SHARED CARE PROTOCOL CHOLINESTERASE INHIBITORS IN ALZHEIMER'S DEMENTIA

Introduction

Alzheimer's disease is the most common cause of dementia. It is characterised by an insidious onset of global mental impairment, and normally slow deterioration. The estimated prevalence of Alzheimer's disease of mild to moderate severity in Tayside is about 1745 patients.

As outlined in NHS circular No 1992 (GEN) 11, when a Consultant considers that a patient's condition is stable he/she may seek the agreement of the GP to share care. Due to the nature of the management of patients with Alzheimer's disease using cholinesterase inhibitors, it may not be possible fully to discharge the patients from the hospital back to their GP while treatment is continuing. Therefore a system of shared care with shared commitment between the hospital and the GP is desirable. This shared care protocol aims to identify the relative responsibilities of primary and secondary care clinicians. In keeping with the draft "NHS Tayside- Principles for the establishment of shared care agreements", this protocol has been developed with clear benefits to patients in mind; equity of service across NHS Tayside, risk management in terms of the completeness of prescribing data available to GP and other community health care professionals, and patient convenience. Sharing care will minimise present risk to the patient, and improve current care.

Treatment of dementia

Currently, most patients with dementia are managed in the community. This document covers the use of Cholinesterase Inhibitors only, and should form part of the multidisciplinary/ multiagency management of people with dementia.

Donepezil, Rivastigmine and Galantamine are cholinesterase inhibitors licensed in the UK.

- Donepezil is a reversible inhibitor of cholinesterase that can be given once daily, and is licensed for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. It is available as tablets and orodispersible tablets, and is taken once a day.
- Rivastigmine is a reversible non-competitive inhibitor of cholinesterase, which is licensed for the symptomatic treatment of mild to moderately severe Alzheimer's dementia or the symptomatic treatment of mild to moderately severe dementia in patients with Parkinson's disease. It is available as capsules and oral solution, and is taken twice a day. Rivastigmine is not recommended for use within NHS Scotland for the treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's Disease.
- Galantamine is a reversible inhibitor of cholinesterase which also has nicotinic receptor agonist properties. It is licensed for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type. It is available as tablets and oral solution for twice daily dosing, or modified release capsules for once daily dosing.

It is intended here to describe appropriate approaches to assessing, implementing and monitoring cholinesterase inhibitor treatment for this condition. The National Institute for Clinical Excellence (NICE) recently reviewed the clinical and cost effectiveness of these drugs for the treatment of Alzheimer's disease[1].The recommendation is that these three drugs should be made available in the NHS as one component of the management of those people with moderate to moderately severe Alzheimer's disease, under specific conditions.

NHS Quality Improvement Scotland (NHSQIS) advises that this NICE appraisal is as valid for Scotland as for England and Wales, with the addition:

- NHSQIS reiterates the view that learning disability specialists are best placed to judge entry and continuation criteria for people with learning difficulties that could be considered equivalent to the general Alzheimer's population [2]

NHSQIS also advises that the Scottish Intercollegiate Guidelines Network (SIGN) guideline 86 "Management of patients with dementia" is consulted for information about the management of dementia.

In line with the amended NICE appraisal in August 2007, it is recognised that:
"When using the MMSE to diagnose moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups…and patients with disabilities." In these cases health care professionals should not rely, or rely solely, on the MMSE in circumstances where it would be inappropriate to do so.

In Tayside it is agreed that patients being considered for therapy should be referred for specialist assessment and treatment. Prescription should not be limited to those living outwith institutional care, although the majority of those receiving the drugs are expected to be residing in their own homes. These drugs should not normally be initiated for patients where dementia is severe, but the patient should not be denied access to other therapies. The following Tayside protocol has been developed from the NICE guidance, taking into account current local practice.

(N.B. Memantine is a NMDA-receptor antagonist that affects glutamate transmission. It is licensed for treating moderate to severe dementia in Alzheimer's disease. Memantine is not recommended for use in NHS Scotland. An exceptional case process applies to clinicians in Tayside wishing to prescribe medicines not recommended for use in NHS Scotland by the Scottish Medicines Consortium.)

PATIENT SELECTION CRITERIA

Being "worried about your memory" is not in itself diagnostic of dementia, nor is carer concern, although this increases the likelihood. Importance must be attached to the presence of functional decline, change in behaviour, personality change and changes in social functioning, employment or driving (should these be relevant).
Thus referrals to psychiatric services should not simply concentrate on problems with memory. It would be better for primary care referrals to concentrate on evidence of changes in other domains rather than rating cognition by scales such as the MMSE, although inclusion of such information would be a welcome extra.

Patients in whom dementia is suspected should be referred by their general practitioner to the local specialist. A decision on treatment will be made using the criteria in Panel 1.

Panel 1

Tayside recommendations

The decision to treat should be based upon:

- A diagnosis of "probable Alzheimer's disease" according to (NINCDS/ADRDA) criteria, made by a clinician with specialist experience of the diagnosis and management of dementia.
- Dementia of moderate or moderately severe degree, categorised by cognitive and non-cognitive domains such as functional decline, change in behaviour, personality change and changes in social functioning or employment (should that be relevant).
- NICE defines dementia of moderate or moderately severe degree as: "Those with a Mini Mental State Examination score of between 10 and 20 points." NICE also recommends: "Health care professionals should not rely on the MMSE score in certain circumstances. These are:

1. In those with an MMSE score greater than 20, who have moderate dementia as judged by significant impairments in functional ability and personal and social function compared with premorbid ability
2. In those with an MMSE score less than 10 because of a low premorbid attainment or ability or linguistic difficulties, who have moderate dementia as judged by an assessment tool sensitive to their level of competence
3. In people with learning disabilities
4. In people who are not fluent in spoken English or in the language in which the MMSE is applied"

For patients in included in 3 or 4 above, see the guidance in the amended NICE appraisal (amended August 2007)

- Ability to comply with medication

PATIENT EXCLUSIONS

These drugs are contra-indicated in patients with known hypersensitivity to the active ingredients or excipients. Rivastigmine and galantamine are contra-indicated in severe hepatic impairment. Patients with severe obstructive airways disease, or established sick sinus syndrome should not be prescribed cholinesterase inhibitors, and they should be used with extreme caution in severe prostatism. The summary of product characteristics should be consulted for other contra-indication before prescribing the drugs.
The drugs should not normally be initiated for patients with severe dementia.

MONITORING

- Patients who are commenced on treatment who are classified as "responders" will remain on treatment long-term. The frequency of review will be determined in part by the degree of patient distress whilst engaging in the re-assessment process. Information from formal and informal carers will be used to evaluate ongoing response.

All patients meeting the inclusion criteria should receive further appropriate tests using cognitive, non-cognitive and observer rating scales. A flowchart (Appendix 1) is provided as an example of treatment options. As there is no evidence that any of the agents is superior to any of the others,

any of the three drugs could be initiated as appropriate to the patient's condition. The clinicians' experience in the use of cholinesterase inhibitors may inform this decision.

The patient and carer should be informed of possible side-effects, and what action to take in the event of serious adverse reactions, including which health care professional to contact. The first specialist review (usually within the first 4 weeks of treatment) should include a review of compliance. This may take the form of a telephone contact. Should side- effects be severe, treatment with cholinesterase inhibitor should be withdrawn, though reintroduction at the same or a lower dose may be reasonable after resolution of the symptoms**.** While cross-sensitivity between these agents may be anticipated, in practice a trial of an alternative agent may be undertaken where the possible benefits are felt to outweigh the risks.

Titration to the optimum dose may take several weeks to achieve, although it may be achieved within 4 weeks. As there is insufficient evidence to recommend specific titration times or optimum dose, the clinicians' judgement will dictate these. The patient may be reviewed after around 12 weeks treatment, depending on local protocol. All patients should be seen after a further 12 weeks, i.e. (a total time of 24 weeks from initial prescription) for assessment of benefit from drug therapy.

Assessment of benefit will usually include at least 2 of the following;

- No decline or an improvement in cognitive test score
- Cognitive, functional or behavioural improvement
- A rating of global improvement by examining clinician
- Carer's views on the patient's condition

Following this assessment the drug should be continued only where there has been an improvement or no deterioration in MMSE score, together with evidence of global improvement on the basis of behavioural and/or functional assessment.

All patients who show improvement at 24 weeks should be offered continued cholinesterase inhibitor therapy and be reviewed six monthly thereafter.

Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally-agreed protocols for review.

Continuity of care by an individual GP is important. The GP should arrange a face to face meeting with the patient and carer as soon as they are brought into the shared care agreement so that they can become familiar with the diagnosis and family circumstances particularly if they are not already familiar with the patient.

DISCONTINUATION/ TREATMENT END-POINTS

- Except in the case of pressing physical illness or poorly tolerated side-effects the decision to discontinue treatment will rest with Secondary Care specialists.
- The decision to terminate treatment in patients with severe dementia will take into account previous response, previous and current language difficulties, current behaviour, social functioning, carer opinion and physical condition. All of these may influence intellectual testing, performance of which in itself will be an insufficient indicator to determine whether or not the patient is withdrawn from treatment.

Entry into care itself does not indicate a failure to respond to treatment, and in itself is not an indication for discontinuation. In most cases it will be possible to identify the optimum time for discontinuation some time in advance of doing so. If a patient deteriorates rapidly (within 4-6 weeks) following discontinuation of treatment, it is acceptable to recommence treatment at the previous dosage.

TREATMENT SCHEDULE

Donepezil tablets or orodispersible tablets initially 5mg once daily at bedtime, increased if necessary after one month to 10mg daily; maximum 10mg daily.
Rivastigmine initially 1.5mg twice daily, increased in steps of 1.5mg twice daily at intervals of at least 2 weeks according to response and tolerance; usual range 3-6mg twice daily; maximum 6mg twice daily. Rivastigmine transdermal patches initially 4.6mg/24 hours for at least 4 weeks, usual maintenance 9.5mg/24 hours. (Note: Rivastigmine oral solution is more expensive than other formulations).
Galantamine initially 4mg twice daily for 4 weeks increased to 8mg twice daily for 4 weeks; maintenance 8-12mg twice daily. Galantamine modified-release capsules initially 8mg once daily for 4 weeks, increased to 16mg once daily for 4 weeks, maintenance 16-24mg daily.(Note: Galantamine oral solution is more expensive than other formulations)

MANAGEMENT OF SIDE-EFFECTS

As with all drugs, presentation of severe side-effects should lead to discontinuation of treatment. Where side effects are mild, they may respond to an initial reduction in dose and more gradual dose titration thereafter. Some side-effects, such as nausea and vomiting, may be transient in nature. Prescription of anti-emetics with a low potential for anticholinergic side-effects, and ensuring adequate fluid intake, may be helpful in managing nausea and vomiting.

PRESCRIPTION

The decision to prescribe should be taken by the local specialist. New prescriptions should be initiated by hospital specialists and dispensed where appropriate, in primary or secondary care. Prescribing responsibility will transfer to primary care only after liaison by the hospital specialist with the patient's GP. The timeframe for this may be different for each patient and GP, but will usually be between 4 weeks and 6 months after commencement of treatment. As specified above, when the consultant considers that a patient's condition is stable he/she may seek the agreement of the GP to share care.

PATIENT/ CARER'S ROLE

The patient and carer can expect to be provided with sufficient advice regarding the possible benefits and risks of treatment to allow them to make an informed decision about cholinesterase inhibitor therapy. They can expect regular follow-up assessments by a specialist, should they opt for treatment. They can expect that care will be shared with their own GP as soon as practicable, to allow easier access to medicines.

The patient and carer will be responsible for attending appointments at the hospital (and GP if necessary). They will also be responsible for collecting prescriptions from the hospital or community pharmacy, and ensuring the prescribed medication is taken as directed. The patient and carer will be expected to monitor the patient's day-to-day functioning, and report any suspected side-effects of medication to their GP or consultant.

MEDICAL STAFF CONTACT DETAILS

Perth and Kinross	Dr P Connelly, Murray Royal Hospital, Perth
Angus	Dr S Logie, Sunnyside Royal Hospital, Montrose
Dundee West	Dr S McLean, Royal Dundee Liff Hospital
Dundee East	Dr J Farrell, Glaxo Day Hospital, Ashludie

PHARMACEUTICAL SUPPORT STAFF

Perth and Kinross	Mrs A McDowell, Senior Pharmacist, Murray Royal Hospital
Angus	Clinical Pharmacist, Sunnyside Royal Hospital
Dundee	Mrs Christine Morton, Pharmacy Department, Carseview Centre

OTHER SUPPORT STAFF

Dundee Anticholinesterase nurse
Billy McLaren, Orleans Centre

REFERENCES

1. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease. National Institute for Health and Clinical Excellence Technology Appraisal Guidance no 111, November 2006. http://www.nice.org.uk/guidance/TA111
2. Dr J Nelson, Head, Clinical Effectiveness Co-ordination Unit, NHS Quality Improvement Scotland. E-mail November 2006 for action, Chief Executives NHS Boards.

Appendix 2- responsibility chart for treatment with cholinesterase inhibitors for Alzheimer's disease.

Responsibilities of the hospital consultant	**Responsibilities of the General Practitioner**
<u>For patients initiated on treatment by the consultant</u>: • ***Diagnosis*** that the form of dementia is Alzheimer's disease; • ***Assessment***: including tests of cognitive, global and behavioural function, of activities of daily living and of likelihood of compliance; • ***Selection & initiation of treatment***; and decision to change to alternative in cases of poor tolerance • ***Prescribing*** of initial treatment, and dosage titration, until agreement with the patient's GP has been reached for prescribing by the GP. • ***Liaison*** with the GP to arrange transfer of responsibility for prescribing. Also liaison with the hospital pharmacy to ensure continuity of supply via hospital or community pharmacy. • ***Review*** at around 4, 12 and 24 weeks and 6 monthly thereafter as appropriate, booked via the hospital out-patient system; • ***Decision to stop treatment*** in cases of non-response or non-compliance, serious adverse effects, deterioration below an MMSE of 12 with clear deterioration in daily functioning • ***Provision of relevant information to the GP in writing, within as short a time as possible following consultation*** which may include: diagnosis; other relevant clinical & product information; treatment to date (doses, times etc); treatment to be undertaken by the GP (dose, route, frequency, etc.); review arrangements; possible side effects of treatment; system for monitoring and recording side-effects; useful contact names & numbers; • ***Patient review/reassessment when requested by the GP;*** • ***Provision of further information or advice*** as required by the GP;	**<u>For patients initiated on treatment by the consultant</u>:** • ***To prescribe medication*** after discussion with specialist, and at any point after initiation as long as both practitioners feel this is appropriate • ***To provide continuity of care*** and to arrange an initial face to face meeting with the patient and carer to become familiar with the diagnosis and family circumstances if they are not already familiar with the patient. • ***Routine monitoring*** – tolerance, side-effects etc.; • ***Provision of relevant information to the consultant*** to support the review process. • ***Provision of general practitioner services*** to patients for other concomitant medical conditions • ***Decision to stop treatment*** in cases of severe adverse effects • ***Dose titration and monitoring*** may be undertaken by appropriately trained GPs if desired **Responsibilities of the community pharmacist/ practice pharmacist** • ***Monitoring for signs of poor compliance*** in the form of prescriptions written or dispensed but not collected, or large amounts of cholinesterase inhibitors being returned for destruction. • ***Provision of information about medication*** in a form appropriate to the patient and carer.

Glossary

AD Alzheimer's disease

NINCDS-ADRDA National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association

MMSE Mini-Mental State Examination Cost of treatment (BNF No 54, September 2007 prices)

Donepezil 5-10mg/ day	£2.27-£3.18 per day	£830- £1160 per year
Rivastigmine 3-6mg twice a day	£2.29 per day	£835 per year
Rivastigmine transdermal patches	£2.79 per day	£1018 per year
Rivastigmine oral solution 3-6mg twice a day	£5.83-11.66 per day	£2128-£4256 per year
Galantamine 8-12mg twice a day	£2.44- £3.00 per day	£890 - £1095 per year
Galantamine XL 16-24mg daily	£2.44- £3.00 per day	£890 - £1095 per year
Galantamine oral solution 8-12mg twice a day	£4.80-£7.50 per day	£1752-£2738 per year