NHS
Oxfordshire
Clinical Commissioning Group

Primary Care Prescribing Protocol to Support the Diagnosis and Management of People with Dementia

This prescribing guideline provides the necessary information and guidance to support clinicians in the appropriate prescribing of acetylcholinesterase (AChE) inhibitors. Patients who are diagnosed with Alzheimer's or predominantly Alzheimer's should be offered a trial of an acetylcholinesterase (AChE) inhibitor in line with NICE.

1. Diagnosis and management may be undertaken in line with the Oxfordshire Primary Care Memory Assessment Service (PCMAS). **Practices who wish to initiate prescribing of acetylcholinesterase inhibitors must sign up to participate in the PCMAS**.

2. Alternatively patients may be referred to the specialist Memory Clinic - for diagnosis and - first prescription may be made in primary care following recommendation from the specialist.

Section A: Diagnosis in PCMAS
Section B: Initiation of AChE inhibitors
Section C: Continuation of AChE inhibitors

Background (NICE TA 217 updated June 2018 and NG97 published June 2018)

- Donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of mild to moderate severity
- Memantine is now recommended as an option for managing moderate Alzheimer's disease, including for people who cannot take AChE inhibitors, and as an option for managing severe Alzheimer's disease.
- For new patients, prescribers should only start treatment with donepezil, galantamine, rivastigmine or memantine on the advice of a clinician who has the necessary knowledge and skills. This could include:
  - secondary care medical specialists such as psychiatrists, geriatricians and neurologists
  - Other healthcare professionals such as GPs, nurse consultants and advanced nurse practitioners with specialist expertise in diagnosing and treating Alzheimer's disease.
  - Once a diagnosis is confirmed and a decision has been made to start an AChE inhibitor or memantine, the first prescription may be issued by the GP.
- For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, GPs may start memantine treatment for patients without seeking specialist advice.
- 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. Assessment of functional impairment is equally important.
- Patients who are started on the drug should be reviewed at 3 months and then annually using cognitive, global, functional and behavioural assessment as appropriate
- 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 side effect profile, expectations around concordance, medical co-morbidity, possibility of drug interactions and dosing profiles.

Definitions

The usual definition of mild, moderate and severe Alzheimer's disease is generally based on the cognitive test score and a consideration of functional level. In terms of prescribing AChE inhibitors, there is no difference in the

management of mild and moderate Alzheimer's disease. There are no direct equivalent scores using alternative cognition scoring methods so the following guidelines are a pragmatic approach to guide prescribing in primary care using a combination of the GPCOG* score system (which is part of the Primary Care memory Assessment Service) and the patient's functional state.

* Please note CCG is currently working with OH to review the local choice of cognitive instrument, in line with national guidance. This document will be updated following the outcome of the review.

A. Diagnosis

The diagnosis is based on cognitive impairment resulting in functional impairment where other causes have been excluded. Assessment of cognitive impairment is based on the GPCOG scoring system and dementia may be diagnosed where:

- ***Mild to Moderate*** Alzheimer's where the GPCOG-patient score is <5 or GPCOG-patient score is 5-8 inclusive and the GPCOG-informant questionnaire is 0-3 (Mini Mental State Examination, MMSE: Mild 21-26, Moderate 10-20.)
- ***Severe*** Alzheimer's disease where the GPCOG-patient score of 0-2 (MMSE less than 10 with severe functional impairment.)

Patients *not* appropriate for initiating prescribing in primary care

AChE inhibitors should **not** be initiated in primary care for the following groups of patients where referral to a specialist service is recommended:

- Patients under the age of 65 should be referred to a neurologist.
- Patient with a history of a serious chronic psychiatric disorder should be considered for referral to an old-age psychiatrist. Patients with delirium should be reassessed once medically stable and cognition has plateaued before medication is considered.
- Where there is a history of hallucinations, or Suspected Lewy Body Dementia (LBD), or dementia in Parkinson's disease (PDD). If an individual has been diagnosed with Parkinson's Disease but is no longer under the care of a neurologist, the PCMAS would still be an option for straightforward cognitive decline but if any complexities, including common psychiatric complications, specialist memory clinic referral would be advised.
- Those in whom there is considerable behavioral disturbance should be referred to the old-age psychiatry service.
- Where there are other patient-related factors that make assessment unreliable or difficult (eg learning disability, language difficulties etc).

B. Prescribing Information for patients identified as appropriate for primary care management in line with the PCMAS diagnosis and management protocol

Mild-Moderate Alzheimer's disease

GPs may issue the first prescription for an AChE in this patient group, following recommendation from a specialist. For GPs taking part in PCMAS, once the diagnosis has been made in primary care (PCMAS), the GP should consider whether a trial of an AChE inhibitor is appropriate, taking into consideration potential adverse effects. The patient and their primary carer should be counselled regarding this and it should be explained that:

- not all patients benefit from the drug

- the effects may be small and short-term (under 6 months)
- if a patient continues to decline significantly, there is no advantage in continuing the medication.
- initial side effects (mainly gastro-intestinal effects) are not uncommon but will often settle after a few weeks.

AChE inhibitors may be used in mixed dementia where the clinical presentation suggests Alzheimer's disease despite risk factors for vascular dementia. Where the clinical presentation suggests primarily vascular dementia, AChE inhibitors are not indicated. However, the majority of older people dying with dementia have mixed and highly heterogeneous pathology and that pure vascular pathology are uncommon. It is therefore important that patients with stroke history or vascular risk factors are not excluded from a trial of medication.

AChE inhibitors should be started at the lowest dose and increased to the standard dose after 1 month if no side effects (see under dosage and administration below.)

First line choice:
Donepezil: 5mg once a day for one month then increased if necessary up to 10 mg daily. Tablets are usually taken in the evening just prior to retiring. Maximum dose is 10mg daily.

Second line options:
Rivastigmine: 1.5mg twice daily with morning and evening meals, increasing at minimum of fortnightly intervals to 3mg bd, then 4.5mg bd to a maximum of 6mg bd. The effective maintenance dose is 3-6mg bd.
If treatment is interrupted for more than several days it should be reinitiated at 1.5mg twice daily.
Rivastigmine patches should be considered in patients unable to swallow or where oral treatment is not tolerated.

- 4.6 mg/ 24 hours for first 28 days, increased if tolerated to 9.5 mg/ 24 hours daily.
- Increase if necessary to 13.3 mg / 24 hours daily if well tolerated after a minimum of six months of treatment at 9.5 mg/24 hours and cognitive deterioration or functional decline. NB. 9.5 mg/24 hours is the recommended daily effective dose.
- If treatment interrupted for more than 3 days, retitrate from 4.6 mg / 24 hours patch.

Information about rivastigmine patches (MHRA December 2014)

- 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 minimize 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. If an overdose is suspected, all rivastigmine patches should be removed immediately and no further patch should be applied for the next 24 hours

Galantamine: 8mg XL daily for 4 weeks, then 16mg XL for at least 4 weeks then to a maximum dose of 24mg XLdaily. Maintenance dose is 16 – 24 XL mg daily.

Cost comparisons of AChE inhibitors

1 Month Treatment (generic)	**Cost £** (Drug tariff -Feb 2019)
Donepezil 10mg tabs (28)	1.00
Rivastigmine 3mg capsules (28)	3.24
Rivastigmine 6mg capsules (28)	29.17
Rivastigmine 9.5mg/24hours transdermal patches (30)	30.02

(second line only)	
Galantamine 16mg MR capsules (28)	64.90

Moderate to severe dementia in Alzheimer's disease

Memantine
Initially 5 mg once daily, then increased in steps of 5 mg every week; usual maintenance 20 mg daily; maximum 20 mg per day.

In new patients currently not taking any AChE inhibitors, GPs may issue the first prescription for memantine following recommendation by the specialist.

For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, GPs may start memantine treatment for patients without seeking specialist advice, as following:

- consider memantine in addition to an AChE inhibitor if they have moderate disease
- offer memantine in addition to an AChE inhibitor if they have severe disease.

C. Ongoing Management and Monitoring

Patients in PCMAS or discharged from Memory Clinic

Response/effectiveness should be assessed at 3 months after treatment initiation by either PCMAS or specialist Memory Clinic. If patients have continued to decline significantly within the first three months of treatment, there is likely to be no advantage in continuing treatment.

Only stable patients should be discharged from the specialist Memory Clinic and this may be arranged after the 3 month review. The Memory Clinic may retain prescribing for the initial 3 months, or alternatively GPs may be asked to issue the first prescription following diagnosis. Thereafter, patients should be reviewed annually.

Review and ongoing monitoring

- Annual review should include patient's physical health such as weight and blood screening as clinically indicated, treatment compliance, as well as assessing if there is any worsening cognition and/or new or distressing symptoms.
- Continuing decline is to be expected on treatment and does not necessarily indicate no benefit of treatment, especially in the first couple of years. Patients who become unstable through challenging behaviour and/or psychiatric symptoms may be referred back to the CMHT.
- Patients should not be referred routinely for reassessment because of dementia progression. The exception might be where the deterioration could be secondary to an underlying medical problem, such as delirium or if subsyndromal delirium is present, where referral to the geratology rapid access clinic might be appropriate.
- Assessment of patients' mental capacity should be undertaken in primary care and/ or social services with respect to the specific decision concerned, and should not be referred to the memory clinic.

Discontinuation of Treatment

- Ongoing benefit should be assessed and a trial discontinuation may be considered if there has been rapid clinical deterioration after a trial of appropriate doses or combinations of anti-dementia drugs. A MMSE score less than 10 is some guide to clinical decision making but should not be the only indication for stopping medication. This would be done in discussion with the Carer and GP.
- Although there is a small risk of further deterioration in function and behaviour associated with AChE inhibitor withdrawal, in most cases there will be no change. If there is a clear deterioration linked solely to the discontinuation of an AChE inhibitor manifesting within 4 weeks, the drug may be resumed if appropriate.
- There is very little evidence of benefit beyond 3 years AChE inhibitor treatment. Therefore a specific review is advised following 3 years AChE treatment to consider whether the drug should be continued.
- There is recent evidence in the DOMINO[1] study that some patients on donepezil will continue to benefit from their treatment even after their dementia becomes severe. 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.
- The NICE economic model assumes that AChE inhibitors are discontinued on admission to a care home. Following admission to a care home memory-enhancing medication should be reviewed. The decision to discontinue treatment should be on an individual basis, and consideration given to family/patient views and expectations.
- 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 below). The patient should be closely monitored for any subsequent deterioration and consideration given to the need to reinstate treatment.

Stopping AChEIs

Donepezil	Long half life, so can be stopped without the need for tapering, however it may be advisable to reduce to 5mg daily for a month and monitor for deterioration before stopping altogether.
Rivastigmine	Short half life. Reverse titration recommended i.e. a reduction of 1.5 to 3mg every 2 to 4 weeks.
Galantamine	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.

Severe Alzheimer's disease

- New trials of AChE inhibitors are not recommended in this patient group.
- For those patients already on an AChE inhibitor, it should not be continued unless there is evidence that it is benefiting the patient. A trial of discontinuation should be considered where the patient has continued to decline cognitively and has concomitant increasing functional impairment. Carers' views should be taken into account and anxieties about the effects of discontinuation should be addressed. Although there is a small risk of further deterioration in function and behaviour associated with AChE withdrawal, in most cases there will be no change. If there is a clear deterioration linked solely to the discontinuation of an AChE inhibitor manifesting within 4 weeks, the drug may be resumed if appropriate.
- A patient who is not currently taking an AChE inhibitor being considered for memantine should be referred for further assessment by the specialist memory services or a specialist clinician. Once a decision has been made to start memantine, the first prescription may be issued by GPs.
- For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, GPs

[1] N Engl J Med 2012; 366:893-903March 8, 2012DOI: 10.1056/NEJMoa1106668

may start treatment with memantine without taking advice from a specialist clinician.

Supporting Prescribing Information for Acetylcholinesterase Inhibitors (see BNF/SPC for full details)

Adverse Effects:
The most common side effects include diarrhoea, muscle cramps, nausea and vomiting, dizziness (incidence >10%). Headache, decreased appetite, renal incontinence, abdominal disturbance & 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.

Contraindications

- Previous documented hypersensitivity to donepezil or rivastigmine or galantamine
- Galantamine – is contraindicated in severe hepatic and renal impairment
- Rivastigmine patch - Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch.

Cautions

- **Cardiovascular conditions**: AChE inhibitors are cautioned in patients with conduction deficits such as sick sinus syndrome and AV or SA node block because they may cause a significant bradycardia. They may 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.
- **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.
- **Genitourinary conditions**: Cholinesterase inhibitors may cause bladder outflow obstruction.
- **Pulmonary conditions**: Due to potential cholinergic effects, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.
- **Neurological conditions**: Due to potential cholinergic effects, the drug may cause generalised seizures (although these may also be a feature of the underlying disease process) and may cause extrapyramidal symptoms, thus worsening Parkinsonian symptoms.
- **Renal or hepatic impairment:** see BNF or SPC for specific advice

Drug Interactions for AChE Inhibitors: (BNF and SPC accessed 1/1/15)

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

* 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 for Memantine (see BNF/SPC for full details)

Adverse Effects
Common side effects are: somnolence, dizziness, raised blood pressure, dyspnoea, constipation, elevated LVFs and headache. Uncommon side effects include: vomiting, heart failure, psychotic reactions, confusion. Rarely seizures have been reported

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.

Cautions
Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy.
Initial dose reductions are required in renal impairment (eGFR < 50)

Drug Interactions for Memantine (BNF and SPC accessed 1/1/15)

Drugs	Interaction
L-dopa, dopaminergic agonists e.g bromocriptine, and anticholinergics	Memantine may increase levels
Barbiturates, antipsychotics	Memantine may decrease levels
Amantadine, ketamine, dextromethorphan	The use of memantine, an NMDA antagonist, with other NMDA antagonists, is predicted to increase the risk of adverse effects
Cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine	May increase plasma levels of memantine
Sodium bicarbonate, Drugs that increase the pH of urine	May reduce the elimination of memantine
Anticoagulants	May enhance anticoagulant effect