WITH 25 YEARS HINDSIGHT, WERE THE CHOLINESTERASE INHIBITORS WORTH DEVELOPING?

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Acetylcholinesterase inhibitors (AChEIs) were first licensed in 1996 in the USA for the treatment of mild to moderate Alzheimer's disease (AD). Since then they have become the de facto standard for treatment of that condition - along with memantine. The history of their first 15 years was punctuated with controversy, not least when the National Institute of Clinical Excellence (NICE) in the UK, first found them to be poor value for money and then restricted their use to moderate AD only. This led to the UK being derided, but other European countries began to follow suit and the bureaucratic regulation of the drugs probably cost almost as much as they did. Meanwhile in the USA, AChEIs were prescribed with abandon at all stages of AD, including those with cognitive symptoms without a formal diagnosis of dementia.

So what are the AChEIs guilty of? Well the main thing is that they offered hope to the many, that because nothing had really preceded them was seized upon by professionals and carers alike. However, hydergine had preceeded these drugs by some 10 years, but had not caught the imagination nearly as vividly. Perhaps because hydergine was a non-specific treatment for dementia, rather than targeted at AD. However cholinergic loss is a feature of several neurodegenerative disorders, especially the Parkinson's complex and so this myth that AChEIs treated AD was incorrect and led to many clinical trials searching out new indications, rather than practical research on how best to use them.

Cholinesterase inhibitors emerged at the same time as evidence-based medicine, increasing elderly numbers, rising dementia incidence and prevalence and tighter fiscal controls in health. Put together, it seemed their very presence may bankrupt health care. This led to even more resistance, which masked underlying ageism in most of our cultures.

So AChEIs are guilty of misleading us in what they actually treat, intimidating our payers and heightening the fear of the growing numbers of elderly. These primal feelings led to many debates and arguments that often did not address the root issues. However, the main issue that remains is do they work?

Well, the evidence says they reach statistical significance in clinical trials, sufficient for Cochrane to grudgingly concede that too. But how did this small effect size translate clinically? Anecdotal cases of lives being changed were undoubtedly true, but only temporarily and on a population basis the effects of AD have barely changed as a result of their introduction. It can be argued that improvement of quality of life for a few months is a laudable achievement in a disease where small victories are rare. There are also observational studies suggesting that long term use does seperate populations a bit. Both are true. But the real crime here is that AChEIs medicalised AD and led to increased detection and referral at earlier and earlier stages. The debate here is that in the absence of an effective treatment is it right that we embark on virtual screening programmes to find people with mild disease, when at this stage all trials of AChEIs have shown no effect? It is well known that people who are told they have a prodromal or mild disease, usually assume the characteristics of that disease straight away. We are struggling with understanding the early stages of AD and how and when to intervene. Clinical trials are contaminated with drugs that may not help clinically, but might interfere in the experiment. For example, in the failed flurizan study of AD MMSE above 21, nearly all participants were on AChEIs, with 42% on memantine as well.

Another effect of medicalisation of AD, is the public notion that it is a disease you may get when you're old and can now fix with a pill. More and more evidence on nutrition and lifestyle suggests that people can influence how they age. This message needs to be promoted, not that there is a pill that will help if you are unlucky.

AChEIs have made dementia interesting and brought in new referrals and increased research funding. Most of that goes on the hunt for a cure for a condition we have not defined - especially when you consider 20% of the solaneuzamab AD PET study did not have amyloid in the brain. However, in doing this, they created a new medicalised image

of AD that may not be helpful. Diagnosis has become the key in dementia care, rather than meeting the needs of the individual. AChEIs are turning up untaken in cupboards these days. Patients are stopping them as they don't perceive them making much difference. The fact that they are all off patent now makes the early arguments irrelevant. They will be taken by everybody and after a few months of some small effect will be taken by those who wish to continue in the biggest social placebo experiment in history.

Were they worth developing? Science has to follow its leads. Were they worth the cost to the health community? That's debatable, but a mute argument now. Have they moved dementia care forward? I fear perhaps not.