There is evidence of a link between the K variant of BuChE, ApoE4 and the incidence of some forms of AD [8]
- Selective BuChE inhibitors can increase ACh levels in rat cortex without affects on AChE [9,10]
- Selective BuChE inhibitors can improve learning in elderly rats [11]

of four globular protein subunits, and a G1 form with a single globular protein moiety. The G4 form of AChE is the most abundant form in the human brain and is the primary agent in the breakdown of ACh. In contrast, the G1 form is present in smaller amounts with a quantitatively smaller role in ACh degradation. In the AD brain, however, G4 activity may be reduced by up to almost two-thirds, while G1 activity remains relatively unchanged, thereby increasing the relative importance of the G1 form. For BuChE, there is an approximate 30–60% increase in primarily the G1 form of the enzyme in AD [12].

X-ray crystallography reveals that both enzymes have an active, primarily hydrophobic gorge that intrudes 20 Å deep into the surface of the enzyme into which ACh enters [13]. Once in the gorge, ACh binds at two locations, a catalytic site close to the base of the gorge and a choline binding site, midway up. Cleavage of ACh then occurs, liberating choline and acetic acid, thus terminating its neurotransmitter action [14]. Whereas AChE is selective for ACh hydrolysis, BuChE is less substrate-specific, accommodating the fit and allowing the metabolism of several different molecules [15]. The ability of BuChE to accept more chemically diverse substrates derives from differences between the amino acids that, three-dimensionally, form the base of the gorge in the two enzymes. Specifically, binding between the acetyl moiety of ACh and the catalytic binding site involves an interaction with three key amino acid residues. Members of a catalytic triad, these elements are involved in a charge relay system, which, for AChE, is centered around a serine (Ser₂₀₀), and involves the imidazole ring of histidine (His₄₄₇) and the carboxylic acid of glutamic acid (Glu₃₃₄). In this region of the gorge, at its very base, the available space for substrate binding is restricted by the presence of two large amino acids, phenylalanines (Phe₂₉₅

and Phe₂₉₇), whose aromatic residues protrude into the gorge. These are replaced by two far smaller amino acids, valine and leucine, in BuChE, thereby creating additional space to allow binding of larger substrates. The kinetics of BuChE further distinguishes it from AChE. Whilst AChE is most efficient at low substrate concentrations and becomes inhibited by excess ACh, the Km for BuChE provides far greater efficiency at high substrate concentrations and avoids substrate inhibition.

BuChE – the forgotten sister in ACh regulation?

In the normal brain, approximately 80% of brain ChE activity is AChE, 20% is BuChE [16]. AChE activity is concentrated mainly in neurons, while BuChE is primarily associated with glial cells [4]. Kinetic evidence indicates a role for BuChE (particularly when associated with glia) in hydrolysing excess ACh.

In advanced AD, however, AChE activity may be reduced to 55–67% of normal levels in specific brain regions. By contrast, BuChE activity increases [17]. The ratio of BuChE to AChE has been found to change dramatically in cortical regions from 0.5 to as high as 11 [18]. It seems likely that these alterations in the ratio as the disease progresses change the supportive role of BuChE in regulating ACh and make this enzyme of increasing functional importance. Interestingly, cytochemical studies have revealed that certain cholinergic neurons contain BuChE instead of AChE [19], suggesting that specific cholinergic pathways are regulated by BuChE alone. Furthermore, recent studies have shown that some 10% of ChE-positive neurones in the human amygdala and hippocampus contain BuChE [5]. Augmentation of the activity of these neurones may be of clinical value.

Both AChE and BuChE are found in plaques and tangles, and accumulate within the amyloid plaques [4]. In line with reduced activity of the G4 form, it appears that levels of the G1 form of the enzymes are positively correlated with plaque density. The above findings suggest that inhibiting BuChE in addition to AChE would augment cholinergic neurotransmission in AD.

Benefits of inhibiting BuChE?

The value of inhibiting BuChE has been demonstrated recently using experimental agents with enhanced selectivity for BuChE (cymserine: 15-fold; bisnorcymserine: 110-fold; phenethylcymserine: 5000-fold) [20,21] and BuChE-selective carbamates such as MF-8622 [9,10]. Selective inhibition of BuChE versus AChE derives from an ability to utilize the additional space present in the gorge of BuChE (Figure 1).

Initial animal studies with newly developed selective BuChE inhibitors show promising results. For example, ACh levels in the cortex, as measured by in-vivo microdialysis experiments in rats, have been shown to increase with selective BuChE inhibition using phenethylcymserine [Pepeu G, University of Florence,

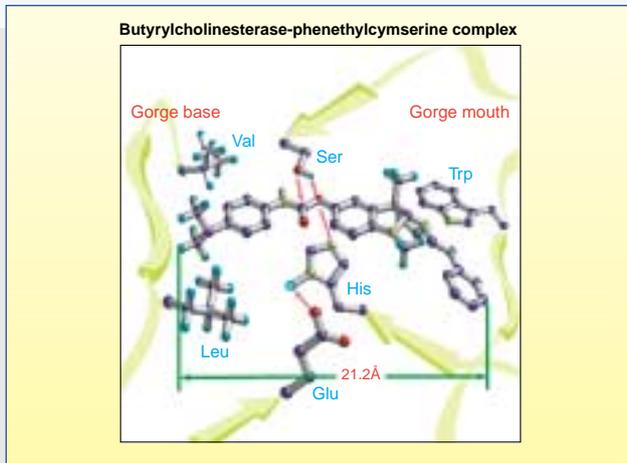


Figure 1. The gorge of BuChE and alignment of the BuChE selective inhibitor, phenethylcymserine, with key amino acids to cause enzyme inhibition.

personal communication], while AChE levels were completely unchanged. The BuChE inhibitor, MF-8622, has also been shown to elevate ACh levels in rat cortex [9]. Both phenethylcymserine and bisnorcymserine improve learning in elderly rats [11]. In learning to navigate a 14-unit T-maze, drug treated rats made fewer errors compared with untreated controls, although results showed that improvements in cognition occurred over a lower dose range than that achieved with the selective AChE inhibitor, phenserine [22,23]. However, since BuChE represents only ~4% of total ChE activity in the rat (Perry T, NIA, personal communication), the potential benefits of inhibiting BuChE in humans could be far greater. Tissue culture studies have demonstrated that both of these agents reduce intracellular and extracellular β -amyloid precursor protein levels, in a dose- and time-dependent manner without toxicity, although, interestingly, the mechanism involved is most likely not cholinergic [24,25]. This leads to significant reductions in β -amyloid protein, the constituent of senile plaques in AD [11]. These results have been confirmed by in-vivo studies in animals carrying a cholinergic lesion in the forebrain. BuChE inhibitors were found to reduce brain β -amyloid precursor protein (APP) levels, compared with controls [26]. Likewise, rivastigmine, which inhibits both AChE and BuChE, has been shown to protect against cholinergic lesion-induced increases in β -amyloid precursor protein [Enz A, Novartis, personal communication]. Interestingly, in naïve rats, BuChE inhibition reduced endogenous levels of β -APP that contained the full length of β -amyloid protein. Regarding the safety of BuChE inhibition, high-doses of cymserine analogues or MF-8622 [9] administered to rodents have not been associated with typical cholinergic toxicity.

The clinical relevance of inhibiting both enzymes has been reported by Costa *et al.* [27]. In this study, inhibition of each of the cholinesterases in the cerebrospinal fluid correlated with cognitive improvement in

patients with AD. Interestingly, however, BuChE inhibition correlated more strongly with cognitive improvement than inhibition of AChE (Table 2) [27].

Table 2. Rivastigmine-induced cognitive improvement in AD patients correlates best with CSF BuChE inhibition [27].

Cognitive performance	Activity	
	AChE	BuChE
CNTB summary score	◆ R=-0.56	◆◆ R=-0.65
CNTB sub-test		
Finger tapping-right		◆
Paired associated learning		◆
Paired associated learning/delayed recall	R=-0.36	◆◆ R=-0.69
Visual memory		

◆ p<0.05, ◆◆ p<0.01

CNTB = Computerized Neuropsychological Test Battery

The development of selective ChE inhibitors should help to elucidate still further the role of BuChE in AD and could assist in developing new treatments. Likewise, agents with the ability to inhibit both enzymes may represent an additional therapeutic strategy for the on-going management of AD.

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Drug switching in AD: focus on cholinesterase inhibitors

An interview with **Bijan Etemad**, University of Pennsylvania, Philadelphia, USA.
 Commentary by **Roger Bullock**, Kingshill Research Centre, Swindon, UK.

Bijan Etemad is currently the Medical Director of Clinical Services in Geriatric Psychiatry at the Hospital of the University of Pennsylvania. He is also Medical Director at the Institute on Aging in Rosemont, Pennsylvania.



Roger Bullock is Director at the Kingshill Research Centre, Swindon, UK, and Consultant and Manager of the Old Age Psychiatry Department in the Avon and Western Wiltshire Mental Health Care NHS Trust. He is committed to research, particularly in psychopharmacology, neuropsychology and the use of both disciplines in all areas of care.

The successful clinical trials and subsequent introduction of the cholinesterase (ChE) inhibitors donepezil [1,2] rivastigmine [3,4] and galantamine [5,6] represent an important treatment option for patients with Alzheimer's disease (AD). The strategy of switching between available agents when faced with failed or failing ChE inhibitor treatment, combined with appropriate evidence and experienced clinical judgement, can help ensure that the maximum treatment benefits are offered. In this issue of *Alzheimer Insights*, we interview **Dr Bijan Etemad**, who discusses his personal clinical experience with ChE inhibitor switching. In addition, **Dr Roger Bullock** describes UK experience with switching and summarizes results of a

recent study examining clinical benefits of switching ChE inhibitor treatment.

Is drug switching a common strategy in psychiatric practice?

It is common practice to switch medication, even in drugs of the same class, once efficacy is questioned or not sustained, or there is occurrence of side effects. For example, if a patient presents with a classic case of depression, antidepressants (e.g., fluoxetine) would be prescribed. Based on your own clinical practice you think that is the right antidepressant, but the patient may return saying that he or she is not able to sleep. Then you adjust the dose, but insomnia continues. Therefore you decide to switch to another selective

serotonin re-uptake inhibitor, and to your surprise the antidepressant you prescribe is effective, and side effects disappear. The reasons for this are often explained in terms of the profile of the drugs involved, but are usually not well understood.

How would you classify a responder/non-responder to ChE inhibitors?

The question of responders or non-responders was based on whether the patient and/or caregiver felt that cognition or activities of daily living showed improvement. Additionally, we now look to see if behavioral problems respond to treatment. If within 1–2 months of initiation of treatment patients respond to a ChE inhibitor, we continue with the agent. However we also know that improvements in some patients plateau after the initial 2 months, and in some cases symptoms may start to deteriorate. In the past we continued treatment with the same ChE inhibitor as there were no other alternatives.

Is there a pharmacological rationale for switching ChE inhibitors?

The ChE inhibitors have differing pharmacological characteristics. Rivastigmine inhibits acetylcholinesterase (AChE) with brain regional selectivity for the cortex and hippocampus, and additionally inhibits butyrylcholinesterase (BuChE). In contrast, donepezil and galantamine are selective for AChE, with galantamine having a putative additional action to allosterically modulate nicotinic ACh receptors. Therefore, if treatment using a selective ChE inhibitor does not produce the required effect, it may be reasonable to offer a trial of an agent with a different pharmacological profile. For example a dual ChE inhibitor, like rivastigmine, may be able to maintain ACh levels over a longer course of the disease, and be more efficacious in certain patients. In addition to the pharmacological rationale, patients switching to rivastigmine switch to an initial dose associated with significant cognitive benefits in the low dose range 1–4 mg/day. This is in contrast to switching from donepezil to other agents acting on AChE alone, which appear to have little clinical efficacy at their initial dose and require titration to a higher dose to be effective.

Which patients benefit/do not benefit from switching to a new ChE inhibitor?

We believe that switching from one ChE inhibitor to another is worthwhile if side effects have become intolerable or if the drug has been ineffective after a period of 2 months or initial efficacy has declined.

How quickly can you switch from one ChE inhibitor to another?

In our clinic the majority of switches are from donepezil to rivastigmine. If patients have failed or are failing on donepezil following 2 months of therapy, we recommend a switch to rivastigmine 1.5 mg twice daily taking place the following morning. We then invite the patient or caregiver to call the clinic daily, if

necessary, to report the appearance of any adverse events. Although a period of 4 weeks is now generally recommended before the first increase in dose, the experience from my practice suggests that a more aggressive dose escalation schedule may be possible. Many of my patients have tolerated an increase to 6 mg/day after intervals of less than 4 weeks. With a more rapid dose escalation schedule such as this, it is of paramount importance to closely monitor the development of any adverse events.

What sort of efficacy and tolerability have you seen following a switch?

Reports from my practice indicate that of 102 patients switched from donepezil to rivastigmine, 82 showed clinically significant improvements in both cognition and global functioning.

Commentary: Dr Roger Bullock UK experience with switching ChE inhibitors

In the UK, a constant concern for purchasers has been the level of non-response to ChE therapy. This is matched by the limited funding available to providers who aim to treat as many patients as possible. As a result, in the UK, patients are often tried on one ChE inhibitor and if this is unsuccessful, it is considered a definitive trial. Although we now have three treatment options, switching between these agents has not been common practice to date due to economic restraints and perceived similarities across this class of drugs. However, as noted by Dr Etemad, these agents do have different pharmacological profiles that may translate into clinically relevant differences. Therefore, switching compounds within the class may extend the positive therapeutic effects of ChE inhibitors. With this in mind we recently performed an open-label retrospective study to see whether switching patients from donepezil to rivastigmine was beneficial. A total of 18 patients switched after experiencing intolerable side effects with donepezil, and 22 patients terminated donepezil therapy due to lack of efficacy. The interval between stopping donepezil and commencing rivastigmine varied across the study. As we tend to be more conservative in the UK, some patients were switched to the lowest dose of the next choice drug overnight, but the average switching time was around 6 days. After switching, a titration schedule was followed as if the patient were initiating ChE inhibitor therapy anew. For rivastigmine the recommendation is to allow 4 weeks between dose increments. Over half of the patients in this study obtained benefits in cognitive function and global functioning by switching to rivastigmine. Furthermore, switching to rivastigmine was well tolerated. These results together with the reports from Dr Etemad suggest that it is sensible to prescribe rivastigmine if donepezil is the first choice of treatment and fails.

Dose–response relationships are variable among the available ChE inhibitors, with only rivastigmine having consistently demonstrated a linear dose–response relationship. Furthermore, while it is often recommended

that agents be titrated to their maximum tolerated dose for full effect, significant clinical efficacy has been demonstrated for rivastigmine at 1–4 mg/day (6–12 mg/day: maximum recommended). However, higher doses have generally been associated with greater therapeutic benefit. No real decisions about the success of switching should be made until at least three months after patients have reached a stable dose. Conventionally a non-responder would be seen as someone who continued to decline on measures of cognition and global functioning, plus, in more recent times, behavioral assessments. This is not so simple, however, as many of these measures are reported via the carer, and are independent of each other. This, plus the fact there are no true markers, biological or otherwise, makes the interpretation of these results quite variable, and no operational criteria can or should exist. Continued decline in all parameters is a good indicator of what is accepted currently as non-response, while declining cognition in early treatment is probably a poor prognostic indicator. As with diagnosis of AD, clinical judgement informs us as accurately as most scales whether these drugs have efficacy and didactic use of measurement can be punitive. Decline in the various parameters can occur at any stage of treatment – it would seem that a switch is useful even after a previous good response with the maximum tolerated dose of an alternative ChE inhibitor.

In our study, most patients who started donepezil either had intolerable side effects in the first few months (even at 5 mg), or were found to have not responded after an average of 5 months (usually at 10 mg). The occurrence of side effects with donepezil was not a predictor of

similar problems with rivastigmine. Similarly, a lack of, or reduced efficacy with donepezil was unrelated to the ability of rivastigmine to provide benefit. This is an indication that switching has validity, and that the class does indeed provide differing clinical outcomes that may be accounted for by different modes of action. Prospective, well designed studies will confirm these initial findings in a more robust way. The clinical evidence presented here would be expected intuitively and should encourage all clinicians to try a different ChE inhibitor should their first choice fail.

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Guidelines for the development of community-based screening programs for cognitive impairment in older people

Prepared by the Work Group on Screening for Cognitive Impairment and Alzheimer's Disease, Alzheimer's Association. The members are:

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Background

Multiphasic screening programs for cognitive disorders in defined population groups have been a cornerstone of the research work in the epidemiology of Alzheimer's disease and other dementing disorders of later life. There is an emerging trend in the USA for the development and implementation of screening programs for cognitive disorders by *community service*

organizations for the purpose of identifying and assisting people with cognitive disorders and their families. The efforts to develop screening programs by non-research groups raise many questions and issues.

The Alzheimer's Association, Chicago, Illinois, USA, formed the Work Group on Screening for Cognitive Impairment and Alzheimer's Disease to develop guidance for its Chapters. The guiding premises of the

discussions of the Work Group were *to do no harm, maximize benefits, respect autonomy, maintain confidentiality* and *to be inclusive of all people*. The following text presents the deliberations of the Work Group.

Principles of Public Health Screening

“Screening is the examination by a single test or procedure of a population of apparently well people for the purpose of detecting those with a particular unrecognized disease or defect” [1]. Principles for disease-detection or screening programs have been developed [1]. Each of the principles is briefly discussed in the context of the current state of knowledge about cognitive impairment in later life and about the scientific and clinical infrastructure of the USA.

1. The condition should be an important health problem.

Cognitive impairment in later life is widely agreed upon to be a serious and growing international public health issue.

2. There should be an accepted treatment for patients with recognized disease.

The treatment of people with cognitive impairment is multi-dimensional and includes not just medications, but the gamut of social, legal and financial services that help affected people to plan for the management of impairment. This principle should be reworded for applications to screening programs for cognitive impairment: *There should be accepted interventions for patients with recognized disease*.

3. Facilities for diagnosis and treatment should be available.

Appropriate facilities and services for follow-up referral for diagnosis and intervention are required. It is mandatory to determine if follow-up resources exist and are adequate to handle the estimated number of possible patients and families. The following issues must be addressed:

- (a) Can the diagnostic and intervention centers or locations manage younger people, as well as older people, with cognitive disorders?
- (b) The cultural competence of the local diagnostic and intervention referral sites must be very carefully evaluated against the ethnic, linguistic, socio-economic, literacy and cultural characteristics of those people who may screen ‘positive’ and need follow-up evaluations.
- (c) There must be a clear and effective system for moving people from a ‘suspicious’ screening performance to a follow-up appointment. The supplying of a set of names, phone numbers or even an appointment date is probably not sufficient for people in many cultural groups and circumstances.
- (d) People must be able to reach the diagnostic and intervention referral sites without excessive or expensive travel.

4. There should be a recognizable latent or early symptomatic stage.

There is an early recognizable stage of cognitive dys-

function in Alzheimer’s disease. The ability to detect dysfunction at this stage depends upon the instrument chosen and the performance characteristics of the instrument. However, from the perspective of evidence-based medicine, there is little evidence that screening of asymptomatic individuals is beneficial. Screening programs for persons with mild impairment may be useful. Additionally, it must be remembered that even at the present, there are very large numbers of people in the community with clearly diagnosable disease who have not been detected.

5. There should be a suitable test for examination.

The usefulness of any screening instrument is dependent upon the severity of cognitive impairment and the educational, cultural, linguistic, and socio-economic characteristics of the population being screened. Many of the available instruments have no published data on use of translated and culturally adapted versions or have only been tested in a few languages other than English. Detection is also limited by the difficulty in establishment of reliable and valid cut off scores in some cultural and linguistic groups and at various educational levels, including both the very low and the very high. The serious consequences of false positives and false negatives must be recognized. The sensitivity, specificity, positive predictive value, and cultural fairness must be considered in selection of an instrument(s). Instruments should have known performance characteristics by age, sex, language, socio-economic status, literacy and health literacy and cultural group. The availability of multiple parallel forms is highly desirable.

6. The test should be acceptable to the population.

The acceptability of many of the available tests and community screening approaches in various population subgroups is not known. While some cultural groups accept cognitive testing, others are upset by it. Any test used in screening programs must be sensitive and respectful of the needs of all cultural groups to whom it is offered.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

The natural history of most of the major causes of cognitive disorder in later life is well enough understood to support the development of screening programs.

8. There should be an agreed policy on whom to treat as patients.

There is real controversy on when and whom to treat for specific causes of cognitive dysfunction. Ideally, the decision to treat should be individualized, i.e., left to the individual physician managing the individual patient.

9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Accurate data, on the cost of screening versus expenses incurred by an earlier diagnosis, is not avail-

Despite the cautions about screening described herein, the authors recognize that some groups will choose to pursue community screening programs. When doing so, such groups should understand that the development and implementation of a community program to screen for cognitive impairment is a complicated and serious undertaking. There are a number of practical questions to be considered in the preparation of a written plan, some of which were discussed under the principles presented below:

Table 1. Questions to consider in the design of community-based screening programs.

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| <ul style="list-style-type: none"> ● What are the goals and the purpose of the screening program? ● Who or what groups will sponsor the screening program? What groups or organizations will fund the screening program? How will the potential participants and follow-up care providers (physicians and community service organizations) be informed about the sponsorship and the funding source(s)? ● Who is asking to be screened? What are the ethical and informed consent issues? Should consent of the cultural communities to be screened be sought? ● What are the risks and benefits, short and long term, for whom? ● Are there any liability issues presented for the sponsoring organizations or groups? ● What cultural groups reside in the communities targeted for screening? ● How will the screening program be advertised? ● What screening instrument(s) will be used? How was the screening instrument(s) selected? Are there adequate data on the performance characteristics of the instrument for all of the cultural groups who will be included in the screening to support its use? ● Who will discuss the screening program with the potential interested participants? How will these people be selected, trained and supervised? Are they culturally and linguistically competent? ● Who will administer the screening instruments? How will these people be selected, trained and supervised? Are they culturally and linguistically competent? ● What is the setting for the presentation of the screening program and administration of the screen? Does it provide adequate privacy and comfort? ● How will the results of the screen be interpreted and presented to the person requesting the screen and the family | <ul style="list-style-type: none"> or care providers? By whom and in what setting? What training and supervision will they receive? Are they culturally competent? ● What educational and counseling activities will accompany the screening program? How will the activities be developed, documented and monitored? Are the materials culturally appropriate for the groups of people likely to participate? Are the educational materials appropriate for people of various literacy levels? Who will provide training and supervision for the counselors? ● Are physicians, specialists, facilities and programs available, in adequate numbers, within a convenient distance to handle the referrals for diagnosis or follow-up? Are they culturally and linguistically competent to care for all people who may participate in the screening program? How will the referrals be made? What system is in place to help people in obtaining the recommended appointments? ● What about the availability of programs and services for treatment and management? Are they culturally and linguistically competent and easy to access? ● What are the plans for long term follow-up and assistance? ● What are the plans for repeat examinations in order to demonstrate cognitive changes? ● How is the screening program to be evaluated? Without adequate scientific evaluation (more than simple counts), it is not possible to determine what components of the screening program are effective and what are harmful. ● How are the data on cost of the screening program to be collected? ● What are the quality control procedures for each step in the screening program? How are they documented and monitored? ● What follow-up information will be presented to the screened communities? How? |
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Any group or organization proposing to develop a community screening program must recognize the total population of people with Alzheimer's disease in the service area and expand efforts to reach ethnically diverse, low literacy groups of people who may have members affected by cognitive impairment or dementia. Before launching a community program to screen for cognitive impairment, the planning group or organization should be able to answer most, if not all, of the above questions. If many of the above questions pose problems, then the sponsoring group or organization may choose to consider the launch of a community education program, in lieu of a screening program.

able. It would be desirable to develop cost data as a component of the design of community screening programs.

10. Case finding should be a continuing process and not a 'once and for all' project.

Case finding, as an ongoing operation, has yet to be addressed in community screening for cognitive impairment. Many scientists and clinicians consider it essential that people be examined at two or more points in time to determine if they are impaired and show progressive deterioration.

In summary, the clinical and scientific infrastructure to support the development of *national or large area* screening programs for cognitive impairment in the USA appears inadequate at the present time. There

are a number of issues to be considered and addressed, with one of the most serious being the availability of standardized, reliable, and valid instruments that are normalized for age, sex, language, literacy, health literacy, and ethnicity. The potential population for screening in the USA is extremely heterogeneous, while the performance characteristics and biases of many potential screening instruments in large population subgroups are unknown. Thus, establishing 'cut-points' for performance (normal versus abnormal) is not easily done.

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Weight loss in Alzheimer's disease: etiology and management

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Alzheimer's disease (AD) is one of the leading causes of death among elderly people. Most studies on patients with AD have focused on cognition. However, these patients will present other complications, such as episodic agitation, falls, immobility, behavioral disorders, and nutritional problems. Nutritional problems are inevitable in practically every AD subject. It is, therefore, not surprising that nutritional management becomes a preoccupation of the attending physician and family.

Weight loss and aversive feeding behaviors (AFBs) in AD

Frailty in AD patients is exacerbated by general weakness and weight loss, which are predictors of mortality [1–4] (Table 1). Weight loss occurs frequently in the first stages of the disease and becomes more pronounced as the illness progresses [2,4]. Moreover, a recent study showed that weight loss precedes AD

diagnosis and could be an early manifestation of the disease itself [5].

In the first stage of the disease, weight loss is probably due to socio-environmental and psychological factors [4,6]. Other hypotheses that have been proposed to explain weight loss in AD include atrophy of the medial temporal cortex [7], biological disturbances [7,8] and increased levels of energy expenditure [9]. The medial temporal cortex (MTC), which is involved in feeding behavior and memory, is affected in the primary stages of AD and continues to be a site of major AD pathology as the disease progresses. Grundman *et al.* [7] showed that a low body mass index in AD patients correlates specifically with atrophy of the MTC. It is further suggested that there is a connection between limbic system damage and low body weight in AD. Atrophy of the MTC might also contribute to weight loss through additional

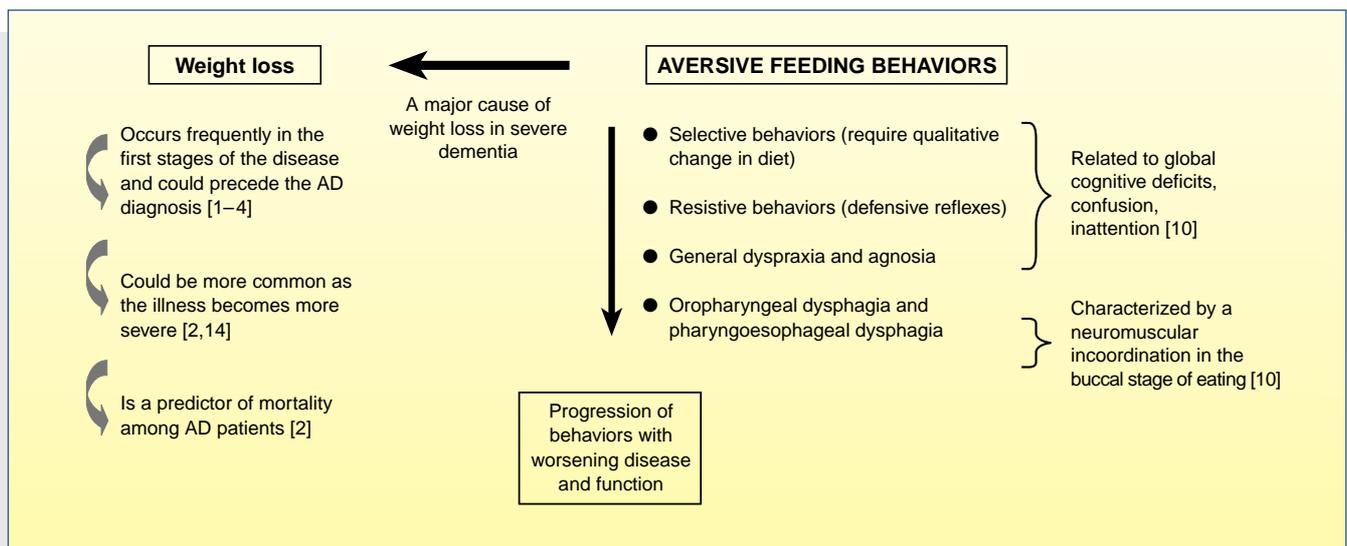


Figure 1. Weight loss and AFBs in AD.

Table 1. Main epidemiologic studies of weight loss in AD.

Studies	Patients and methods	Results	Conclusion
White, <i>et al.</i> [1]	Mild-to-moderate AD patients (n=362) and controls (n=317), recruited from the CERAD,* with two or more weight measurements taken a year or more apart were included in this analysis. The average period of follow-up was >2 years for both subjects	Nearly twice as many AD patients experienced a weight loss of 5% or more when compared with controls (men p=0.003, women p=0.001) When other possible causes of weight loss were controlled using a multivariate model, a diagnosis of AD remained a significant predictor of ≥5% weight loss (p<0.001)	Clinically important weight loss occurs more frequently among patients with AD than among cognitively intact control subjects
White, <i>et al.</i> [2]	666 AD subjects from the CERAD were enrolled for this study. Body weight was measured on entry and at annual follow-up examinations as part of standardized clinical assessment for a ≤6-year period	Each change in stage of AD was associated with an estimated average weight loss of nearly 1 kg (p=0.001). The correlation between change in stage of AD and weight change was statistically significant (r=0.09, p=0.005) which indicates a greater tendency toward weight loss with progression of AD. Weight loss of ≥5% in any year before death was a significant predictor of mortality	The risk of weight loss tends to increase with severity and progression of AD. Weight loss is a predictor of mortality among subjects with AD
Cronin-Stubbs [3]	Body weight and height, from a stratified random sample of the population age 65 years and older of East Boston, were collected during five annual structured clinical evaluations. AD was diagnosed on the basis of neurological and neurophysiological examination	After adjustment for both age and sex, the body mass index in subjects without AD decreased by an average 0.14 per year, compared with 0.52 per year in similar subjects with AD (p<0.01)	AD is recognized as responsible for weight loss. Many AD subjects had mild disease, and the magnitude of weight loss in this group did not support the idea that weight loss in AD is confined to those with severe disease
Barrett-Connor, <i>et al.</i> [5]	Older community-dwelling men (n=134) and women (n=165) were followed for 20 years before they were diagnosed as cognitively intact or suffering from dementia. Weight was measured at three clinic visits between 1972–74, 1984–87, and 1990–93	Approximately 50% of men and women who developed dementia had lost 5 kg of weight since their first evaluation 20 years previously, compared with about 25% of men and women who were cognitively intact according to detailed neurological and neurophysiological examination	Weight loss precedes mild-to-moderate dementia. Early weight loss is, therefore, unlikely to be a consequence of AD patients being unable or unwilling to eat

*Consortium to Establish a Registry for Alzheimer's Disease

mechanisms other than cognitive impairments (e.g., lack of food preparation, diminished skills, reduced appetite, and increased physical activity). Moreover, some disturbances associated with weight loss, such as increased cortisol and tumor necrosis factor concentrations, or decreased estrogen concentrations, worsen atrophy of the MTC and, consequently, dementia itself [7]. It has also been reported that cholinergic medications used in the treatment of the AD may contribute to weight loss [10,11].

Progressive dementia is associated with increasing dependency in performance of activities of daily living (ADL). Feeding dependency is a prominent feature and a major cause of malnutrition (Figure 1). In severe dementia, patients hinder or prevent oral nutrition by a variety of behaviors including: refusal to eat, resistive behaviors and dysphagia. Blandford *et al.* [12], developed an 'Aversive Feeding Behaviors Inventory' to identify aversive eating behaviors, enhance specific feeding strategies, and plan patient care in late-stage dementia. Behaviors which affect only the act of eating are termed 'selective', requiring a change in quality or quantity of what is eaten. Oropharyngeal dysphagia, in contrast, is characterized by neuromuscular unco-ordination in the buccal stage of eating (i.e., mouth and tongue control, mastication, bolus formation, passage of bolus to the pharynx). Behaviors which indi-

rectly hinder or prevent food from reaching the mouth are divided into resistive and non-oral dyspraxia [12]. There is a progression of behaviors from selective through resistive to oropharyngeal dysphagia as AD severity increases [12]. Persistent oropharyngeal dysphagia is a predictor of imminent death, probably attributable to a specific brain pathology [12].

Weight loss-related complications (muscle atrophy, functional dependence, increased frequency of falls, fractures, and decubitus ulcers) increase the burden of the disease and worsen the patient's and caregiver's quality of life. Therefore, it seems important to understand the pathogenesis of the AD-associated weight loss and develop preventive strategies. Identifying factors determining muscle atrophy or muscle mass maintenance have important health implications for AD patients. Dvorak *et al.* [13], showed that higher levels of physical activity and energy intake were associated with higher appendicular skeletal muscle mass in AD patients. Nutritional and physical activity interventions may therefore represent practical and inexpensive management strategies in AD patients.

Caregivers' influence on nutritional status and therapeutic management in AD

Caregivers may have an important and dramatic influence on the course of the AD, particularly on the

frequency and severity of behavioral problems, and on whether the patient becomes institutionalized [14]. Amella [15], recently examined the extent to which caregiver interaction during feeding, and characteristics of the caregiver (i.e., empathy and power) influenced the proportion of food consumed by older nursing home residents with dementia. Fifty-three dyads composed of nursing home residents with late-stage dementia (mean Mini-Mental Status Examination [MMSE] score of 4.2 ± 5.5) and Certified Nursing Assistants (CNAs) were observed during breakfast. The proportion of food consumed by the residents was measured by weight. The quality of the interaction between the resident and the CNA was assessed by using the Interaction Behavior Measured-Modified (IBM-M) scale. The CNA empathy and power were also evaluated, respectively, with the Interpersonal Reactivity Index and the Control subscale of the Fundamental Interpersonal Relations Orientations-Behavior (FIRO-B). The results showed that specific patient behaviors and the ability of the CNA to allow another person to control a relationship were most predictive of the variance with the proportion of food consumed. The quality of the resident-CNA interaction accounted for 32% of the variance in the proportion of food consumed. One aspect of power was correlated significantly to the proportion of food consumed whereas CNA empathy was not. Examining the interactional components of meals within the caregiving dyad is probably one of the best strategies to ensure that patients with dementia receive adequate nutrition, especially in late-stage dementia.

In preliminary reports [4,16], we found that weight loss in AD patients was significantly associated with higher scores on standardized measures of caregiver burden and stress. Caregivers who consider themselves overburdened by the behavioral and autonomic disorders associated with the disease are probably unprepared to invest the additional resources necessary to allow AD patients to receive proper nourishment. Given the serious consequences of weight loss and the influence of caregivers' stress on weight loss in AD patients, we developed a program of nutritional education and health promotion supported by the European Commission, to detect weight changes and coordinate earliest nutritional intervention [17]. The program aimed to educate caregivers to prevent weight loss and react positively when AD patients developed eating behavior disorders. It was intended to last 1 year for 150 AD patients living at home with a caregiver in Toulouse (France), Brescia (Italy) and Barcelona (Spain).

Comprehensive functional and neuropsychological evaluations were performed at the beginning of the study, after 6 months and after 1 year. Cognitive functions were measured with the MMSE, depression with the Cornell Scale and behavioral disorders with an adapted version of the Cohen-Mansfield Scale. Assessment of Activities of Daily Living (ADL) and the

instrumental Activities of Daily Living (IADL) were used to assess patient autonomy. The caregivers' quality of life and caregiver burden were also evaluated, with the Leipad instrument and the Zarit Scale, respectively. Several tools were used to follow nutritional status and body weight, such as the Mini Nutritional Assessment (MNA) [18], the Blandford Scale [14], and a nutritional calendar. The MNA is an 18-item nutritional questionnaire, which distinguishes elderly patients with adequate nutritional status ($MNA > 23.5$), protein energy malnutrition ($MNA < 17$) and risk of malnutrition (MNA between 17 and 23.5). The MNA was specially designed to guide nutritional intervention by identifying risk factors requiring correction [18]. In cognitively impaired subjects, this test requires help from the family and/or healthcare workers. The nutritional calendar is a standard diary which provides areas for recording each month the patient's and caregiver's body weight (caregivers, often elderly, stressed or depressed, can also suffer considerable weight variations). The MNA also contains physical and nutritional advice, and recommendations in cases of AD patients losing more than 2 kg or decreasing appetite. Finally, caregivers were encouraged to increase their knowledge on AD and nutrition. They were provided with nine 1 hour courses within 1 year. Five meetings were scheduled during the first month; then one meeting in months 2, 3, 6, and 12. This group of 150 couples 'AD patients-caregivers' (intervention group) was compared with a control group (74 couples 'AD patients-caregivers'), where the caregiver did not attend nutritional educational courses. Results indicated that the percentage of significant weight loss (more than 4% of initial body weight in 1 year) was significantly decreased in AD patients whose caregivers attended nutritional educational courses (13% vs 29% in the control group; $p < 0.005$). Moreover, the progression of the cognitive deterioration examined by the MMSE was slower in the intervention group. We also found that caregivers' status (sex, age, family relationship) may influence the risk of weight loss in AD patients. The risk of weight loss was significantly increased when the caregiver was a child or male. In terms of levels of nutritional need, in-home family help with spouses was probably the best caregiving arrangement (unpublished data). Consequently, to efficiently prevent nutritional problems during AD, it seems important:

- to develop interventions for caregivers
- to assess, manage and treat the caregivers' stress
- to pay particular attention to young or male caregivers during intervention programs.

In conclusion, studying weight loss in AD is very important: first, to have a better understanding of the natural history of the disease; second, to develop preventive strategies. Maintaining a satisfactory nutritional status might prevent malnutrition-related

complications and reduce the social and economic costs of AD. It seems to be prudent to recommend regular monitoring of the AD patient's nutritional status (regular monitoring of body weight, MNA, nutritional calendar) as soon as AD is suspected. To date, nutritional educational programs for the caregivers of AD patients seem to be the best way to prevent weight loss and improve the nutritional status of these patients.

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