

EDITORIAL

Cholinesterase inhibitors: in search of cholinergic deficits

Ross Overshott & Alistair Burns

The 2001 National Institute for Clinical Excellence (NICE) guidelines for the use of cholinesterase inhibitors were instrumental in increasing the availability of these drugs to people with Alzheimer's disease, as well as heightening awareness of dementia among professionals and the public. They provided legitimacy to the prescribing of cholinesterase inhibitors and, along with the National Service Framework for Older People (Department of Health, 2001), have been a major driving force in the development of services for older people, for example memory clinics.

It was hoped by many that cholinesterase inhibitors would be used in the future for the treatment of other conditions where there is a cholinergic deficit. However, their use in Alzheimer's disease, never mind other conditions, is now in doubt following the publication this spring of the draft revised NICE guidelines (National Institute for Clinical Excellence, 2005). These confirm the findings of the 2001 guidelines that donepezil, rivastigmine and galantamine are effective and safe in the treatment of Alzheimer's disease, but it is concluded that, on current evidence, these drugs are not cost-effective and should not be prescribed by the National Health Service (NHS). Use of the N-methyl-D-aspartate (NMDA) antagonist memantine in Alzheimer's disease is also not recommended. If the draft guidelines come to fruition, the implications for NHS patients are huge. Many would still receive the medications through private prescriptions and there would be an increase of unmonitored use. For those who are unable to afford cholinesterase inhibitors there may be an increase in the use of neuroleptics to manage hallucinations, agitation or other behavioural disturbances. However, in light of the recent concerns over the safety of unlicensed treatments

such as antipsychotic medication, it seems unwise to promote their increased use.

Other potential consequences are equally worrying. With the lack of availability of cholinesterase inhibitors, patients and family members would have less incentive to seek medical help for memory problems and general practitioners might be less likely to pursue a diagnosis. This could lead to patients presenting to services later in the course of their illness, perhaps in a crisis. This would increase the pressure on already busy community services and might increase the cost of care. With a reduction in emphasis on diagnosis and treatment, there will be an increase in the stigma associated with dementia and previously commonly held views that dementia is a natural consequence of old age will return. This might lead to the disbanding of memory clinics, which would reduce the opportunities of diagnosing not only dementia but also other conditions, such as depression, that present with cognitive difficulties.

Such concerns resulted in the largest ever response (over 8000) during the initial consultation period for the new NICE guidelines, with carer and professional interests spearheaded by the Alzheimer's Society and the Old Age Faculty of the Royal College of Psychiatrists, respectively. This period of uncertainty may provide time for researchers and clinicians to reflect on what evidence is needed for ongoing prescribing and for use of cholinesterase inhibitors in other conditions.

The NICE appraisal

With increasing demands on NHS resources, NICE has a responsibility to recommend only treatments that prove to be cost-effective. It has concluded from

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its evaluations that cholinesterase inhibitors do not fit this description. There are, however, areas of concern with the recent NICE appraisal. NICE had underestimated the cost of full-time institutional care and had not considered fully the potential benefits the medications can have for carers. For example, the use of cholinesterase inhibitors can reduce carer input by half an hour to an hour a day (Sano *et al*, 2003). For a professional carer this constitutes a minimum saving of £2.50 a day, which is also the cost per day of treatment with a cholinesterase inhibitor. The benefits of a similar reduction in carer time for an informal carer are easy to imagine but more difficult to quantify.

The economic model used by NICE does not reflect the use of the drugs in clinical practice, where only patients who respond to treatment continue to receive the medications. In practice, non-responders acquire no benefit from treatment, but the cost is relatively low as they receive the drugs for a few months and only need two or three out-patient appointments. The NICE model, however, assumed that all patients are treated and continue treatment irrespective of their response. Their analysis therefore included patients who accumulate costs but gain no benefit, and who in reality would have their treatment discontinued and the cost curtailed.

The assessment of quality of life of people with dementia is difficult. There is no consensus definition and it is only recently that dementia-specific quality of life instruments such as the Dementia Quality of Life Scale (Brod *et al*, 1999) have been developed. There are many potential predictors or determinants of quality of life in dementia. These include dementia severity, functional impairment, neuropsychiatric symptoms and caregiver factors.

NICE mistakenly simplified the matter by using stage of dementia as a proxy for quality of life for their quality-adjusted life year calculation. In a mistaken attempt to simplify the matter, NICE tried using stage of dementia as a proxy for quality of life in quality-adjusted life year calculations. They had previously recognised the difficulties of evaluating quality of life and did not use these calculations in the preparation of the 2001 guidelines (National Institute for Clinical Excellence, 2001). In their new draft guidelines they did not take such a heedful approach. Researchers, however, must take notice of NICE's concerns and future studies must concentrate more on the measurement of quality of life in dementia. Specific dementia quality of life measures should be utilised and more emphasis should be placed on evaluating the benefits the medication may have for carers, as well as patients.

Despite the problems with NICE's analysis, it is right to question the strength of evidence for the cost-effectiveness of cholinesterase inhibitors. Future research must address these concerns.

Other uses of cholinesterase inhibitors

Cholinesterase inhibitors have been tested extensively in Alzheimer's disease and are the current drug treatment of choice. There is, however, increasing evidence of their effectiveness in other conditions. They should be considered as symptomatic treatments which may prove beneficial in conditions affecting the cholinergic system. If there is to be more widespread use of these drugs, then as in Alzheimer's disease, cost-effectiveness as well as clinical effectiveness will need to be demonstrated.

Vascular dementia

Cholinergic deficits are well documented in vascular dementia, the second most common type of dementia, independently of any concomitant Alzheimer's disease. The basal forebrain nuclei and cholinergic pathways are particularly vulnerable to ischaemia. Erkinjuntti *et al*, 2004 have shown a modest improvement in cognitive and global function as well as stabilisation of activities of daily living following treatment of vascular dementia with cholinesterase inhibitors. There is also evidence of improvement of some psychotic symptoms associated with dementia, such as hallucinations and apathy. There is insufficient evidence regarding improvements in quality of life and delay in institutionalisation. The drugs currently do not have a licence for vascular dementia and without better evidence of cost-effectiveness, even if licensed, they might not meet NICE's requirements.

Lewy body dementia and dementia in Parkinson's disease

Cholinergic deficits are also prominent in patients with dementia with Lewy bodies and dementia associated with Parkinson's disease. Both conditions are associated with cognitive slowing, attentional deficits, memory impairment and psychotic symptoms, particularly visual hallucinations. The treatment of patients with these types of dementia is challenging. Antipsychotic medications, even atypical ones, can precipitate a profound, even fatal worsening in the motor symptoms of patients with

parkinsonism. On the other hand, dopaminergic agents for parkinsonism frequently cause worsening of hallucinations and cognitive function. Cholinesterase inhibitors have therefore offered hope in the treatment of these dementias, which are difficult to manage. Rivastigmine has been the drug most studied and has been shown to improve cognitive functioning and neuropsychiatric symptoms, particularly hallucinations, in patients with Lewy body dementia (McKeith *et al*, 2004) and those with vascular dementia (Emre *et al*, 2004). As the presence of neuropsychiatric symptoms is associated with reduced quality of life in dementia, cholinesterase inhibitors are likely to offer meaningful benefits for these people.

Delirium

Cholinesterase inhibitors have a potential use in the prevention and treatment of the symptoms of delirium. Delirium has a multitude of causes and its pathogenesis is not clearly understood. It is most likely that delirium represents a response to diffuse cerebral dysfunction, reduced metabolism and disordered neurotransmitter synthesis. The strongest evidence is for disturbance of cholinergic neurotransmitter synthesis, which would explain the reduction in attention which is a key symptom in patients with delirium. In clinical practice, delirium is poorly detected but is associated with several adverse outcomes, including length of hospital stay, poor functional status, persistent cognitive impairment and need for institutional care (Cole & Primeau, 1993). There have been several reports of cholinesterase inhibitors preventing episodes of delirium (e.g. Dautzenberg *et al*, 2004) as well as reducing duration and symptoms of established delirium (e.g. Moretti *et al*, 2004a). There are, however, no current published randomised controlled trials, and research in delirium is difficult to conduct. It will therefore likely be many years before cholinesterase inhibitors could be considered a frontline treatment for delirium. However, if it is confirmed that they are effective in delirium by reducing symptoms, duration and length of hospital stay, then the benefits would be highly significant to patients and services.

Traumatic brain injury

There has also been interest in the use of cholinesterase inhibitors in patients with traumatic brain injury in whom cholinergic systems are disrupted. Donepezil has been shown to increase scores on neuropsychological tests of short-term memory and sustained attention in these individuals (Zhang

et al, 2004). It is hoped that this may be a viable approach to restore memory and attention, since these impairments are known to have a significant impact on a person's ability to function independently and to return successfully to previous vocational activities following traumatic brain injury.

Other possibilities

Other areas where cholinesterase inhibitors may have a future role include the treatment of fronto-temporal dementia (Moretti *et al*, 2004b), Korsakoff's syndrome (Cochrane *et al*, 2005), Huntington's disease (Petrikis *et al*, 2004) and, if evidence improves and is consistent, mild cognitive impairment (Saykin *et al*, 2000).

The future

The recent NICE draft guidelines on the use of cholinesterase inhibitors in Alzheimer's disease highlight the need for improved evidence of quality of life and cost-effectiveness to ensure that patients are still able to receive these medications under the NHS. The initial NICE guidelines in 2001 reduced the post-code prescribing of cholinesterase inhibitors; any new restriction of prescribing would create a two-tier system, where only those who could afford private prescriptions would receive the drugs. It is almost inconceivable that the only treatment agreed to be effective for a distressing, degenerative condition would be unavailable to NHS patients.

The evidence for the efficacy of cholinesterase inhibitors in the treatment of other conditions is growing. We must, however, be mindful of the recent concerns over their use in Alzheimer's disease, so we can be prepared and have the evidence that would unequivocally allow widespread access to effective treatment.

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Clinical Governance in Mental Health and Learning Disability Services: A Practical Guide

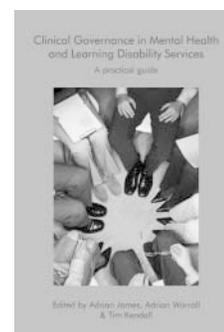
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June 2005, Hardback, 360 pages, ISBN 1 904671 12 8, Price £35.00



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