DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER’S DISEASE

Shared Care Agreement

This protocol provides prescribing and monitoring guidance for acetylcholinesterase inhibitors and memantine. It should be read in conjunction with the shared care responsibilities document, the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Background

- Donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer’s disease of mild to moderate severity.
- Memantine is recommended as an option for:
  - Managing moderate Alzheimer’s disease where the patient is intolerant of or has a contraindication to acetylcholinesterase (AChE) inhibitors
  - Severe Alzheimer’s disease
- NICE clinical guideline 42 recommends that prescribing should be considered for patients with Lewy Body Dementia (DLB) who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges; people with mild, moderate or severe Alzheimer’s disease who have non-cognitive symptoms and/or behaviour that challenges causing significant distress or potential harm to the individual if:
  - A non-pharmacological approach is inappropriate or has been ineffective, and
  - Antipsychotic drugs are inappropriate or have been ineffective.
- Treatment with the above drugs should only be initiated by specialists in the care of patients with dementia (i.e. psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people).
- Carers’ views on the patient’s condition at baseline and follow up should be sought.
- When assessing the severity of Alzheimer’s disease and the need for treatment, healthcare professionals should not rely solely on cognition scores if: The cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient’s dementia because of learning difficulties or level of education, sensory impairments, linguistic or other communication difficulties; language difficulties in using the tool; or if other similar reasons apply to using a cognition score alone would be inappropriate for assessing the severity of dementia.
- There needs to be equality of access to treatment for patients from different ethnic groups in particular those from different cultural backgrounds.
- Patients who continue on the appropriately prescribed medicine should be reviewed regularly using cognitive, global, functional and behavioural assessment as appropriate.
- Treatment should be reviewed by an appropriate specialist team unless there are locally agreed protocols for shared care.
- It is recommended that therapy should be initiated with a drug with the lowest acquisition cost - however, an alternative AChE inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions and dosing profiles.

Prescribing and Review

General Considerations

- Carers views on the patient’s condition at baseline and follow up should be sought.
- The drug with the lowest acquisition cost should be prescribed – taking into account adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions and dosing.
  - **Donepezil is the first line choice** based on the current Drug Tariff price (see table 1) with other AChE inhibitors considered where there are contraindications or adverse effects.
• For patients with swallowing difficulties – offer orodispersible donepezil tablets, rivastigmine oral solution or galantamine oral solution.
• For patients unable to swallow – offer rivastigmine patch.

Table 1: Twenty-eight day treatment cost

<table>
<thead>
<tr>
<th>Cholinesterase inhibitor</th>
<th>Usual dose</th>
<th>Drug tariff price (Dec 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>5 – 10 mg daily</td>
<td>£1.33 - £1.76</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>3 – 6 mg twice daily</td>
<td>£6.54 - £32.72</td>
</tr>
<tr>
<td>Rivastigmine patch</td>
<td>4.6 mg/24 hours</td>
<td>£72.77</td>
</tr>
<tr>
<td></td>
<td>9.5 mg/24 hours</td>
<td>£29.57</td>
</tr>
<tr>
<td></td>
<td>13.3 mg/24 hours</td>
<td>£72.77</td>
</tr>
<tr>
<td>Galantamine</td>
<td>8 – 12 mg twice daily (immediate release)</td>
<td>£59.29 - £74.10</td>
</tr>
<tr>
<td></td>
<td>16 – 24 mg daily (XL)</td>
<td>£64.90 - £79.80</td>
</tr>
</tbody>
</table>

Diagnosis: by specialist secondary care clinician

• Mild Alzheimer’s: Diagnosed by, e.g. cognitive test score equivalent to mini mental state examination (MMSE) score 21 - 26 or clinical judgement where high or low premorbid IQ, learning difficulties or level of education, sensory impairments, linguistic or other communication difficulties; language difficulties in using the tool.

• Moderate Alzheimer’s: Diagnosed by, e.g. cognitive test score equivalent to MMSE 10 - 20, or in some cases it may be useful to supplement assessment with global, functional (e.g. Bristol Activities of Daily Living Scale (BADLS+)) and behavioural assessments.

• Moderately severe Alzheimer’s: Diagnosed by, e.g. cognitive test score equivalent to MMSE 10 - 15 or behavioural/functional assessment.

• Severe Alzheimer’s disease: Diagnosed by, e.g. cognitive test score equivalent to MMSE <10 or behavioural/functional assessment.

Prescribing: Initial prescribing for first 3 months by secondary care.

Mild to Moderate Alzheimer’s

• Secondary care specialist to prescribe AChE inhibitor and review symptoms/adverse effects after one month and increase dose, review AChE inhibitor as indicated by adverse effects. Continue prescribing up to 3 months and review cognitive function/global, functional and behavioural assessment, as appropriate, at 3 months.

• If patient has a diagnosis of mild Alzheimer’s disease, has responded to the AChE inhibitor, is clinically stable and has no complex needs, e.g. behavioural problems, - discharge back to GP for:
  - Monthly prescribing of AChE inhibitor.
  - Review of symptoms/adverse effects 6 - 12 monthly.
    - It is not necessary to follow up patients on anti-dementia drugs with repeat scores to assess the effectiveness of the treatment.4
    - It is more important to make an assessment of the global functioning of the patient, as small changes in scores may not be significant. For GP management it is anticipated that, providing the patient is tolerating the treatment and there are no contraindications the treatment will be maintained until such a time as it becomes inappropriate such as in extreme frailty.4

• Referral back to secondary care can be made at any time if there is a significant deterioration in cognition or in behaviour, or if there are any general concerns.

• If patient has a diagnosis of mild or moderate Alzheimer’s disease and ongoing complex needs request shared care prescribing and continue review by secondary care specialist at 6 - 12 monthly intervals (or more frequently if clinically indicated) in memory clinic/other setting.
Moderate Alzheimer’s

- Prescribe memantine* only where patient is intolerant or has contraindication to AChE inhibitor. For challenging behaviours, preliminary reports suggest memantine may have a role in managing behavioural problems such as agitation or aggression in dementia, but practitioners are recommended to try more conventional therapies (including non-pharmacological) first. Prescribe and review in first 3 months as above.

Severe Alzheimer’s disease with behavioural problems

- Prescribe memantine* and review symptoms/side effects after one month and increase dose, review as indicated by side effects. Continue prescribing up to 3 months and review cognitive function, global, or functional and behavioural assessment as appropriate at 3 months.
- After 3 months consider shared care prescribing with GP and continue review by secondary care specialist at 6 - 12 monthly intervals monitoring response to treatment.

*Patients prescribed a combination of memantine and an AChE inhibitor are not included in this shared care agreement.

Admission to a Care Home (on account of dementia)

- Unless there are challenging behaviours medication would not normally be initiated once in a care home - the NICE economic model assumes discontinuation of medication on admission to care homes (see below).
- If an AChE inhibitor is started, the patient is settled on the medicine, and a decision is made to continue it, it may be more appropriate for the GP to follow up the patient.

Patients new to the area:

- A small population of patients who are on a stable dose of AChE having been trialled and stabilised elsewhere in or outside the UK may come into the area and register with a Buckinghamshire GP. In this situation, GP prescription and follow-up can be continued according to this SCP and there is no need for a second trial of AChE or referral to secondary care, unless there is a genuine clinical question.

Discontinuation of Treatment

- If there are concerns about response to treatment or if the patient develops adverse effects, refer back to the specialist for a review of treatment and discontinuation if necessary. If adverse effects are significant, the GP should stop treatment in advance of the specialist’s review.
- The NICE economic model assumes that AChE inhibitors are discontinued on admission to a care home. Stopping an AChE inhibitor may result in deterioration in behaviour and the risk of destabilising the care home placement must be taken into account. There is recent evidence in the DOMINO study⁵ that some patients on donepezil will continue to benefit from their treatment even after their dementia becomes severe. This may translate into a delay to care home placement. However, the trial was very small with a high drop-out rate and the benefit only referred to a small reduction in deterioration of MMSE and BADLS scores.
- Deciding if medicines for Alzheimer’s disease should continue should be made on an individual basis and should include family/patient views and expectations. The following guidance may help with the decision about whether to continue or stop dementia medicines:

Previous NICE guidance gave clear guidance on when to stop a cholinesterase inhibitor (ChEI) but this was not based on empirical data and often caused distress to families. Since then, the DOMINO study (2012) indicates that patients may benefit from longer term use of ChEI than previously thought (see above). The DOMINO study showed that patients who were kept on donepezil for a year after they reached an MMSE score of 10 (or equivalent) did better than those who came off. However, there was a significant drop-out period in the 1 year study period. Although it is likely that benefits from ChEI will drop off with time, it is not possible to give a simple ‘cut-off’ anymore.

Factors that need to be taken into account when/if considering stopping ChEI:

- A subacute decline in cognitive performance, in the absence of other causes, may indicate that the ChEI is no longer effective.
- Family/patient views and expectations need to be taken into account.
Any medical complications? For patients with increasing physical problems, the risks of stopping ChEIs need to be weighed against the likelihood of developing new complications on continuing ChEIs. To what extent is the ChEI contributing to the patient’s quality of life if they are increasingly physical frail?

For patients at risk of entering care home, stopping a ChEI may disrupt care and hasten admission.

Once a patient is in a care home individual patient factors need to be taken into account when deciding if memory-enhancing medication is right for them.

- There is no firm evidence on how to stop AChE inhibitors however it is recommended that discontinuation should be by gradual dose reduction (see table 2). The patient should be closely monitored for any subsequent deterioration and consideration given to the need to reinstate treatment.

**Table 2: Stopping AChEIs**

<table>
<thead>
<tr>
<th>ChEI</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Long half life, so can be stopped without the need for tapering, however it may be advisable to reduce to 5 mg daily for a month and monitor for deterioration before stopping altogether.</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Short half life, reverse titration recommended – i.e. a reduction of 1.5 to 3 mg every 2 to 4 weeks.</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Long half life, so can be stopped without the need for tapering, however it may be advisable to gradually reduce the dose over a month and monitor for deterioration before stopping altogether.</td>
</tr>
</tbody>
</table>

**Specialist Responsibilities**

**The specialist will:**

1. Discuss benefits and side effects of treatment with the patient and carer and give treatment information. Discuss future treatment discontinuation with patient and carers. Evaluate likely compliance.
2. Initiate AChE inhibitor for patients with mild or moderate Alzheimer’s disease, e.g. for guidance, in those with an MMSE score between 26 - 10 - or in the case of those patients where MMSE is not an appropriate tool another appropriate assessment¹²,- or people with DLB (off-label use) who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges.²
3. Prescribe memantine in severe Alzheimer's disease and in moderate Alzheimer's disease only where patient is intolerant or has contraindication to AChE inhibitor. Preliminary reports suggest memantine may have a role in managing behavioural problems such as agitation or aggression in dementia, but practitioners are recommended to try more conventional therapies (including non-pharmacological) first.
4. Be responsible for the review of symptoms/adverse effects within one month and increase dose, review drug as indicated.
5. Prescribe for the patient and assess the benefit over 12 weeks.
6. Ask the GP whether they are willing to participate in shared care if there is evidence of improvement in either - cognitive, global, functional or behavioural scores or evidence of positive improvement by carers’. The completed agreement form will be faxed to the GP and the diagnosis, behavioural, functional, and cognitive issues including any monitoring scores will be communicated.
7. Discharge patients with a diagnosis of mild Alzheimer’s disease, who have responded to AChE inhibitor, who are clinically stable and who have no complex needs, e.g. behavioural problems, back to the GP for prescribing and review until further deterioration occurs or carer concerns.
8. Request shared care prescribing for patients with a diagnosis of mild or moderate Alzheimer’s disease and ongoing complex needs or severe Alzheimer’s disease and continue with secondary care specialist review at 6 - 12 monthly intervals (or more frequently if clinically indicated) in the memory clinic or other setting.
9. Ensure appropriate assessment of effectiveness of treatment at 6 - 12 monthly intervals for patients continuing under shared care and communicate ongoing assessment details and carers’ views on the patient's condition to the GP.
10. Promptly communicate any changes in treatment to the GP.
11. Discontinue prescribing, where appropriate, if the patient is referred back to secondary care due to deterioration in their condition.
12. Report serious adverse events to the MHRA.
13. Ensure clear arrangements for back-up, advice, and support.
**General Practitioner Responsibilities**

The GP will:

1. Reply to the request for shared care as soon as practicable – returning faxed agreement form within 2 weeks of receipt.
2. Prescribe AChE inhibitor or memantine once patient is stabilised on treatment (after 12 weeks).
3. Follow specialist advice on any changes in treatment.
4. Advise the specialist of any changes in treatment and of any changes in medical co-morbidity, new drugs prescribed and any relevant treatment issues noted, e.g. adverse effects or treatment adherence.
5. Monitor patients with mild Alzheimer’s disease who have responded to an AChE inhibitor, who are clinically stable, and who have no complex needs that have been discharged back to GP care. Follow the guidance on page 3 to determine whether AChE inhibitors should be discontinued. Refer back to secondary care if there is a significant deterioration or carer’s concerns, or if the GP is unsure how to progress care.
6. Report to and seek advice from the specialist on any aspect of patient care which is of concern to the GP and may affect treatment. If there are concerns about response to treatment or the patient develops adverse effects refer back to the specialist for a review of treatment and discontinuation if necessary.
7. Rapidly refer the patient to the specialist in the event of an unexpected or problematic deteriorating clinical condition, e.g. unmanageable behaviour.
8. Report adverse events to specialist and the MHRA.

**Patient's/Carer’s Role**

The patient/carer will:

1. Report any adverse effects to their specialist or GP whilst treated with AChE inhibitor or memantine.
2. Share any concerns they have in relation to treatment with AChE inhibitor or memantine.
3. Contact the prescriber if treatment adherence becomes a problem.
4. Ask the specialist or GP if they do not have a clear understanding of their treatment.

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**SUPPORTING INFORMATION: AChE Inhibitors**

*Licensed indications*

AChE inhibitors are licensed for the symptomatic treatment of mild to moderately severe Alzheimer’s disease. They are not licensed for use in severe Alzheimer’s disease or other dementias (although rivastigmine is licensed for mild to moderately severe dementia in patients with idiopathic Parkinson’s disease).

*Dosage and Administration*

Full instructions on dosage, side effects, etc. are provided in the SPC.

AChE inhibitors are usually administered orally. An orodispersible formulation of donepezil, oral solutions of rivastigmine and galantamine, and a rivastigmine transdermal patch are available for use when there are swallowing difficulties.

**Donepezil:** 5 mg once a day increasing to 10 mg once daily after one month. Tablets usually taken in the evening just prior to retiring. Maximum dose 10 mg daily. An orodispersible form is available for those with swallowing difficulties. For missed doses or breaks in treatment (see table 4).

**Rivastigmine tablets:** 1.5 mg twice daily (bd) with morning and evening meals, increasing at minimum of fortnightly intervals to 3 mg twice daily, then 4.5 mg twice daily to a maximum of 6 mg twice daily. The effective maintenance dose is 3 - 6 mg twice daily. For missed doses or breaks in treatment (see table 4).

**Rivastigmine patches:**

Information about rivastigmine patches (MHRA June 2010):

- Only one patch should be applied per day to healthy skin on the upper or lower back, upper arm, or chest.
- The patch should be replaced by a new one after 24 hours, and the previous day’s patch must be removed before application of a new patch to a different skin location.
- Application to the same skin location within 14 days should be avoided to minimise skin irritation.
- The patch should not be cut into pieces.
Rivastigmine should only be started if a caregiver is able to regularly give and monitor treatment, and the patient has difficulty swallowing medication. If an overdose is suspected, all rivastigmine patches should be removed immediately and no further patch should be applied for the next 24 hours.

Treatment is started at a dose of 4.6 mg/24 hour patch. After a minimum of 4 weeks, and if well tolerated, the dose should be increased to 9.5 mg/24 hour, the daily recommended effective dose.

If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 hours, the treating physician may consider increasing the dose to 13.3 mg/24 hours in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24 hours.

Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than 3 days. Otherwise, treatment should be re-initiated with rivastigmine 4.6 mg/24 hours (see table 4).

Table 3: Switching from rivastigmine capsules or oral solution to transdermal patches

<table>
<thead>
<tr>
<th>Current oral dose (mg/day)</th>
<th>Recommended initial patch dose (mg/24 hours)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If well tolerated increase to 9.5 mg/24 hours after a minimum of 4 weeks.</td>
</tr>
<tr>
<td>6</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If well tolerated increase to 9.5 mg/24 hours after a minimum of 4 weeks.</td>
</tr>
<tr>
<td>9</td>
<td>9.5*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>* If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 hours transdermal patches is recommended.</td>
</tr>
<tr>
<td>12</td>
<td>9.5</td>
<td></td>
</tr>
</tbody>
</table>

Apply the first transdermal patch on the day following the last oral dose.

Galantamine: 4 mg twice daily preferably with morning and evening meals or 8 mg XL capsules once daily in the morning preferably with food for at least 4 weeks, increasing to 8 mg twice daily (XL preparation 16 mg once daily). Maximum dose 12 mg twice daily (24 mg XL once daily). For missed doses or breaks in treatment (see table 4).

Table 4: Re-titration following AChEI missed doses or planned treatment breaks

<table>
<thead>
<tr>
<th>Treatment break</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>7 days or less: Resume at the same dose</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days: Re-titrate from 5 mg daily</td>
</tr>
<tr>
<td>Rivastigmine (capsules and oral solution)</td>
<td>3 days or less: Resume at the same dose</td>
</tr>
<tr>
<td></td>
<td>&gt;3 days: Re-titrate from a dose of 1.5 mg twice a day</td>
</tr>
<tr>
<td>Rivastigmine patch</td>
<td>3 days or less: Resume at the same dose</td>
</tr>
<tr>
<td></td>
<td>&gt;3 days: Re-titrate from 4.5 mg/24 hours</td>
</tr>
<tr>
<td>Galantamine (oral solution, tablets or XL capsules)</td>
<td>7 days or less: Resume at the same dose</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days: Re-titrate from a dose of 8 mg daily (4 mg twice a day if oral solution or tablets, 8 mg once a day if XL capsules)</td>
</tr>
</tbody>
</table>

Contraindications

Hypersensitivity to donepezil or rivastigmine or galantamine, or derivatives, or excipients in the formulation.

Donepezil – there are no data for patients with severe hepatic impairment and it is contraindicated.

Rivastigmine is contraindicated in patients with severe liver impairment as this has not been studied.

Galantamin is contraindicated in patients with severe renal dysfunction and severe hepatic impairment.
Precautions

Cardiovascular conditions: AChE inhibitors should be used cautiously in patients with conduction deficits such as sick sinus syndrome or other supraventricular cardiac conduction disturbances such as sinoatrial or atrioventricular block because they may have vagotonic effects on heart rate, e.g. bradycardia. Advice from a cardiologist should be sought in these instances and recording pulse rate and rhythm may be advisable.

AChE inhibitors have variable effects on blood pressure, which may be increased, or underlying hypotensive conditions may be exaggerated, possibly leading to falls. Any electrolyte disturbance must be corrected before use.

Concomitant medication that significantly reduces the heart rate requires caution.

Patients with other cardiovascular diseases, e.g. the immediate post-myocardial infarction period, new onset atrial fibrillation (AF), second degree heart block or greater, unstable angina pectoris or congestive heart failure should be treated with caution.

Gastrointestinal conditions: Caution is recommended in patients with active gastric or duodenal ulcers or who are predisposed to those conditions because cholinesterase inhibitors may increase gastric acid secretion, e.g. patients receiving concurrent non-steroidal anti-inflammatory drugs. An increase in ulcers has not been observed in trials.

Adverse effects such as nausea, vomiting and diarrhoea occur commonly, particularly when initiating treatment and/or increasing the dose. These reactions occur more commonly in women.

Patients taking rivastigmine and galantamine should have their weight monitored as weight loss has been noted.

GenitourINARY conditions: Cholinesterase inhibitors may cause bladder outflow obstruction.

Pulmonary conditions: Caution is recommended in patients with a history of asthma, obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).

Neurological conditions: Drugs that potentiate cholinergic effects may cause generalised seizures, although these may also be a feature of the underlying disease process. Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms and thus worsen Parkinsonian symptoms.

Renal or hepatic impairment: Donepezil and rivastigmine do not require any dose adjustment in mild to moderate renal or hepatic impairment, observation for adverse drug reactions (ADRs) in severe renal impairment is recommended. There is a lack of experience in severe hepatic impairment and donepezil and rivastigmine are contraindicated by the manufacturers.

Galantamine should begin with a 4 mg daily dose, preferably taken in the morning, for at least one week in moderate to severe hepatic or renal impairment. Thereafter the patients should continue with dosage increases and dose reviews at monthly intervals with a lower maximum dose of 8 mg twice daily recommended.

Surgical and medical procedures: Cholinesterase inhibitors are likely to exaggerate succinylcholinetype muscle relaxation during anaesthesia.

Side effects:
The most common side effects (incidence >10%) include diarrhoea, muscle cramps, nausea and vomiting, dizziness. Headache, abdominal disturbance and pain, fatigue and insomnia have also been reported (incidence <10%).

Rarely seizures, cardiac conduction disturbances and psychiatric disturbance such as aggression, hallucinations and agitation have been reported.
Table 5: Drug interactions

<table>
<thead>
<tr>
<th>Interacting drugs</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics (antimuscarinics) e.g. procyclidine, oxybutinin</td>
<td>Potential antagonistic effect, monitor for reduced efficacy of either drug (see later for further details)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinomimetics e.g. suxamethonium</td>
<td>Potential additive effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs slowing heart rate e.g. digoxin, ß blockers</td>
<td>Potential additive effect, monitor for side effects (e.g. bradycardia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 inhibitors e.g. paroxetine, fluoxetine</td>
<td>Donepezil levels possibly increased*</td>
<td>Galantamine levels possibly increased*</td>
<td>unlikely</td>
</tr>
<tr>
<td>CYP3A4 inhibitors e.g. erythromycin, ketoconazole,itraconazole</td>
<td>Donepezil levels possibly increased*</td>
<td>Galantamine levels possibly increased*</td>
<td>unlikely</td>
</tr>
<tr>
<td>Inducers of CYP2D6 + CYP3A4 e.g. alcohol,phenytoin,carbamazepine, rifampicin</td>
<td>Donepezil levels possibly reduced**</td>
<td>Galantamine levels possibly reduced **</td>
<td>unlikely</td>
</tr>
</tbody>
</table>

* Dose reduction of CE not necessary unless side effects occur
** Interaction may not be clinically significant, but should be considered if lack of efficacy occurs

SUPPORTING INFORMATION: Memantine

Licensed indications

Memantine (Ebixa®) is licensed for treatment of patients with moderate to severe Alzheimer’s disease.

Dosage and Administration

Tablets – available as 10 mg and 20 mg (5 mg and 15 mg in initiation packs)
Oral solution (pump pack) – available as 5 mg/pump

The maximum daily dose is 20 mg daily. In order to reduce the risk of undesirable effects the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

- Week 1 (day 1 - 7): The patient should take one 5 mg tablet/half a 10 mg tablet/0.5 mL solution per day for 7 days.
- Week 2 (day 8 - 14): The patient should take one 10 mg tablet/1 mL solution per day for 7 days.
- Week 3 (day 15 - 21): The patient should take one 15 mg tablet/one and a half 10 mg tablets/1.5 mL solution per day (15 mg) equivalent to three downward pumps, per day for 7 days.
- From week 4 onwards: The patient should take one 20 mg tablet/two 10 mg tablets/2 mL solution once a day.

The liquid pump formulation can be used for patients who have difficulty taking tablets.

Table 6: Re-titration following missed doses or planned treatment breaks

<table>
<thead>
<tr>
<th>Treatment break</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine (oral solution or tablets)</td>
<td></td>
</tr>
<tr>
<td>2 days or less</td>
<td>Resume at the same dose</td>
</tr>
<tr>
<td>7 days or less</td>
<td>Re-titrare treatment from 10 mg daily</td>
</tr>
<tr>
<td>More than 7 days</td>
<td>Re-titrare from 5 mg daily</td>
</tr>
</tbody>
</table>

Renal impairment: In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day.

Hepatic impairment: Administration of memantine is not recommended in patients with severe hepatic impairment.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients. The oral solution contains sorbitol - patients with rare hereditary problems of fructose intolerance should not take this medicine.
**Precautions:**
Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy. Patients with recent myocardial infarction, decompensated heart failure or uncontrolled hypertension should be closely supervised.

**Side effects:**
The most common side effects are: Somnolence, dizziness, raised blood pressure, dyspnoea, constipation, headache. Uncommon side effects include: Vomiting, heart failure, psychotic reactions, confusion. Rarely seizures have been reported.

**Table 7: Drug Interactions**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-dopa, dopaminergic agonists e.g bromocriptine, and anticholinergics</td>
<td>Memantine may enhance the effects of these drugs.</td>
</tr>
<tr>
<td>Barbiturates, antipsychotics</td>
<td>Memantine may reduce the effects of these drugs.</td>
</tr>
<tr>
<td>Amantadine, ketamine, dextromethorphan</td>
<td>The use of memantine, an NMDA antagonist, with other NMDA antagonists, is predicted to increase the risk of CNS related adverse effects such as psychosis and combined use should therefore be avoided.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Isolated cases of INR increases have been reported. No causal relationship established but the manufacturer advises closely monitoring.</td>
</tr>
</tbody>
</table>

**BACK-UP ADVICE AND TREATMENT**

**Older Adult Community Mental Health Teams**

- North Older People MHT, Whiteleaf Centre, Aylesbury - 01865 901468
- South Older People MHT – Haleacre - 01865 901400
- South Older People MHT - Shrublands, High Wycombe - 01865 901309
- Whiteleaf Centre Reception - 01865 902000

<table>
<thead>
<tr>
<th>Community Mental Health Team</th>
<th>Tel:</th>
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<tbody>
<tr>
<td>Community Psychiatric Nurse</td>
<td>Tel:</td>
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<tr>
<td>G.P: Dr…..</td>
<td>Tel:</td>
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<tr>
<td>Oxford Health NHS Foundation Trust Medicines Information</td>
<td>Tel: 01865 904365 <a href="mailto:med.info@oxfordhealth.nhs.uk">med.info@oxfordhealth.nhs.uk</a></td>
</tr>
<tr>
<td>Community Pharmacist</td>
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**References**


<table>
<thead>
<tr>
<th>Title of Guideline</th>
<th>Donepezil, Galantamine, Rivastigmine and Memantine for the Treatment of Alzheimer’s Disease Shared Care Agreement</th>
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<tbody>
<tr>
<td>Guideline Number</td>
<td>786FM</td>
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<td>November 2018</td>
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<td></td>
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<tr>
<td>Oxford Health Drugs and Therapeutics Committee</td>
<td>April 2015</td>
</tr>
<tr>
<td>Medicines Management Joint Executive Team</td>
<td>May &amp; July 2015</td>
</tr>
<tr>
<td>Formulary Management Group</td>
<td>October 2011</td>
</tr>
<tr>
<td>Clinical Guidelines Subgroup</td>
<td>8th October 2015</td>
</tr>
<tr>
<td>Area Prescribing Committee</td>
<td>7th October 2015</td>
</tr>
<tr>
<td>Author/s</td>
<td>Rachel Brown, Clinical Lead Pharmacist – Medicines Information and Evidence Based Medicine, Oxford Health NHS Foundation Trust Dr Brian Murray, Consultant Psychiatrist, Oxford Health NHS Foundation Trust</td>
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<tr>
<td>SDU(s)/Department(s) responsible for updating the guideline</td>
<td>Pharmacy, Oxford Health NHS Foundation Trust</td>
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<tr>
<td>Uploaded to Intranet</td>
<td>11th November 2015 &amp; 7th March 2016</td>
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Buckinghamshire Healthcare NHS Trust/Oxford Health NHS Foundation Trust/ Aylesbury Vale and Chiltern Clinical Commissioning Groups
Buckinghamshire shared care agreement form
For use when prescribing one or more Amber Protocol drug

This form is used to agree shared care between the specialist, patient and GP as follows:
1. Specialist to estimate date of GP prescribing continuation.
2. Specialist to provide pre-treatment counselling and discuss patient responsibilities.
3. Specialist and patient to complete and sign the shared care agreement form.
4. Copy to be filed in patient’s hospital notes.
5. Agreement form, drug specific protocol and responsibilities to be faxed to the GP and copies given to patient.
6. GP to complete and sign agreement form. If unwilling to ‘share care’, provide reason.
7. Scan copy of shared care agreement form, protocol and responsibilities into patient’s notes.
8. Fax signed copy back to specialist.

For completion by specialist

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Indication</th>
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Date of first prescription by specialist

Patient weight kg

Estimated date for prescribing to be continued by GP

Specialist additional comments / advice

We accept:
- the Buckinghamshire shared care responsibilities and
- the requirements defined in the drug specific shared care protocol(s)

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<thead>
<tr>
<th>Patient name, NHS number and address or sticker</th>
<th>Contact details</th>
<th>Signature and date</th>
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<td></td>
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Specialist name and designation:
Tel.
Fax
Email

GP Name and Practice
Tel
Fax
Email

To the GP: If unwilling to “share care” - please define reason(s) below: