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Negative argument for debate with V. O. Emery for J Neural Transmission

Alzheimer's disease: are we intervening too late? No we are not

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Abstract Alzheimer's disease (AD) represents a major public health challenge. It is the most common cause of dementia, the worldwide prevalence of which will double every 20 years in the foreseeable future. It would be good if it were possible to treat AD early to diminish its impact, but current evidence does not support early intervention. Vitamin E was no more effective than placebo in a study of vitamin E and donepezil against placebo in mild cognitive impairment (MCI). Vitamin E is associated with a higher rate of haemorrhagic events than is placebo. Neither donepezil nor galantamine has been shown to be helpful in retarding progression from MCI to AD. Gingko biloba was ineffective in delaying the onset of AD in a large prospective trial involving over 6,000 participants. Gamma secretase inhibitors have not yet been shown to retard the progression of AD and they seem to have a high incidence of adverse effects, especially rashes. Antibody therapy has not yet been shown to be helpful in the treatment of established AD, let alone its prevention. Metalloproteinase modifiers such as PBT2 may be useful AD therapies, but current evidence gives no support to their immediate use in pre-symptomatic AD. No evidence can yet be adduced to support the use of antibody therapies in MCI or early AD. Thus, it is clear that the early treatment of AD cannot be justified as yet, no matter how desirable this goal may be. Treatment of established AD with cholinesterase inhibitors and memantine, coupled with referral of interested patients to evaluative drug trials, is the best we can do at present.

Keywords Alzheimer's disease · Treatment · Early intervention · Cholinesterase inhibitors · Novel therapies · Evidence

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Introduction

Alzheimer's disease (AD) is the commonest cause of dementia (Cummings and Benson 1992). Dementia prevalence is doubling every 20 years (Ferri et al. 2005, Alzheimer's Disease International 2009) and the disorder causes profound disability and engenders enormous social, emotional and financial costs (Ferri et al. 2010). Thus, the prevention of symptomatic AD or the delay of the point at which its disabling symptoms appear in a specific individual is a worthy goal. If effective treatments that could retard the appearance of the symptoms of dementia were available, or if there were evidence that the earlier application of existing treatments would ameliorate the course of the disease, then earlier intervention than is currently practised should be favoured. Assuming that to 'treat earlier' implies intervening with individuals whose brains are affected by the pathological cascade that leads to manifest AD (Masters 2010, Ritchie et al. 2010), but who do not yet have sufficient symptoms to enable a clinical diagnosis of probable or possible NINCDS–ADRDA AD (McKhann et al. 1984) to be made, instead of merely giving current available treatments such as cholinesterase inhibitors or memantine to individuals who already fulfil criteria for diagnosed AD (Kurz and Lautenschlager 2010), we are faced with two specific problems.

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Our inability to diagnose pre-symptomatic AD with a high degree of accuracy

The first problem that faces the earlier treatment of AD is that we cannot reliably diagnose pre-symptomatic AD. One-third of people with mild cognitive impairment (MCI), the construct that best identifies a group of individuals at high risk of developing symptomatic AD within a few years, (Petersen et al. 1999) never develop AD, no matter how long they are followed (Petersen et al. 1999, 2001), and even for the two-thirds who will get AD, only around one-fifth of this group will develop AD each year (Petersen et al. 1999). Biomarkers such as APOE ε4, CSF tau/amyloid ratios, hippocampal atrophy or PiB PET scans all identify populations at increased risk of developing symptomatic AD (Pantel and Hampel 2010, Barber and O'Brien 2010, Villemagne and Rowe 2010), but none of these methods can yet determine with very good accuracy the point at which those individuals doomed to contract AD will display symptoms, nor can they tell us which of the at-risk individuals will not develop symptomatic AD before their death from other causes and whom it would be utterly pointless to treat (Lautenschlager and Kurz 2010). If we cannot distinguish those who will develop AD from those who will not, then how can we justify giving them therapies or administering other interventions, which will at least cost money and consume time and may, indeed, be toxic in some cases?

We lack safe, effective treatments or interventions proven to prevent or delay the onset of AD even in susceptible individuals

The second problem that we face is that we have no effective proven ability to prevent or delay the onset of AD. Potential disease-modifying drugs have been and are being trialled in subjects with established symptomatic AD (Woodward 2010). To date, the experience with gamma secretase inhibitors, antibody therapies and other novel interventions such as metalloproteinase modulators has not been particularly encouraging or, at best, research is insufficiently advanced (Lannfelt et al. 2008) to be able to conclude whether these therapies are of any use or none at all. To date, none of these drugs has been shown to treat established AD with any efficacy and several have toxic side effects of one type or another (Woodward 2010). Of course, it may be the case that in trials conducted to date, these treatments are being given too late in the disease process to do any good. Perhaps it would be better to try them out in people who are developing AD, but whose symptoms do not yet meet criteria for dementia. I would support such trials, but until they have been undertaken, we can hardly advocate the use of such potentially toxic entities as routine treatments to delay or prevent AD.

Insofar as treatments which are already in use for established AD are concerned, prophylactic treatment with vitamin E and cholinesterase inhibitors has proven ineffective in delaying conversion to symptomatic AD in individuals with MCI in large well-designed trials and as well as being utterly useless for the prevention of AD; administration of high dose vitamin E is associated with a slight excess of deaths from haemorrhagic causes (Frank and Gupta 2005, Kurz and Lautenschlager 2010, Lautenschlager and Kurz 2010, Woodward 2010). Likewise, ginkgo biloba did not delay the appearance of AD in a population of over 6,000 at-risk individuals treated for over 6 years (DeKosky et al. 2008). So, there is no case for giving existing AD treatments earlier than we do.

People with MCI should be seen and reviewed regularly by experienced, competent clinicians and when they develop the clinical symptoms of AD, they should be treated with those therapies that have been shown in trials to be modestly helpful for individuals with established AD symptoms (Kurz and Lautenschlager 2010).

Epidemiological evidence suggests that exercise, reduction of vascular risk factors, maintenance of social engagement and enhancement of cognitive activity all *may* be associated with lower AD incidence or prevalence (Lautenschlager and Kurz 2010), but these epidemiological findings have yet to be translated into preventive interventions *proven* to be effective in prospective randomized double-blind controlled trials. It is all very well to get excited about epidemiologic findings that suggest a particular potentially modifiable risk factor or exposure may make AD more or less likely, but the failure over two decades of translation of such findings with regard to female hormone use, anti-inflammatory drug exposure or lowering of homocysteine into effective therapies that can be applied to populations should give us pause for thought and temper premature enthusiasms (Lautenschlager and Kurz 2010, Woodward 2010). Similarly, although there is hope that cognitive retraining may delay the emergence of symptomatic AD in subjects with MCI, it should only be offered as a component of evaluative trials until we know whether or not the inconvenience, costs and stresses associated with the application of such therapies are worth the effort involved in their administration (Lautenschlager and Kurz 2010).

Conclusion: *primum non nocere* (first do no harm)

If we cannot prevent or delay the emergence of AD in susceptible individuals as yet, what should we be doing at present? We certainly should encourage the development

of biomarker panels that can identify not only who will and will not develop symptomatic AD, but also when this will happen. To this end, I am co-leader of a large national study [the Australian Imaging, Biomarkers and Lifestyle (AIBL) flagship study of ageing] that aims to do just that (Ellis et al. 2009). But, this will take time. In the meantime, we should also encourage and facilitate the randomization of individuals with MCI to evaluative trials of preventative interventions including exercise, modification of vascular risk factors and memory retraining, as well as their enrolment in trials of drugs that may retard the pathological cascade of AD, in order to see whether any of these interventions is indeed helpful. But to advocate earlier treatment of a condition whose inception we are unable to predict with great accuracy, and for which we have no evidence that earlier treatment has any efficacy would seem to be premature at this stage. Indeed, one could argue that to advocate earlier treatment of AD in our present state of knowledge might actually retard the discovery of effective disease-modifying or symptom-delaying interventions, as to do so inevitably will diminish the pool of individuals who can be offered randomization into disease-modifying or symptom-delaying treatment or intervention studies.

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