Shared Care Guideline

Donepezil, Galantamine, Rivastigmine and Memantine - Alzheimer's Disease

Executive Summary

- This guideline covers the use of donepezil, rivastigmine, galantamine (AChEIs) and memantine in adult patients with a diagnosis of Alzheimer's disease in line with NICE TA 217.
- Acetylcholinesterase inhibitors are one component of the management of people with mild to moderate Alzheimer's disease; memantine is an option for patients with moderate disease who are intolerant of first line AChEIs or have a contra-indication to AChEIs and for patients with severe disease.
- Responsibilities:

  The GP is expected to:
  - Forward blood test results to specialist with referral
  - Initiate treatment and manage repeat prescribing as advised by the specialist during the first three months of treatment and beyond
  - Monitor for side effects and drug interactions
  - Monitor patient's overall health and well being beyond the first three months of treatment

  The specialist is expected to:
  - Confirm the diagnosis and assess the level of severity of the disease
  - Discuss treatment options with patient and carers and provide written information on the medication
  - Advise the GP in writing of the initial treatment dose and any subsequent changes in dose during the first three months of treatment
  - Monitor patient compliance with medication
  - Monitor and evaluate side effects reported by the patient or GP during the first three months of treatment
  - Assess for evidence of response at the end of three months and inform GP of maintenance dose

- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope
Adult patients with a diagnosis of Alzheimer's disease

2. Aim
To clarify the responsibilities and roles of specialists and GPs in the drug treatment of Alzheimer's disease

3. Introduction
NICE Technology Appraisal Guidance (TA 217 – Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease) published March 2011 indicates that the ongoing management of Alzheimer's patients should take place in primary care. It is acknowledged by the authors of this SCG that the NICE guidance is due for review and recommendations may change in light of more recent evidence and accepted practice.

Acetylcholinesterase Inhibitors

The use of three AChE inhibitors Donepezil, Galantamine and Rivastigmine for Alzheimer's disease was reviewed by NICE in March 2011. NICE recommends that these drugs should be available in the NHS as one component of the management of people with mild to moderate Alzheimer's disease.

AChE inhibitors have been shown to be effective for some, but not all patients with mild to moderate Alzheimer's disease. There is no evidence to show that they slow progression of the disease or affect survival. They may show a modest effect on cognition and some behavioural benefits The least expensive of the three drugs should be prescribed taking into account required daily dose and the price per dose once shared care has started. However if this is not possible due to an adverse event profile, problems with concordance, medical co-morbidity, drug interactions or dosing profiles an alternative AChE inhibitor could be prescribed.

Generic donepezil is the least expensive AChE inhibitor and therefore on that basis should be the first treatment choice unless there is good reason not to use it.

This shared care guideline also covers patients with dementia associated with Parkinson's disease and Lewy Body Dementia for whom the same criteria for treatment should be applied as for Alzheimer's disease
(NB rivastigmine capsules, not patches, are licensed for dementia in Parkinson's disease)

NMDA receptor antagonist

Memantine blocks the effects of elevated levels of glutamate that may otherwise lead to neuronal dysfunction. It does not slow the progression of Alzheimer's disease. It appears to have behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms and may therefore have the potential to reduce the need for antipsychotics. NICE recommends monotherapy with memantine as an option for managing Alzheimer's disease for people with:

- moderate Alzheimer's disease who are intolerant of or have a contraindication to cholinesterase inhibitors or

- severe Alzheimer's disease

Assessment of severity of Alzheimer's disease by specialist

Severity of Alzheimer's disease is frequently defined by the Mini Mental State examination (MMSE) score:

- mild Alzheimer's disease: MMSE 21-26
- moderate Alzheimer's disease: MMSE 10-20
- moderately severe Alzheimer's disease: MMSE 10-14
- severe Alzheimer's disease: MMSE less than 10

Whilst this is a scoring system, other tools to assess the severity of the disease are frequently used as an aid to diagnosis.

Specialists should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These circumstances include patients with learning or other disabilities (e.g. sensory impairment), where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent or there are similarly exceptional reasons why the use of the MMSE, or the use of the MMSE by itself, would be an inappropriate tool for assessing the severity of the patient's dementia. In these cases another appropriate method of assessment should be used by specialists.

Treatment

The aims of treatment are to promote independence, maintain function and treat symptoms including cognitive, non-cognitive, behavioural and psychological symptoms.

NICE guidance recommends monotherapy with donepezil, galantamine, rivastigmine or memantine under the following conditions:

A clinical diagnosis of mild to moderate Alzheimer's disease is confirmed (if severe then only memantine can be prescribed) **and**
The patient is considered suitable for treatment by either a psychiatrist, physician specialising in the care of older people or neurologist, any of whom specialise in the care of people with dementia (including those with learning disabilities)

Carer's views of the patient's condition at the start of treatment and at follow-up should be sought.

It may be found that a combination of an AChE inhibitor and memantine is effective. Although this is not anticipated to be a common scenario, GPs may be asked to prescribe both together.

Although NICE recommends stopping treatment when there is no longer any perceived benefit, in light of recent evidence, The Domino-AD trial (Howard, R et al. (2012). Donepezil and memantine for moderate-to-severe Alzheimer's disease. New England Journal of Medicine 2012 March 8; 366(10):893-903) the author's of this SCG would recommend that treatment is continued.

Abbreviations

- SCG Shared Care Guideline
- AChE Acetylcholinesterase
- NMDA N-methyl-D-aspartate
- LFTs Liver function tests
- U&Es Urea and electrolytes
- CPFT Cambridgeshire and Peterborough NHS Foundation Trust
- FBC Full blood count

4. Dose and Administration

Solid oral dose formulations should be used as first line treatment. Other formulations are available if solid oral doses are inappropriate (eg orodispersible tablets, liquids and patches). **Generic Donepezil tablets are the least expensive formulation of an AChE inhibitor.** If by increasing the dose of any treatment the patient experiences intolerable side effects the dose can be reduced or an alternative treatment considered.

- Donepezil tablets: 5mg daily (patient information leaflet says in the evening) increasing to 10mg after 4 weeks if tolerated
  Therapeutic dose range 5-10mg daily
- Galantamine MR capsules: 8mg daily (patient information leaflet says in the morning, preferably with food), increasing every 4 weeks to 16mg then 24mg daily if tolerated
  Therapeutic dose range 16-24 mg daily
- Rivastigmine capsules: 1.5mg twice daily with morning and evening meals increasing every 4 weeks (minimum of 2 weeks) to 3mg, 4.5mg then 6mg twice daily if tolerated
  Therapeutic dose range: 3-6 mg twice daily
  If treatment is interrupted for more than several days, rivastigmine should be re-initiated at 1.5 mg twice daily and re-titrated as above
  Rivastigmine patches: 4.6mg/24hr increasing to 9.5mg/24hr after 4 weeks if tolerated.
  Therapeutic dose: 9.5mg/24hr
  After a minimum of six months of treatment at 9.5 mg/24hr, the treating physician may consider increasing the dose to 13.3 mg/24hr in patients who have demonstrated a cognitive or functional deterioration while on the recommended daily effective dose of 9.5 mg/24hr
- Memantine: 5mg daily, increasing by 5mg each week to 10mg, 15mg and 20mg daily by the fourth week of treatment.
  Therapeutic dose: 20mg daily

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc

5. Adverse Effects

Very common (≥ 1 in 10)

- Donepezil:
  Diarrhoea, nausea, headache
- Galantamine:
  Vomiting and nausea
- Rivastigmine capules:
  Anorexia, nausea, vomiting, diarrhoea, dizziness.
  In patient's with Parkinson's disease also tremor and falls
- Memantine:
  None listed

Common (≥ 1 in 100 and < 1 in 10)

- Donepezil:
  Anorexia, hallucinations, agitation, aggression, abnormal dreams/nightmares, syncope, dizziness, insomnia, vomiting, rash, muscle cramps, urinary incontinence, fatigue
- Galantamine:
  Anorexia, hallucinations, depression, syncope, dizziness, headache, lethargy, bradycardia, hypertension, diarrhea, dyspepsia, abdominal discomfort, hyperhidrosis, muscle spasm, fatigue
- Rivastigmine capsules:
  Agitation, confusion, anxiety, headache, somnolence, tremor, abdominal pain, dyspepsia, hyperhydrosis, fatigue, malaise, weight loss
  In patient's with Parkinson's disease also decreased appetite, dehydration, insomnia, visual hallucinations, depression, dizziness, worsening of Parkinson's disease, movement disorders, bradycardia, hypertension, salivary hypersecretion
- Rivastigmine patches:
  Application site skin reactions (erythema, pruritus, oedema, dermatitis, irritation), delirium, pyrexia, decreased appetite, urinary incontinence, urinary tract infection
- Memantine:
  Hypersensitivity reactions, somnolence, dizziness, balance disorders, hypertension, dyspnoea, headache, constipation, raised LFTs

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Donepezil:
  Seizure, bradycardia, GI haemorrhage/ulcers
- Galantamine:
  Dehydration, auditory and visual hallucinations, seizures, blurred vision, tinnitus, supraventricular extrasystoles, atrioventricular block first degree, sinus bradycardia, palpitations, hypotension, increased hepatic enzyme activity
- Rivastigmine capsules:
  Insomnia, depression, syncope, raised LFTs, falls
- Rivastigmine patches:
  Psychomotor hyperactivity
- Memantine:
  Fungal infections, confusion, hallucinations, abnormal gait, cardiac failure, thromboembolism,

fatigue, vomiting

Rare (≥ 1 in 10000 and < 1 in 1000)

- Donepezil:
  Extra-pyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction
- Galantamine:
  Hepatitis
- Rivastigmine capsules:
  Seizures, angina, gastric and duodenal ulcers, rash
- Rivastigmins patches: Falls
- Memantine:
  None listed

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc

6. Cautions

- AChE inhibitors generally:
  Patients with sick sinus syndrome or conduction defects, active gastric or duodenal ulcers or a predisposition to these conditions, history of asthma or obstructive pulmonary disease, predisposition to urinary obstruction or seizures
- Donepezil:
  Due to possible increased exposure in mild to moderate hepatic impairment dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.
- Galantamine:
  In moderate hepatic impairment dosing should begin with 8 mg MR capsule once every other day, preferably taken in the morning, for one week. Thereafter, patients should proceed with 8 mg once daily for four weeks. In these patients, daily doses should not exceed 16 mg.
- Rivastigmine:
  The use of rivastigmine patches may lead to contact dermatitis. Contact with the eyes should be avoided after handling the patches. Hands should be washed with soap and water after removing the patch.
- Memantine:
  Epilepsy, former history of convulsions or patients with predisposing factors for epilepsy.
  In moderate renal impairment the daily dose should be 10 mg. If tolerated well after at least 7 days of treatment, the dose can be increased up to 20 mg/day according to the standard titration scheme. In severe renal impairment the daily dose should be not exceed10 mg.
  Concomitant use of NMDA antagonists such as amantadine, ketamine or dextromethorphan should be avoided.
  Memantine is not recommended in severe hepatic impairment
  Patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension should be closely supervised.

  Further information can be found in the Summary of Product Characteristics
  http://www.medicines.org.uk/emc

7. Contraindications

- Donepezil:
  Known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients
- Galantamine:
  Known hypersensitivity to the active substance or to any of the excipients. Severe renal or hepatic impairment or where there is both significant renal and hepatic dysfunction.
- Rivastigmine:
  Known hypersensitivity to the active substance, to other carbamate derivatives or to any of the excipients. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patches.
- Memantine:
  Known hypersensitivity to the active substance or to any of the excipients.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc

8. Interactions

- AChE inhibitors generally: May exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed. Should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.
- Donepezil:
  Ketoconazole, quinidine other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil.
- Galantamine:
  Initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine or fluoxetine) or CYP3A4 (e.g. erthyromycin, ketoconazole or ritonavir) may cause an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting. A reduction of the galantamine maintenance dose could therefore be considered in these circumstances.
- Rivastigmine:
  As for AChE inhibitors above
- Memantine:
  The effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.
  Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. The same may be true for ketamine and dextromethorphan. There is one published case report on a possible risk also for the combination of memantine and phenytoin. Other active substances such as such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.

There may be a possibility of reduced serum level of hydrochlorothiazide when co-administered with memantine.
Close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc

9. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- Baseline U&Es, LFTs, blood pressure, pulse and weight
- There are no set requirements for ongoing monitoring although pulse and blood pressure should be measured at monthly intervals during titration.
- Monitor for side effects to medication
- Annual review by GP

10. Shared Care Responsibilities

a. Hospital specialist:

- Assess patient's cognitive, global, functional and behavioural condition, including activities of daily living. Consider a neuropsychological assessment where appropriate.
- Confirm diagnosis of mild to moderate Alzheimer's disease. Consider recommending an AChE inhibitor (**generic donepezil tablets are the least expensive formulation of an AChE inhibitor)** or memantine if there is a contraindication or intolerance to AChE inhibitors.
- Consider recommending memantine only for those patients presenting with symptoms of severe dementia where there is likely to be some benefit.
- Discuss options for treatment with the patient and assess likelihood of patient/carer compliance if medication is to be prescribed as part of care.
- Counsel patients and carers as to the likelihood of potential benefits and side effects of treatment using CPFT leaflets 'Medication for dementia (Acetylcholinesterase Inhibitors and memantine)' available from www.cpft.nhs.uk by following links to publications, leaflets and medicines information leaflets. Ensure the patient knows what significant adverse effects/events to report urgently to the specialist (or GP)
- Advise patient/carer of possible rapid deterioration in the condition if treatment is stopped.
- Provide any advice to the patient/carer when requested.
- Send a letter to the GP requesting shared care for the patient and for GP to initiate treatment with recommended medication when next prescription for patient's regular medication is due (if applicable) Refer GP to shared care guidelines available from: http://www.cambsphn.nhs.uk/CJPG/SharedCareGuidance.aspx
- In Cambridgeshire and Peterborough, a recommendation for treatment will normally be made by a psychiatrist for older people but this Shared Care Guideline is applicable whichever specialist recommends treatment, including neurologists and physicians specialising in the care of older people.
- During the first three month's of treatment monitor regularly for compliance, side-effects and signs of deterioration. Consider increasing the dose at appropriate intervals or switching to an

alternative medication/formulation if there are signs of intolerance. Evaluate any adverse events including those reported by the GP and where appropriate report using the yellow card scheme.
- Inform the GP in writing after each assessment if there is any change to dose/treatment or monitoring so that changes can be made by the GP when the next prescription is due.
- Assess for evidence of response at the end of 3 months and inform GP of maintenance dose. Medication should be continued only where there has been an improvement or no deterioration in cognition, behavior and function.
- Inform GP of patients who do not attend clinic appointments.
- Ensure that the GP is aware of when to refer back to secondary care for further assessment (if in the GPs clinical opinion the patient's mental health needs have changed significantly)

b. General Practitioner:

- Refer to specialist using referral proforma when diagnosis of Alzheimer's disease is suspected and potentially treatable causes of memory loss have been eliminated.
- Forward copies of the following blood test results to specialist: FBC (including vit B12 and folate), renal, liver and thyroid function, serum glucose and calcium levels
- Agreement to shared care guideline by the GP
- Initiate treatment and manage repeat prescribing of donepezil, rivastigmine, galantamine or memantine on the advice of a specialist, according to this shared care guideline and NICE guidance.
- Continue to monitor the patient beyond three months (at annual review)
- Ensure that the patient/carer is clear of the follow up arrangements and by whom
- Ensure the patient knows what significant adverse effects/events to report urgently to the GP (or specialist)
- Check for possible drug interactions when prescribing new medication or stopping concurrent medication. Avoid prescribing drugs with anticholinergic side effects, as these may reduce the efficacy of the AChE inhibitors.
- Monitor patient's general health. Advise specialist if there is a clinical need for the prescribing of any medication that might interfere with the action of the AChE inhibitors or memantine prescribed for the Alzheimer's disease: discuss options and agree a treatment plan with specialist and patient/carer.
  (NB Cambridgeshire and Peterborough NHS Foundation Trust or specialists will not be involved in the patient's care unless there are other mental health issues apart from that needing treatment with AChE inhibitors or memantine).
- Report any suspected adverse events to the specialist team.
- Report any severe adverse events using the yellow card scheme.
- Refer back to secondary care if, in the GPs clinical opinion, the patient's mental health needs have changed significantly.

c. Patient or parent/carer:

- Report any adverse effects to the GP or specialist team whilst taking donepezil, rivastigmine, galantamine or memantine.
- Report to GP or specialist team if they do not have a clear understanding of or any concerns with their treatment with donepezil, rivastigmine, galantamine or memantine.

- Report to GP if the patient misses several days doses as dose re-titration may be needed or if the patient has taken too many tablets.
- Not to exceed the recommended dose.
- To attend their scheduled clinic and blood test appointments (where relevant).
- To inform other clinical staff that they are receiving treatment.

11. Contact numbers for advice and support

Cambridgeshire and Peterborough NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Pharmacy	Cavell Centre Peterborough	01733 776006
Pharmacy	Fulbourn Hospital	01223 218518
Cambridge Rural Team (Sawston)	CMHT out patients	01223 776068
Cambridge City Team (Fulbourn)	CMHT out patients	01223 726022
Consultants Office	Fulbourn	01223 218890
East Cambs Team (Ely Princess of Wales Hospital)	CMHT out patients	01353 652084
Young Persons with Dementia Team (Ida Darwin, Fulbourn)	Specialist Team	01223 884301
Huntingdon Team (Newtown centre)	Memory Clinic Team	01480 415364
Fenland Team (Alan Conway Court, Doddington)	Memory Clinic Team	01354 644233
Peterborough Team (Dementia Resource Centre,144 Lincoln Road, Peterborough)	Memory Clinic Team	01733 895688

Cambridge University Hospital Foundation Trust		
Specialist	**Post**	**Telephone**
Dr Claire Nicholl	Medicine for the Elderly, Addenbrooke's Hospital	01223 217783
Dr Andrew Graham	Consultant Neurologist, Addenbrooke's Hospital	01223 217554 (secretary)
Pharmacy	Addenbrooke's Hospital	01223 217502/217478

12. Monitoring compliance with and the effectiveness of this document

The effectiveness of this document will be monitored, on a risk assessed basis, by review of CPFT and primary care prescribing of anti-dementia medication.

13. Equality and Diversity Statement

This document complies with Cambridgeshire and Peterborough NHS Foundation Trust's service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

Document ratification and history	
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics http://www.medicines.org.uk/emc