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"I think therefore I am" - Improving cognition

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Purpose of review : In the absence of a specific treatment for dementia, the effective management of cognitive symptoms is a clinical priority.
Recent findings : While some differences have been observed in the profile of cognitive complaints observed in sub-types of dementia, there is increasing recognition of common, interacting neurobiological causes suggesting the need to seek a common treatment applicable to all causes of cognitive deterioration. There is also increasing interest in intervening at the level of minor cognitive dysfunction by reducing risk factors for sub-clinical states.
Conclusion : Pharmacological treatment of cognitive disorder is beneficial but has only temporary benefit for a sub-group of patients. Pharmacogenetics may have an important future role to play in deciding which patients may best benefit from treatment. Low side-effect therapies such as cognitive therapy and acupuncture show some benefits but their utility in combination with pharmaco-therapies remains to be demonstrated. Prevention of milder forms of cognitive disorder by controlling risk factors such as hypertension and diabetes may reduce rates of more severe cognitive degeneration. Persons with cognitive dysfunction are commonly excluded from making decisions about the implementation of cognition-enhancing treatments although they wish to do so.

Key words : cognitive dysfunction, therapy, decision-making, MCI

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Cognitive dysfunction is the central symptom of dementia and a cause of distress to both the person and his care-givers. Affecting attentional, mnesic, linguistic and visuospatial abilities it is thus the principal cause of a wide range of disabilities. In the absence of an effective means of reversing the underlying neuropathology of the dementias, treatment has focused on slowing the cognitive deterioration with a view to extending functional independence for as long as possible. Recent advances in the treatment of the cognitive deficits seen in dementia have taken into account sub-types of dementia and exploring the possibilities of intervening preventively at pre-clinical phases of mild cognitive decline. Finally the question is raised as to whether cognitive deficits in dementia prevent patients from making decisions about the treatment of their cognitive deficit.

Cognition and type of dementia.

Increasing evidence for differences in profiles of cognitive loss and rate of cognitive deterioration according to type of dementia has led to the exploration of 'tailored treatments' according to dementia sub-type.

Alzheimer's disease (AD). Following observations of substantial presynaptic cholinergic abnormalities in the post-mortem brains of persons with dementia, cholinergic treatments have become the dominant therapeutic approach for the stabilization of cognitive deficits. Results so far have been relatively modest. An extensive Cochrane Collaboration review (1)** recently concluded that of the 13 randomized, double-blind placebo controlled trials so far conducted with donepezil or rivastigmine or galantamine, that treatment for periods of 6 months to one year is efficacious in improving cognitive deficits as measured by the ADAS-Cog Scale in mild to moderate AD, but that it is not possible using clinical criteria to identify those who will respond to treatment. The authors also conclude that there is little difference between the type of treatment in terms of efficacy but that there appears to be less adverse effects with Donezepil. Titration with Donezepil was also considered to be easier and lowered doses could be considered. However, a once-daily formulation of galantamine has been recently proposed (2). A recent study of age effects (3) concluded that AD patients under 75 years of age have a better treatment response to rivastigmine than to donepezil which appears to be due to the inhibition of BuChE in addition to AChE by rivastigmine. AD patients with symptoms suggestive of concomitant Lewy body pathology also appear to have a better treatment response to rivastigmine than to donezepil, and also appear to have fewer adverse effects on either drug than AD patients without Lewy bodies (4).

Recent reviews have questioned the cost-effectiveness of anti-cholinergic treatments given that less than 20% of Alzheimer disease patients are moderate

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responders (5; 6). A number of possible reasons have been suggested to explain variable treatment response (for example the importance of forebrain acetylcholine in cognition and memory may have been overestimated, and numerous other neurotransmitter deficits may be implicated in AD-related cognitive deficits which may limit the potential effect of increasing Ach levels alone). The reasons for treatment failure remain unknown but pioneering pharmacogenetic studies on the other hand have demonstrated that the therapeutic response in Alzheimer's disease is genotype-specific and estimate that pharmacogenomic factors may account for 60-90% of the cognitive improvement observed (5)*. The development of pharmacogenomic/genetic protocols for the estimation of individual treatment response is therefore feasible and may lead to the development of more cost-effective treatments.

An alternative strategy is based on observations of overactivity of the excitatory amino acid glutamate, recognized as a cause of neurotoxicity. Strategies to block its binding site on the NMDA receptor have been tried to reduce this excitotoxicity which is known to favour tangle formation. The drug memantine, a glutamate blocker, has thus been licensed for use in moderate to severe AD. A recent review by the Cochrane Dementia and Cognitive Improvement Group found a six month beneficial effect on cognition in moderate to severe AD, but the effects on mild to moderate AD remain unknown (7). A report of a recent case suggests that memantine may also reduce behavioural disorder and thus permit the withdrawal of neuroleptic treatment (8). It has been shown, however, that both donepezil and memantine have effects on other neurotransmitter systems (notably on extracellular levels of serotonin, norepinephrine and their metabolites) (9). Such studies suggest the need to examine further the other neurotransmitter systems involved in cognitive disorder, as well as the diverse molecular pathologies associated with cognitive decline (neurotoxic peptides, interleukins etc). Stephenson et al. (10) propose an alternative approach by identifying a common receptor shared by diverse proteins implicated in AD with a view to ultimately designing a "one drug multiple receptors" therapeutic strategy.

Alternative non-specific approaches to improving cognitive performance continue to be explored, notably the use of vitamin supplements, statins and oestrogens. The observation of high blood homocysteine levels in dementia and vascular disorders has led to some interest in the use of folic acid to improve cognitive functioning, supplemented by vitamin B12 to counter undiagnosed B12 deficiency. An analysis of studies reported to date by the Cochrane register showed no effect of 750 mcg of folic acid per day on cognition in healthy women or patients with cognitive decline or dementia. Folic acid plus vitamin B12 was, however, found to reduce serum homocysteine levels. The authors concluded that more trials are needed (11). Data from the Canadian Longitudinal

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Study of Health and Aging has reported that antioxidant vitamin supplements appear on the other hand to have a protective effect in relation to cognitive decline, but without reducing the incidence of AD or other forms of dementia (12). Consumption of fatty fish was found to be associated with a reduced risk (28%) of AD-related cognitive decline for those without an ApoE 4 allele (13).

While previous case-control studies have suggested a protective effect on cognitive performance with statin use, recent results from the Cardiovascular Health Study (14) have shown no effect of statins on the development of AD-related cognitive decline or vascular dementia, suggesting that should such an effect exist it may be limited to a sub-group of persons at risk. While there has been past evidence for improvement in cognitive functioning (principally verbal memory) in post-menopausal women taking hormonal replacement therapy, with four recent meta-analyses converging to suggest a positive protective effect on AD (reducing risk by 29 to 44%) observations are nonetheless conflicting, suggesting there may be a sub-group of hormone-sensitive women for whom such therapies may be of greater benefit than for others (15). Given the secondary effects of oestrogens and their related health risks, particularly the cerebrovascular system, the use of selective estrogen receptor modulators is an alternative which has yet to be evaluated. A recent sudy of raloxifene in postmenstrual women with osteoporosis found that 120 mg per day, but not 60 mg perday, significantly reduced risk of AD and had some protective effect against milder forms of cognitive impairment (16).

A number of low-risk, low side-effect approaches are also being examined. Ginkgo bilboa is still commonly used in Europe as a neuroprotector and to enhance cognition in normal elderly, but whether or not it is able to reduce cognitive symptomatology or delay onset of AD is still undetermined. A further double-blind placebo-controlled trial on 513 AD patients found no difference between placebo and treated groups in terms of cognitive functioning over 26 weeks (17), however the authors suggest that lack of decline in the placebo patients may have compromised the sensitivity of the trial to a treatment effect. An eight year placebo-controlled randomized trial on 3000 subjects is currently underway (the GEMS study, 18) which will hopefully clarify its potential role in reducing cognitive decline. In Asia there has been increased interest in the use of chinese medicine as a means of alleviating cognitive symptomatology with some limited success (19). Finally a randomized controlled trial of Cognitive Stimulation Therapy (20) showed a continuous 6 months improvement in cognitive function provided maintenance sessions were provided. The potential utility of these types of treatment in conjunction with other types of therapy remains to be evaluated.

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Vascular dementia (VaD)or mixed dementia. There is presently evidence-based data supporting the targeting of neurotransmitter deficits in VaD, notably the treatment of an acetycholine deficit even in the absence of AD, as vascular factors appear to play a central part in the onset of cholinergic neuronal abnormalities in both VaD and AD (21). A recent combined analysis of two trials found that VaD patients treated with Donepezil showed significant benefit in cognition and associated instrumental activities of daily living (22). A recent Cochrane review (7) found no significant six month effect on cognition in VaD with memantine. Use of calcium channel blockers has also been proposed but little evidence for their efficacy was reported due to lack of clinical data when the first Cochrane review was performed in 2002, however the more recent third-generation dihydropyridine calcium antagonists have demonstrated clear improvement in carotid atherosclerosis (23) and thus offer promising future treatment for cognitive disorders in VaD.

Dementia with Lewy-bodies (DLB). The nosological status of this disorder remains uncertain – notably its relationship to AD and Parkinson's disease; its clinical presentation being influenced in particular by the extent of co-occurring AD pathology. Given that cholinergic deficiency in DLB is even more severe than in AD, acetylcholinesterase inhibition has been the treatment of choice with most studies continuing to show significant improvement in both cognitive and behavioural symptoms in all studies. A recent study reports the use of memantine with DLB (24), concluding that it may be safely used in patients with DLB, many of whom show beneficial effects in memory performance. Some patients did, however, worsen or respond adversely to the drug, suggesting the need for further studies. Authorisation has also been given for the use of rivastigmine in Europe for cognitive dysfunction in Parkinson's disease.

Tailored or common treatments ?

While differences in patterns of cognitive dysfunction have been observed between dementia sub-types, randomized control studies suggest they mainly respond to common treatments thus raising numerous questions concerning the underlying biological mechanisms related to cognitive decline observed in different types of dementia. Recent studies show considerable interaction between the different physiopathological processes implicated in cognitive degeneration; the protein pathologies (tau, amyloid, alphasynuclein) being linked in a non-random way (25). This common physiopathological interface suggests the desirability of seeking new treatment approaches applicable to all dementia sub-types.

Preventing cognitive decline

Following earlier reports that treating hypertensive patients reduced dementia risk, studies such as SCOPE (26; 27) and ALLHAT (28) have published results

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suggesting that this may be a possible approach to the reduction of cognitive symptoms before they degenerate into dementia. The large SCOPE study (2477 treated subjects and 2460 controls) recently reported benefits of candesartan treatment for both cognitive functioning and quality of life. There is subsequently increasing interest in the development of preventive programmes targeting a range of risk factors, notably those linked to cerebrovascular changes such as hypertension, lipid levels, and more recently, diabetes. A recent meta-analysis of 14 longitudinal population-based studies found higher rates of cognitive decline leading to both vascular dementia (six of nine studies) and AD (8 of 13 studies). Vascular disease, changes in glucose, insulin and amyloid metabolism appear to underlie the pathophysiology (29)*. These findings together support previous recommendations that a combined treatment approach of a statin, blood pressure stabilizers aspirine and folic acid to reduce serum homocysteine over age 55 be implemented to protect cognitive functioning (30).

The development of diagnostic algorithms for the identification of sub-clinical cognitive deficits, notably Mild Cognitive Impairment (MCI), has given rise to new treatment trials targeting this patient group. As the diagnosis of this syndrome has focused principally on memory problems, it is not surprising that the cholinesterase inhibitors have emerged as the preferred form of treatment (31). However more recent studies cast some doubt as to whether the cholinergic model holds up in MCI – regional up-regulation of choline acetyltransferase in MCI suggesting some form of compensatory mechanism (32) and that the course of MCI to dementia is non-linear . Despite this all three currently marketed ChEIs are undergoing long-term trials in MCI. A first double-blind study of Vitamine E plus Donepezil recently published (33) suggest Donepezil to be associated with a slowing in the rate of cognitive decline, notably memory, in the first 12 months only with no benefit from Vitamin E. A recent study has also suggested that many of the medications taken by elderly persons have anticholinergic activity which although probably not increasing risk of dementia, are likely to cause cognitive decline sufficient for the person to be classified as MCI (34).

Cognitive enhancement and treatment decisions

Finally, some recent studies have raised the circular question as to whether elderly persons with cognitive impairment are excluded from making decisions concerning treatment with cognitive-enhancing drugs which in turn may improve decision-making capacity. Patient interviews with AD patients with mild to moderate cognitive disorder found almost all wish to participate, whereas only 71% of caregivers thought their relative would wish to make such decisions (35). Caregivers also appeared to be poor judges of whether their relatives were capable of decision-making, and that female spouse care-givers of less demented persons were more likely to involve the AD patient in decision-

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making with regard to cognitive therapies (36). According to a prospective cohort study of 77 AD patient-carer dyads, the level of care-giver reported patient involvement in decision-making appears to decline when MMSE scores fall below 20 with older age of patients and mounting care-giver burden being the most significant predictors of exclusion from decision-making (37).

Conclusion

While different patterns of cognitive deficit may be identified in dementia, the trend is towards a common treatment. Cholinergic therapies appear to be effective but only for a short period of time and in some persons, however pharmacogenetic studies may in the future indicate those persons most likely to benefit from treatment. Preventive therapies for milder forms of pre-clinical cognitive deficit also appears to be promising with the future possibility of combined treatments targeting multiple risk factors.

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* Cacabelos 2005 Pharmacogenetics is clearly one of the most interesting new avenues for more accurate application of cognitive therapies. This is a very clear overview of possible applications

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