



Drug treatments in dementia

New drug treatments continue to raise the profile of dementia, in particular Alzheimer's disease. How do they work, what questions do they raise, and what does the future hold?

The last five years has seen a growth in the number of drugs being developed for people with dementia, particularly Alzheimer's disease (AD). The currently available treatments offer symptomatic relief, for periods between six and eighteen months. The main class of such compounds is the cholinesterase inhibitors, which demonstrate a consistent effect. Four have been licensed for use in many countries. Future compounds will aim to delay progression of the illness (eg amyloid metabolism modifiers) while work continues to identify treatments that may delay the appearance of the illness; and ultimately, drugs that may alleviate the underlying pathology.

Cholinergic therapies

A core problem in AD is a failure of the central cholinergic system. This leads to a loss from the brain of acetylcholine, the most important chemical for memory. Most therapeutic work has therefore been aimed in this direction, with drugs to boost the availability of acetylcholine, usually by preventing its breakdown in the synapses of the brain. Such treatments include the anti-cholinesterase inhibitors, which inhibit the enzyme responsible for breaking down acetylcholine. The earliest drug of this class, tacrine (Cognex), was associated with significant side effects and has largely been superseded by newer acetyl cholinesterase inhibitors. The best known examples are donepezil (Aricept®) and rivastigmine (Exelon®); and now a third galantamine (Reminyl®) has been licensed in Sweden and is awaiting European approval. The effect of these is to boost the effect of the remaining neurones in the brain, by keeping released acetylcholine in the synapse longer. Clinical trials have shown this improves or stabilises cognition and general functioning in the activities of daily life in some people with AD over about nine months. Newer information suggests that the cholinergic drugs may also help maintain, and even

improve, activities of daily living and common behavioural disorders. Their overall effect impacts on all domains of the illness, producing a clinically significant impact in approximately half of patients who receive these treatments. The three well-documented behavioural symptoms that respond best are apathy, agitation and psychotic symptoms – especially visual hallucinations. These come high in the list of causes of carer distress.

This response can only last as long as there are viable neurones still producing acetylcholine and receptors able to receive the message, so as the disease progresses the drugs stop working.

Another approach to enhancing cholinergic function has been to mimic the acetylcholine with compounds called agonists. To date, none of those tried has had a significant effect on cognition in clinical trials at the doses tolerated, which means they have been withdrawn. These are mainly muscarinic agonists, but similar difficulties have been found using nicotinic agonist drugs in clinical studies. They do seem to improve other domains in dementia, but this is not sufficient indication for licensing at present.

In general, the new generation of cholinergic drugs has proved to be easy to take, usually with once or twice daily doses, and so far safe in long-term use. Apart from some initial nausea and other mild gastrointestinal symptoms in 10-20% of those who take them, the side effects are relatively few.

Non cholinergic therapies

Other chemical systems, namely the serotonergic, dopaminergic or noradrenergic systems in the brain, have been studied but results as regards dementia have been disappointing. They are of course implicated in depression, both with and without dementia. There is also evidence to suggest that aggression in dementia may respond to treatment with selective serotonin re-uptake inhibitors (SSRIs) – a type of antidepressant.

Another antidepressant, trazodone, is frequently used as a tranquiliser in people with dementia.

Another system in the brain that could be used therapeutically is the monoamine oxidase system (MAO). Inhibition of this with selegiline or lazabemide (type-B inhibitors) has benefit in clinical trials, although the exact mechanism is not clear, and may be more to do with a number of interrelated factors, rather than one specific action. Selegiline is not routinely recommended in AD, and lazabemide has been withdrawn due to liver toxicity difficulties. However, drugs that affect the MAO system may still remain a future area of promise.

Anti inflammatory drugs, oestrogen and Vitamin E

Epidemiological research has pointed towards new therapeutic avenues. People with arthritis and those women on post-menopausal hormone replacement have a reduced incidence of AD. This seems to be due to modification of the inflammatory process that plays a part in the neuronal destruction in the disease. As a result non-steroidal anti-inflammatory drugs and oestrogens are being studied, both as possible treatments and in the prevention of AD. Some of the new anti-inflammatory drugs, the cyclooxygenase II or Cox II inhibitors, such as celecoxib, may be relatively free of side effects. Until the results of trials with anti-inflammatory drugs and oestrogen drugs are available, their use is not recommended routinely, as both classes of drug have side effects in long term use, which at present outweigh any proven benefit.

Antioxidants are protectors of the body against the harmful effects of free radicals – which we deal with less well as we age. Vitamin E has this protective effect on the brain, and trials with this, on its own and in combination with selegiline, have shown some benefit. While further work is needed to be more conclusive, its use at high dose (1000iu

once or twice daily) has become common practice in the USA and Europe.

Other areas of research – where biology is leading us

While much of the focus in AD has been on the cholinergic system, there is increasing evidence that glutamate toxicity may play a role, as it does in stroke related illnesses. To this end a drug called memantine, which partially blocks one of the glutamate receptors, has just completed trials with encouraging effect in both AD and vascular dementia. It is now being filed with the European regulatory authorities. It may prove to be a useful adjunct to the cholinesterase inhibitors, and an alternative for those who cannot tolerate their side effects.

Glial cells are cells in the brain that usually support neurones and clean up any damage that occurs. They become activated by the disease, and participate in the cell death that occurs in Alzheimer's disease. Inhibition of their activation slows down cell destruction and could slow disease progression. Unfortunately, drugs that have the ability to stop this activation have not been shown to have sufficient efficacy in trials to date, and while this is a very plausible mode of action, there are no current programmes with them.

The cholinergic neurones run a long and complex course. As such they are dependent on nerve growth factor (NGF) to survive. NGF does not cross the barrier between blood and the brain, so cannot be given as a drug – subtypes of it are being formulated for trial work. A trial of a xanthine derivative (Neotrofin) that may boost NGF and slow neurone loss is about to commence.

The genetics of AD offers clues as to the role of amyloid and tau proteins in AD. Knowledge of their metabolism is leading to new treatments and compounds that may interrupt damaging mechanisms occurring in the brain. Some of these drugs are in early clinical trials – the best publicised of which are the 'vaccines', where β -amyloid is injected into the patient so as to immunise the patient against the amyloid, which is thought to be producing the harm. If it works it will be the first true modification of the disease itself.

Current position

A great deal more is known about dementia than before, but new treatments pose new questions. The anti-

cholinesterase inhibitors bring about a temporary change in symptoms in some of the people they are given to. However it is not possible to predict who will respond. It is also not clear whether people who do not respond to one anti-cholinesterase inhibitor will respond to another. Further systematic clinical research will determine this. Ways of measuring and defining response, and knowing when to stop medication are important but complex issues.

Anticholinesterase inhibitors are the only proven treatment at present in AD. Effective use requires a good baseline assessment with validated scales for objective measurement. Expectations and outcomes should be explained and discussed with the person with dementia and their carer. The dose of the drug should be gradually increased to the recommended dose, to minimise gastro-intestinal side effects, and the individual reviewed at one month. After this, three monthly reviews will provide an indication of the effect of the drug, and decisions can be made about its continuation. Other important aspect of these visits is to check on other medication that may interact with cholinergic drugs, and to minimise cerebrovascular risk factors such as hypertension and stress.

The anticholinesterase inhibitors are licensed for use in mild to moderate AD. Severe AD is also being studied, and although theoretically the outcomes should be poorer early results do not confirm this. Memantine has been shown to have a beneficial effect in severe cases.

Whether to add in other treatments is at present not clear. Vitamin E is safe, but needs to be used at high doses. Selegeline, oestrogen and anti-inflammatory drugs are not proven enough as yet for routine use, as they all have long term problems with their use. Nootropics, such as Ginkgo biloba are available in many countries, often over the counter. Ginkgo seems to improve cerebral blood flow, and randomised trials show some effect in AD and vascular dementias – but methodological flaws mean more research is required. Adding it to licensed treatment does not seem to be unsafe, but whether it improves outcomes is not known.

Vascular and other dementias

Currently there are no licensed treatments for vascular dementia. Memantine is about to be submitted for approval,

and the cholinergic drugs are being evaluated in clinical trials. Low dose aspirin, control of high blood pressure, regular exercise, control of high lipid levels and diabetes (if present) are often recommended. Measuring change in this condition may prove even more difficult than AD.

A clinical trial in dementia with Lewy bodies showed improvement with rivastigmine, with reduction in neuropsychiatric symptoms and increase in the cognitive scales.

No treatments yet exist for frontotemporal dementia, Creutzfeldt-Jakob disease or Huntingdon's disease.

Future challenges

Chronic medical conditions rarely respond to one drug and dementia is no different. Important factors other than cognitive functions and activities of daily living need to be studied in pragmatic trials. Learning to combine the new drug therapies with each other as well as with carer interventions, to maximise their effects, will require systematic clinical research. This will include outcomes such as time to institutionalisation, quality of life issues and health economic evaluations. These data will convince the funding authorities of the merit of the treatments.

Currently only symptomatic treatments exist. The challenge for scientists is to develop compounds that slow disease progression and ultimately halt the process, or better still, prevent the disease occurring. The challenge for clinical services is to diagnose dementia early, learn to treat it effectively at its less debilitating stages and to deliver the right treatment to the right person at the right time.

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