SHARED CARE GUIDELINE

Pennine Care NHS
NHS Foundation Trust

Title: The prescribing and monitoring of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's Disease.	
Scope: Pennine Care NHS Foundation Trust NHS Bury NHS Oldham NHS Heywood, Middleton and Rochdale NHS Stockport NHS Tameside & Glossop	**Version:** Version 3

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To be read in conjunction with the following documents:	• British National Formulary (BNF) • Summary of Product Characteristics (SPC) for individual products • Pennine Care NHS Foundation Trust Guidelines for prescribing donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (MM011)
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1. Introduction

Alzheimer's Disease (AD) is the most common cause of dementia. It is characterised by deterioration in cognition (thinking, memory, calculation and language), functional ability (activities of daily living) and behaviour and mood.

Cognitive deterioration has been observed to be associated with progressive loss of cholinergic neurones, and consequent decreasing levels of acetylcholine in the brain. The cholinesterase inhibitors, donepezil, galantamine and rivastigmine (CEIs) act to boost acetylcholine concentrations by inhibiting its breakdown by the enzyme cholinesterase.

Galantamine also enhances the action of acetylcholine at nicotinic receptors.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

NICE technology appraisal 217 (Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, March 2011) and NICE clinical guideline CG 42 (Dementia) (November 2006, updated March 2011) recommend CEIs treatment of cognitive symptoms in patients with mild to moderate Alzheimer's disease (ie Mini Mental State Examination (MMSE) score of 10-26).
(These replace technology appraisal 111 (November 2006), and the relevant section in Clinical Guideline CG 42 (2006), which restricted CEIs to patients with moderate Alzheimer's disease only.)

In addition, memantine is now recommended as an option for people with moderate Alzheimer's disease who are intolerant of, or who have a contraindication to, CEIs or who have severe Alzheimer's disease.

NICE CG 42 also recommends CEIs for non-cognitive symptoms and/or behaviour that challenges in patients with mild, moderate or severe Alzheimer's disease, if it is causing significant distress or potential harm to the patient and/or carers, and antipsychotic drugs are unsuitable. This is, however, an unlicensed indication.

Under the terms of this Shared Care Guideline, the patient and carer can expect to be provided with sufficient advice regarding the possible benefits and risks of treatment to allow them to make an informed decision about CEI therapy.

They can also expect regular follow-up assessment, and that care will be shared with their own GP as soon as practicable, to allow easier access to medicines.

This Shared Care Guideline has been developed based on clinical decision making. There may be outstanding commissioning issues which are outside the remit of the document.

The guidance in this document should be used in conjunction with Trust Guidelines for prescribing donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (MM011), the British National Formulary (BNF), Summary of Product Characteristics (SPC) and Patient Information Leaflets (PILs).

2. Clinical condition being treated

2.1 Cholinesterase inhibitors (CEIs)

Licensed indications

Mild to moderate dementia in AD (donepezil and galantamine)
Mild to moderate dementia in AD and Parkinson's disease (rivastigmine)

NICE Technology Appraisal TA217 recommends that any of the three CEIs may be used for the treatment of mild to moderate Alzheimer's disease in patients whose MMSE score is 10-26 points.

Once a decision to prescribe has been taken NICE recommends that the drug with the lowest acquisition cost should be started. (See the current edition of the BNF for pricing details).

An alternative CEI may be prescribed where it is considered appropriate having taken into account the adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions and dosing profiles.

2.2 Memantine

Licensed indications

Moderate (MMSE 10-20 points) to severe (MMSE less than 10 points) Alzheimer's disease.

Memantine is recommended for
i) people with moderate Alzheimer's disease who are intolerant of, or who have a contraindication to, CEIs or
ii) people who have severe Alzheimer's disease.

2.3 Assessment

The severity of Alzheimer's disease and the need for treatment should be assessed and regularly reviewed using global, cognitive, functional and behavioural assessments as well as the MMSE rating scale, an appropriate specialist team.

When using assessment scales, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results, and make any adjustments they consider appropriate.

Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

3. Product information and treatment regimens to be used

See Tables 1 and 2

4. Regimen Management

Responsibilities of the Consultant / Specialist Team

- To assess the patient and establish the diagnosis.
- To determine the appropriate treatment, initiate and up-titrate the dose and prescribe until the patient is stable. Alternatively, where this is agreed locally, to supply instructions/directions to the GP for initiation and titration of the drug treatment to a suitable dose.
- To ensure the patient and carers are fully informed about the treatment, including potential side effects and other difficulties relating to treatment, monitoring arrangements and the circumstances under which treatment may be withdrawn.
- To write to the General Practitioner (GP) detailing the diagnosis, global assessment, MMSE score, the reason for treatment, and the preferred medication, requesting that shared care arrangements, including prescribing, commence.
- To undertake a review of the patient's condition 6-9 months after initial assessment and where the patient is stable and there is continuing clinical benefit, to discharge the patient to the GP's care.
- To be available for advice if the patient's condition changes.
- To advise that prescribing be discontinued when it is no longer appropriate.
- To include MMSE scores in any follow-up letters to the GP, so that the GP is aware of any changes.
- To monitor and liaise with GP regarding any adverse drug reactions (ADRs) which occurred during treatment, including the reporting of any serious ADRs to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card System.

Responsibilities of the General Practitioner (GP)

- To refer patients suspected of suffering from a cognitive impairment for specialist advice as deemed necessary.
- To prescribe the medication recommended by the Consultant/ Specialist Team at monthly intervals once shared care has commenced
- To monitor the patient's condition at six-monthly intervals, by means of the Mini Mental State Examination, and by global impression gained after talking to the patient and/or his/her carers.
- To monitor concordance and to inform the Consultant/ Specialist Team if there are any difficulties.
- To contact the Consultant/ Specialist Team if any of the following occur
    - Sudden deterioration in cognitive function
    - Change or discontinuation in the recommended medication
    - Patient intolerance or adverse side effects to medication
    - Non-concordance
    - Signs or symptoms of toxicity

    - Initiation of potentially interacting medication.
- To request guidance from the Consultant/Specialist team as to the discontinuation of treatment when it is deemed no longer appropriate
- Where appropriate, to remind patients to keep their appointments with the Consultant/ Specialist Team.
- To liaise with the Consultant/Specialist Team regarding any ADRs including the reporting of any serious ADRs to the MHRA via the Yellow Card System.
- If unable to agree to the sharing of care and the prescribing of medication to inform the Consultant/Specialist team of the nature of any concerns.

5. Summary of cautions, contra indications, side-effects

See Appendix 1
Further details may be obtained from the BNF and SPC. Prescribers should be alert to the possibility of adverse effects and interactions as yet unknown due to limited clinical experience, and report them via the Yellow Card System

6. Back-up care available to GP from Hospital, including emergency contact procedures and help line numbers

Written correspondence from the Consultant/ Specialist Team following appointments and follow–up visits detailing the next review date and recommended any dose adjustments.
Telephone advice from the Consultant/ Specialist Team during office hours.

7. Statement of agreement

Shared care is an agreement between the Consultant/ Specialist Team and GP. This Shared Care Guideline is a request by the Consultant/ Specialist Team to share the suggested care pathway of the patient. GPs unable to agree to the sharing of care and prescribing of medication should make this known to the Consultant/ Specialist Team, within 14 days, stating the nature of the concern.

8. Written information provided to the patient

Manufacturers Patient Information Leaflets for donepezil, rivastigmine galantamine and memantine.

Table 1 – CEIs - summary of formulations and treatment regimens

Formulation	Strength	Dose range	
		Initiation	Maintenance
Donepezil (as hydrochloride) Aricept™, Aricept Evess ™			
Tablets	5mg 10mg	5mg daily at bedtime for 4 weeks	Increase if necessary to 10mg daily on clinical assessment. Maximum 10mg daily.
Orodispersible tablets *(For patients with swallowing or compliance difficulties. Should be placed on the tongue, allowed to disperse, and swallowed)*	5mg 10mg		
Galantamine (as hydrobromide) Reminyl™, Reminyl XL™			
Tablets	8mg 12mg	4mg twice daily for 4 weeks *(preferably with breakfast and evening meals)*	Increase to 8mg twice daily for 4 weeks; maintenance dose 8-12mg twice daily
Oral solution *(For patients with swallowing or compliance difficulties)*	4mg/ml (with pipette)		
Capsules (modified release) *(For patients where a once daily dosage would be advantageous)*	8mg 16mg 24mg	8mg daily for 4 weeks	16mg daily for 4 weeks; maintenance 16-24mg daily
Rivastigmine (as hydrogen tartrate) Exelon™			
Capsules	1.5mg 3mg 4.5mg 6mg	1.5mg twice daily for a minimum of 2 weeks *(with breakfast and evening meal)*	If tolerance is good increase at two weekly intervals by 1.5mg to a maximum of 6mg twice daily.
Oral solution *(For patients with swallowing or compliance difficulties)*	2mg/ml (with oral syringe)		
Patches *(For patients with swallowing or compliance difficulties)* *(For details of equivalence of oral and transdermal formulations, consult British National Formulary, or Summary of Product Characteristics)*	4.6mg/24hrs 9.5mg/24hrs	Apply a 4.6mg patch daily *(to a new area of dry skin)* for a minimum of 4 weeks.	If well tolerated increase to 9.5mg daily. *(If patch is not applied for more than several days' treatment should be restarted with 4.6mg patch.)*

Table 2 – Memantine - summary of formulations and treatment regimens

Formulation	Strength	Dose range	
		Initiation	Maintenance
Memantine (as hydrochloride) Ebixa ™			
Tablets	10mg 20mg	5mg daily	Increase in steps of 5mg at weekly intervals to max. 20mg daily
Oral solution *(For patients with swallowing or compliance difficulties. Should be dosed onto a spoon or into a glass of water before administration)*	5mg per actuation (10mg per ml)		

9. Supporting References

British National Formulary (BNF) Edition 61, March 2011

NICE clinical guideline CG42 Dementia, November 2006 (Amended March 2011)

NICE technology appraisal guidance TA217 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, (review) March 2011

Donepezil. Summary of Product Characteristics.
http://www.medicines.org.uk/emc/ Accessed 6th April 2011

Rivastigmine. Summary of Product Characteristics.
http://www.medicines.org.uk/emc/ Accessed 6th April 2011

Galantamine. Summary of Product Characteristics.
http://www.medicines.org.uk/emc/ Accessed 6th April 2011

Memantine, Summary of product Characteristics
http://www.medicines.org.uk/emc/ Accessed 5th May 2011

Donepezil

Adverse effects *Predominant* *Less frequently / Rarely*	Nausea, vomiting, diarrhoea, fatigue, insomnia, muscle cramps, anorexia, common cold and abdominal disturbances Liver dysfunction including hepatitis, S/A or A/V block, convulsions, gastric and duodenal ulcers, psychiatric disturbances, hepatitis, bladder outflow obstruction. Extrapyramidal symptoms. Minor increase in serum concentrations of muscle creatine kinase.	
Contra-indications	Pregnancy and breastfeeding. Hypersensitivity to donepezil or piperidine derivatives, or to excipients used in the formulation.	
Special warnings / precautions for use	Donepezil may exaggerate succinylcholine-type muscle relaxation during anaesthesia. Donepezil may have vagotonic effects on heart rate (e.g. bradycardia) – important for patients with sick sinus syndrome and other S/V cardiac conduction conditions including S/V and A/V block. Patients at increased risk of developing ulcers; patients with a history of peptic ulceration and concurrent NSAIDs should be monitored for the development of gastric ulceration. Donepezil may cause bladder outflow obstruction. Cholinomimetics are believed to have the potential for generalised convulsions, and to exacerbate or induce extrapyramidal symptoms. Care should be taken in patients with a history of asthma or COPD.	
Renal impairment	Limited data suggests that donepezil clearance is not significantly altered in moderate to severe renal insufficiency suggesting that dose adjustment is not necessary in these patients.	
Liver disease	Donepezil has not been associated with liver function test alterations in available studies.	
Monitoring (by Consultant/ Specialist Team)	Monitor for signs / symptoms of toxicity e.g. persistent nausea or vomiting, 6 monthly.	
Interactions	*Cholinergic agonist (cholinomimetic)*	Synergistic effect with donepezil
	Enzyme inducers	Rifampicin, phenytoin, carbamazepine, alcohol, can reduce effects of donepezil.
	Enzyme inhibitors	Inhibitors of CYP34A and CYP2D6, including fluconazole, itraconazole, erythromycin, fluoxetine, paroxetine may inhibit metabolism and increase side effects
	Antimuscarinics	Possibly antagonise the effect of donepezil
	Donepezil	Possibly enhances the effect of suxamethonium.

Galantamine

Adverse effects *Predominant* *Women* *Other effects* *Rarely*	Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, anorexia, fatigue, dizziness, headache, somnolence, and weight loss. More susceptible to nausea, vomiting and anorexia. Confusion, fall, injury, insomnia, rhinitis, UTIs. Tremor, syncope, bradycardia.	
Contra-indications	Prior hypersensitivity to galantamine hydrochloride, or known hypersensitivity to any excipients used in the formulation. Orange yellow S, aluminium lake (E110) present in the 12mg tablets may cause allergic reaction. Severe hepatic (Child-Pugh score >9) and severe renal impairment (creatinine clearance <9ml/min). Patients with galaxies tolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.	
Special warnings / precautions for use	Galantamine may exaggerate succinylcholine-type muscle relaxation during anaesthesia. Due to association with weight loss, patient's weight should be monitored. Galantamine may have vagotonic effects on heart rate (e.g. bradycardia) – important for patients with sick sinus syndrome and other S/V cardiac conduction conditions including S/V and A/V block or who use drugs that significantly reduce heart rate. Patients at increased risk of developing ulcers; patients with a history of peptic ulceration and concurrent NSAIDs should be monitored for the development of gastric ulceration. Galantamine is not recommended in patients with gastrointestinal obstruction of recovering from gastrointestinal surgery. Galantamine may cause bladder outflow obstruction and is not recommended for patients with this condition or recovering from bladder surgery. Cholinomimetics are associated with generalised convulsions and may exacerbate or induce cholinomimetics symptoms. Care should be taken when prescribing cholinomimetics for patients with a history of asthma or COPD.	
Liver disease	Dose reduction for moderate to severe hepatic impairment.	
Monitoring (by Consultant/ Specialist Team)	Monitor for signs / symptoms of toxicity e.g. persistent nausea or vomiting, 6 monthly.	
Interactions	Galantamine may exaggerate succinylcholine-type muscle relaxation during anaesthesia.	
	Cholinergic agonists	Synergistic effect with galantamine (e.g. pilocarpine)
	Anticholinergics	Antagonistic effects (e.g. drugs for urinary incontinence)
	Enzyme inhibitors	Inhibitors of CYP34A and CYP2D6, including fluconazole, itraconazole, erythromycin, fluoxetine, paroxetine may inhibit metabolism and increase side effects

Rivastigmine		
Adverse effects *Predominant* *Females* *Rarely* *Potential for*	Headache, nausea, vomiting, dizziness, diarrhoea, fatigue, anorexia, asthenia, weight loss, agitation, confusion, depression, insomnia, sweating, malaise, tremor, dyspepsia, URTI, UTIs and somnolence. Increased sweating, malaise, weight loss and tremor. More susceptible to nausea, vomiting, weight loss and loss of appetite. Angina pectoris, gastrointestinal haemorrhage, syncope, gastric and duodenal ulcers, bradycardia, seizures and rashes. Bladder outflow obstruction, convulsions.	
Contra-indications	Prior hypersensitivity to rivastigmine, or known hypersensitivity to carbamate derivatives or to any excipients used in the formulation. Severe liver impairment. Breastfeeding.	
Special warnings / precautions for use	Rivastigmine may exaggerate succinylcholine-type muscle relaxation during anaesthesia. Nausea, vomiting and gastrointestinal disturbances may occur particularly when initiating treatment and/or increasing the dose. Due to association with weight loss, patients weight should be monitored. Care must be taken in patients with sick sinus syndrome or conduction defects (including S/A and A/V block). Rivastigmine may increase gastric acid secretions therefore patients with a history of peptic ulceration and concurrent NSAIDs should be monitored for the development of gastric ulceration. Cholinomimetics are associated with generalised convulsions and may exacerbate or induce extrapyramidal symptoms. Care should be taken when prescribing cholinomimetics for patients with a history of asthma or COPD. Caution is recommended in patients predisposed to urinary obstruction and seizures.	
Renal impairment	Information available suggests dosage adjustment is not necessary in renally impaired patients.	
Liver disease	Information available suggests dosage adjustment is not necessary in hepatically impaired patients.	
Monitoring (by Consultant/ Specialist Team)	Monitor for signs / symptoms of toxicity e.g. persistent nausea or vomiting, 6 monthly.	
Interactions	Rivastigmine may exaggerate succinylcholine-type muscle relaxation during anaesthesia. Potential for inhibition of butyrylcholinesterase mediated metabolism of other drugs.	
	Cholinergic agonists	Synergistic effect with rivastigmine (e.g. pilocarpine)
	Anticholinergics	Antagonistic effects (e.g. drugs for urinary incontinence)

Memantine		
Adverse effects *Predominant* *Less frequently / Rarely*	Constipation, hypertension, dyspnoea, headache, dizziness, drowsiness Vomiting, thrombosis, heart failure, confusion, fatigue, hallucinations, abnormal gait. Seizures, pancreatitis, psychosis, depression, suicidal ideation	
Contra-indications	Hypersensitivity to memantine or any excipients	
Special warnings / precautions for use	Caution in patients with a history of convulsions, recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension. Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided.	
Renal impairment	Dose adjustment may be required in moderate to severe renal function. Consult the SPC for details.	
Liver disease	No dose adjustment necessary in mild to moderate hepatic impairment. Avoid in severe liver impairment.	
Monitoring (by Consultant/ Specialist Team)	Monitor for signs / symptoms of toxicity 6 monthly.	
Interactions	*Ketamine*	Increased risk of CNS toxicity
	Dextromethorphan	Increased risk of CNS toxicity
	Warfarin	May enhance anticoagulant effect
	Primidone	May reduce anticonvulsant effect
	Antimuscarinics	Possibly enhances effect
	Antipsychotics	Possibly reduces effect
	Barbiturates	Possiblt reduces effect
	Dopaminergics	Possibly enhances effects of dopaminergics, selegiline and amantadine; increased risk of CNS toxicity
	Muscle relaxants	Possibly modifies the effect of baclofen and dantrolene