Treatme

nt of Alzheimer’s disease

- Acetylcholinesterase inhibitors: Donepezil, Rivastigmine, Galantamine
- NMDA- receptor antagonist: Memantine

Specialist: Please complete letter on page 9 before sending guideline to GP

GP: Please indicate whether you wish to share patient’s care by completing letter on page 9 and return to specialist

Aim of treatment

Background: Alzheimer’s disease is the commonest form of dementia. Dementia affects one in 20 people over the age of 65 and one in five over the age of 80. As definitive diagnosis is made by demonstration of pathological features in brain tissue, diagnostic criteria (e.g. ICD10, DSM IV, or NINCDS/ADRDA) have been developed to provide an assessment tool to assist diagnosis.

Acetylcholine (ACh) is a neurotransmitter that appears depleted in the brains of patients with Alzheimer’s disease. Acetylcholinesterase (AChE) inhibitors elevate the levels of ACh by inhibiting an enzyme responsible for its breakdown leading to an improvement in symptoms for some patients though not altering the outcome of the disease.

Indications for the purposes of this guideline:

NICE has issued the following guidance (TA 217):
- The three AChE inhibitors donepezil, galantamine and rivastigmine are recommended as options for mild to moderate Alzheimer’s disease.
- Memantine is recommended as an option for people with:
  - Moderate Alzheimer’s disease who are intolerant of or have a contraindication to AChE inhibitors or
  - Severe Alzheimer’s disease
- Combination treatment with an AChE inhibitor and memantine is not recommended.
- If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), start treatment with the drug with the lowest acquisition cost. However, if this is not suitable, an alternative AChE inhibitor can be prescribed.

Specialist responsibilities

- Identify criteria to be used to assess response to treatment and make a baseline assessment encompassing cognitive, global and behavioural functioning and assess activities of daily living.
- When using assessment scales to determine the severity of Alzheimer’s disease, take account of any disabilities or communication difficulties that could affect results and make any appropriate adjustments. Do not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. Be mindful of the need for equal access to treatment for patients from different ethnic and cultural backgrounds.
Specialist responsibilities continued

- Seek carer’s view on patient’s condition at baseline and at follow-up.
- Make the diagnosis of Alzheimer’s disease and assess whether the patient is suitable for treatment.
- Seek consent from the patient and his/her carer or advocate.
- Identify a suitable person to ensure concordance with treatment (e.g. relative or other carer).
- Make the carer aware of the nature of the effect of treatment and that it could be stopped.
- Choose most appropriate drug, initiate treatment, prescribe and monitor all medication for the first three months, or until maintenance dose is achieved, whichever is later.
- Assess the response to treatment at around 12 weeks. If response is satisfactory and maintenance dose is reached ask the GP whether they are willing to participate in shared care.
- Assess at yearly intervals whether the treatment should be discontinued or modified. Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional and behavioural assessment. If the patient does not clearly benefit from the drug treatment, the specialist should stop the drug at a review consultation.
- Assess patient between yearly reviews for review of medication if GP considers patient’s Alzheimer’s disease has progressed to severe.
- Accept patient for review between yearly reviews if GP has concerns that there has been a change in the patient’s health status.
- Ensure that memantine is not prescribed in combination with donepezil, rivastigmine or galantamine.
- Liaise with CPN or care agencies as appropriate.
- Prompt verbal communication followed up in writing to GP of changes in treatment, results of monitoring, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP.
- Reporting adverse events to CHM.

General practitioner responsibilities

If GP has agreed to share care:

- Prescribing of Donepezil / Rivastigmine / Galantamine / Memantine after communication with specialists regarding the need for treatment and once the maintenance dose has been established.
- Provide symptomatic treatment for minor adverse effects.
- Provide information on the patient’s progress to the consultant on request.
- For patients initially diagnosed with mild or moderate Alzheimer’s disease, refer patient to specialist if routine review of progress indicates that the severity of the patients Alzheimer’s disease has progressed to severe. A medication review by the specialist will be required.
- Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt referral to specialist if there is a change in patient’s health status.
- Ensure that memantine is not prescribed in combination with donepezil, rivastigmine or galantamine.
- Respond to advice from secondary care on dose changes.
- Report adverse events to specialist.
- Stop treatment in case of a severe adverse event.
Patient/patient carer responsibilities

- Take the prescribed Donepezil / Rivastigmine / Galantamine / Memantine as prescribed
- Report any adverse effects to their GP and/or specialist regarding their treatment.
- Ensure that they have a clear understanding of their treatment benefits and limitations.
- Ensure they attend for monitoring requirements as per shared care guideline.
- Be aware that treatment may be stopped if patient does not attend for monitoring.

Back-up advice and support

<table>
<thead>
<tr>
<th>Contact details</th>
<th>Telephone No</th>
<th>E-mail address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr S Black</td>
<td>01392 674142</td>
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</table>
Supporting Information

This guideline highlights significant prescribing issues, not all prescribing information and potential adverse effects are listed. Please refer to SPC/data sheet for full prescribing data.

DONEPEZIL

Dose: Donepezil should be taken orally in the evening, just prior to bedtime. The initial dose is 5mg/day, but this may be increased to 10mg/day after one month, if clinically indicated. The maximum recommended daily dose is 10mg.

Special patient groups: Mild to moderate hepatic impairment: dose escalation according to individual tolerability. No data is available for patients with severe hepatic impairment.

Donepezil Contraindications
- Hypersensitivity to donepezil or piperidine derivatives.

Donepezil Precautions
- AChE inhibitors have vagotonic effects on heart rate (e.g. bradycardia). This is important for patients with sick sinus syndrome or other supraventricular cardiac conduction abnormalities (e.g. sinoatrial or atrioventricular block).
- There have been reports of syncope and seizure with donepezil. In investigating such patients, the possibility of heart block or long sinusual pauses should be considered.
- Susceptibility to peptic ulcers.
- Asthma or chronic obstructive pulmonary disease. Avoid concomitant administration with other inhibitors of acetylcholinesterase, agonists or antagonists of cholinergic system.
- May exacerbate or induce extrapyramidal symptoms.
- No data for patients with severe hepatic impairment.
- Contains lactose.

Donepezil side effects

Very common: Diarrhoea, nausea

Common: Increased risk of common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, vomiting, abdominal disturbance, rash, pruritus, muscle cramps, urinary incontinence, headache, fatigue, pain, accident.

Uncommon: Seizure, bradycardia, gastrointestinal haemorrhage, gastric and duodenal ulcers, minor increase in serum concentration of muscle creatine kinase.

Donepezil Drug interactions– see BNF/SPC

RIVASTIGMINE

Dose: Capsules and oral solution: Initially 1.5 mg orally twice daily with morning and evening meals, increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to response and tolerance; usual range 3–6 mg twice daily; max. 6 mg twice daily. The capsule should be swallowed whole.

If treatment is interrupted for more than several days, it should be re-initiated at 1.5mg twice daily. Dose titration should be carried out as described above.
Patches: Start treatment with 4.6mg/24 hour. After a minimum of four weeks and if well tolerated, increase dose to 9.6mg/24 hour. The recommended daily maintenance dose is 9.6mg/24 hour. Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Treatment can be resumed at the same dose if treatment is not interrupted for more than several days. Otherwise, re-initiate treatment with 4.6mg/24 hour. See SPC for information on switching from capsules and solution to patches.

Special patient groups

Oral formulations: moderate renal impairment and mild to moderate hepatic impairment – titrate according to individual tolerability.

Rivastigmine Contraindications
- Hypersensitivity to carbamate derivatives.
- Severe liver impairment (oral formulations).

Rivastigmine Precautions
- Gastrointestinal disorders: Rivastigmine is associated with weight loss. During therapy, patient’s weight should be monitored. In cases of severe vomiting, dose adjustments must be made. Some cases of severe vomiting may be associated with oesophageal rupture. These events occurred particularly after dose increments or high doses of rivastigmine.
- Sick sinus syndrome or conduction defects (sinoatrial block, atrioventricular block).
- Active gastric or duodenal ulcers or patients predisposed to these conditions.
- History of asthma or chronic obstructive pulmonary disease.
- May induce or exacerbate urinary obstruction and seizures.
- Oral solution contains sodium benzoate, a mild irritant to the skin, eyes and mucous membrane.
- May exacerbate or induce extrapyramidal symptoms.

Rivastigmine Side effects

Very common: Dizziness, nausea, vomiting, diarrhoea, loss of appetite. (GI side effects may be more common in women).

Common: Agitation, confusion, headache, somnolence, tremor, abdominal pain and dyspepsia, sweating increased, fatigue and asthenia, malaise, weight loss.

Uncommon: Insomnia, depression, syncope, accidental fall, increased LFTs Additional adverse reactions associated with transdermal patches: anxiety, delirium, pyrexia (common).

Rivastigmine Drug interactions– see page BNF/SPC

GALANTAMINE

Dose: Initially 4 mg orally twice daily, preferably with morning and evening meals for 4 weeks increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily. The equivalent daily modified release may be considered instead. Adequate fluid intake must be maintained during treatment.
GALANTAMINE CONTINUED

Special patient groups: Moderately impaired hepatic function – begin dosing at 4mg once daily (taken in morning) for at least one week. Thereafter, proceed with 4mg twice daily for at least four weeks. In these patients, daily doses should not exceed 8mg twice daily. Galantamine is contraindicated in patients with severe hepatic impairment. No dosage adjustment required for patients with mild hepatic impairment.

Renal impairment: Contraindicated in patients with severe renal impairment.

Galantamine contraindications

- Known hypersensitivity to galantamine or orange yellow S aluminium lake [E110] (present in the 12mg tablet) may cause allergic reactions.
- Severe renal or severe liver impairment.

Galantamine precautions

- Moderate hepatic impairment (doses not to exceed 8mg bd).
- Sick sinus syndrome or other supraventricular conduction defects or use of drugs which significantly reduce heart rate, for example, digoxin and beta blockers for patients with uncorrected electrolyte disturbance (e.g. hyperkalaemia, hypokalaemia). Caution required for patients with cardiovascular disease e.g. immediate post-myocardial infarction period, new onset atrial fibrillation, second degree heart block or greater, unstable angina pectoris, or congestive heart failure, especially NYHA groups III-IV.
- Susceptibility to peptic ulcers. Not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.
- Asthma or chronic obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).
- Avoid in urinary retention or in patients recovering from bladder surgery.
- Pregnancy.
- May cause seizures or worsen Parkinsonian symptoms.

Galantamine side effects

Very common: Vomiting, nausea.

Common: Decreased appetite, anorexia, hallucination, depression, syncope, dizziness, tremor, headache, somnolence, lethargy, bradycardia, hypertension, abdominal pain, abdominal pain upper, diarrhoea, dyspepsia, stomach discomfort, hyperhidrosis, muscle spasms, fatigue, asthenia, malaise, weight decreased, fall.

Uncommon: Dehydration, visual hallucination, auditory hallucination, paraesthesia, dysgeusia, hypersomnia, vision blurred, tinnitus, supraventricular extrasystoles, atrioventricular block first degree, sinus bradycardia, palpitations, hypotension, flushing, retching, muscular weakness, hepatic enzymes increased.

Galantamine drug interactions– see BNF/SPC.
### Product Information – donepezil, rivastigmine, galantamine

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<th>Formulations</th>
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<td><strong>Donepezil</strong></td>
<td>Tablets and dispersible tablets (5mg, 10mg)</td>
<td>5mg od</td>
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<td>Patches</td>
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* Calculated May 2011

**MEMANTINE**

**Dose:** Take tablets or solution once a day and at the same time every day.

Dose titration: The starting dose is 5mg/day which is increased by 5mg a week to the maintenance dose of 20mg/day.

Pump oral solution 5mg/ml:

Week one: 0.5ml solution (5mg) equivalent to one downward pump per day for 7 days
Week two: 1ml solution (10mg) equivalent to two downward pumps per day for 7 days
Week three: 1.5ml solution (15mg) equivalent to three downward pumps per day for 7 days
Week four: 2ml solution (20mg) equivalent to four downward pumps per day for 7 days

The maximum daily dose is 20mg/day.

Dose in renal impairment:

Mild renal impairment (creatinine clearance 50-80mL/min), no dose adjustment required.
Moderate renal impairment (creatinine clearance 30-49mL/min) the daily dose should be 10mg. If tolerated well after at least 7 days, the dose could be increased to 20mg/day.
Severe renal impairment (creatinine clearance 5-29mL/min) the daily dose should be 10mg.

**Memantine contraindications**

- Hypersensitivity to memantine.
MEMANTINE CONTINUED

Memantine Precautions

- Caution is recommended in patients with epilepsy, history of convulsions or predisposing factors for epilepsy.
- Avoid concomitant use of NMDA-antagonists (amantadine, ketamine or dextramethorphan).
- Patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV) or uncontrolled hypertension were excluded from most clinical trials. Only limited data are available, patients with these conditions should be closely supervised.
- Contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take memantine.

Memantine interactions

Effects on other medicines: Avoid concomitant amantadine, ketamine and dextromorphin due to risk of pharmacotoxic psychosis. The effects of L-dopa, dopaminergic agonists and anticholinergics may be enhanced.

Other interactions –see BNF/SPC

Memantine side effects

Common: drug hypersensitivity, somnolence, dizziness, hypertension, dyspnoea, constipation, headache.

Uncommon: fungal infections, confusion, hallucinations, gait abnormal, cardiac failure, venous thrombosis/thromboembolism, vomiting, fatigue.

Memantine product information

Memantine tablets: 5mg, 10mg, 15mg, 20mg. Cost of 28 days treatment at 10mg/day (£34.50), 20mg/day (£69.01)

Memantine 5mg per actuation (10mg/ml) /pump oral solution. Cost of 28 days treatment at 10mg/day (£34.50), 20mg/day (£69.01)

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<tr>
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<td>June 2013</td>
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Shared Care Agreement Letter - Consultant Request

To: Dr. .................................................................

Practice Address: ............................................................

DIAGNOSED CONDITION: ..............................................

I recommend treatment with the following drug: ......................

I request your agreement to sharing the care of this patient according to the North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Principles of shared care:

**GPs are invited to participate. If GP is not confident to undertake these roles, then they are under no obligation to do so.** In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed: ........................................................................ Date: ......................................

Consultant name: ........................................................

Contact telephone number: ............................................

GP RESPONSE

I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: ............................................................ Date: ......................................

GP name: ........................................................... *Delete as appropriate