

Guidance for the prescribing of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's dementia

This guidance has been prepared and approved for use in Worcestershire in consultation with NHS Worcestershire, Worcestershire Health and Care NHS Trust and the Worcestershire Acute Hospitals NHS Trust. The guidance is based on NICE Technology Appraisal (TA217) 'Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease'. The objective of this guidance is to define the key responsibilities of each health care professional in the management of selected patients identified for treatment.

Principles

- Treatment is initiated by a medical specialist (or a member of their team) in the care of people with dementia, usually Older Adult or Learning Disability Psychiatrists, Neurologists or Geriatricians.
- The patient has consented to treatment or the carer's views have been taken into consideration to reach a best interest decision if the patient does not have capacity to consent.
- The responsibility for each prescription lies with the individual prescriber.
- It is the responsibility of all three parties (patient/carer, specialist team and GP) to ensure that appropriate information is available to each party as required.
- Once stabilised on treatment in secondary care, ongoing treatment and monitoring may take place in primary care if deemed clinically appropriate.
- Re-referral back into specialist services may be necessary to assess if treatment is no longer indicated or to assess if alternative treatment is appropriate.
- Treatment should generally only be continued for donepezil, rivastigmine or galantamine when there has been an improvement or no deterioration in at least one clinical domain (global, cognitive, behavioural, neuropsychiatric or activities of daily living) or until the Folstein MMSE score falls below 10 (if this is clinically appropriate).
- Treatment should generally only be continued for memantine when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
- In cases where there is a mixed dementia, manage according to the condition that is thought to be the predominant cause of the dementia (NICE CG42).

Background

The acetylcholinesterase inhibitor (AChI) drugs donepezil, galantamine, rivastigmine are recommended by NICE for the treatment of the cognitive symptoms of mild to moderate severity Alzheimer's dementia (AD). These drugs act by increasing or maintaining levels of acetylcholine within the brain, through inhibiting the enzyme acetylcholinesterase.

NICE also supports the use of AChI in Dementia with Lewy bodies and Parkinson's disease dementia where there are non-cognitive symptoms (e.g visual hallucinations) causing significant distress or leading to behaviour that challenges (NICE CG42).

NICE recommends memantine (a glutamate modulator acting on the NMDA receptor unit) as an option for AD management in;

- moderate AD where patients are intolerant of or have a contra-indication to an AChI
- severe AD

Once the decision to prescribe an AChI has been taken, NICE have recommended the use of a drug with the lowest acquisition cost. However, an alternative AChI 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. See Appendix 1 for further prescribing information.

Assessing severity in Alzheimer's dementia

The severity of Alzheimer's dementia can be assessed using several methods, depending on the setting (for example research or clinical practice) and the outcome being assessed. Clinical practice uses a variety of measures, often along with clinically based assessments. Severity is commonly defined by the Folstein Mini Mental State Examination (MMSE) score as follows:

mild AD:	MMSE 21–26
moderate AD:	MMSE 10–20
severe AD:	MMSE <10.

The MMSE score may not be the preferred measure of severity in the following circumstances:

- High pre-morbid intelligence
- Poor educational achievement
- English not first language
- Learning or other disability (e.g., sensory impairment)
- Clinical features of dementia that may affect the score, including depression, anxiety or dysphasia.

In these cases another appropriate method of assessment should be used.

Diagnosis performed by a specialist should include cognitive, global, behavioural and functional assessment. Improvement is usually defined as no decline in MMSE score together with evidence of global improvement on the basis of behavioural and/or functional assessment. For those patients who do not show improvement, or a slowing down of the rate of cognitive decline in the first few months, it is unlikely that they will show benefit later on and the medication should be stopped. Patients and carers will be advised on the likely magnitude of clinical effect, possibility of adverse effects, the possibility of treatment failure and when treatment will be stopped.

Responsibilities of the Consultant / Specialist Team

- To assess the patient, establish the diagnosis of Alzheimer's dementia, and determine an individual patient management plan.
- Before treatment starts to ensure the patient and carers are fully informed about the treatment including associated problems, how to avoid them and when treatment may be stopped.
See <http://www.choiceandmedication.org.uk/worcestershire> to access information resources
- To initiate therapy, monitor the patient and review his/her therapy at regular, appropriate intervals (six weeks, three months and then annually if patient remains in secondary care).
- To provide the patient's treatment until their dose and condition are stabilised.
- To invite the GP to take over prescribing when appropriate, with a clear written plan
- To be clear early on in treatment (usually around three months) that treatment is beneficial and should continue longer term.
- Treatment should generally only be continued for AChI when there has been an improvement or no deterioration in at least one clinical domain (global, cognitive, behavioural, neuropsychiatric or activities of daily living) or until the Folstein MMSE score falls below ten (if this is clinically appropriate) i.e. 'severe impairment'.
- Treatment should generally only be continued for memantine when it is considered to be having a worthwhile effect on cognitive, global, functional and behavioural symptoms.
- To be available for advice if the patient's condition changes.
- To monitor and liaise with the GP for any adverse drug reactions (ADRs) which occur during treatment including reporting of serious ADRs to the MHRA.
- To be available for advice on the initiation and discontinuation of AChI and memantine with re-referral back into secondary care if deemed clinically appropriate.

Responsibilities of the General Practitioner

- To carry out an initial assessment prior to referral to specialist for diagnosis to include a clinically appropriate physical examination, basic cognitive assessment and prerequisite investigations
- To prescribe these medicines ONLY on the advice of a specialist and once patient is stabilised on treatment.
- To carry out a review at least every twelve months (to include MMSE if clinically appropriate) if agreed it is clinically appropriate for patient to be discharged back to primary care.
- Treatment should generally only be continued for AChI when there has been an improvement or no deterioration in at least one clinical domain (global, cognitive, behavioural, neuropsychiatric or activities of daily living) or until the Folstein MMSE score falls below ten (if this is clinically appropriate) i.e. 'severe impairment'.
- To liaise with specialist when AChI treatment appears no longer to be indicated and consider re-referral back to specialist for consideration of memantine if clinically appropriate.
- Treatment should generally only be continued for memantine when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
- To liaise with the specialist regarding any adverse drug reaction (ADR) including the reporting of any serious ADRs to the MHRA.

Responsibilities of the Patient or Carer

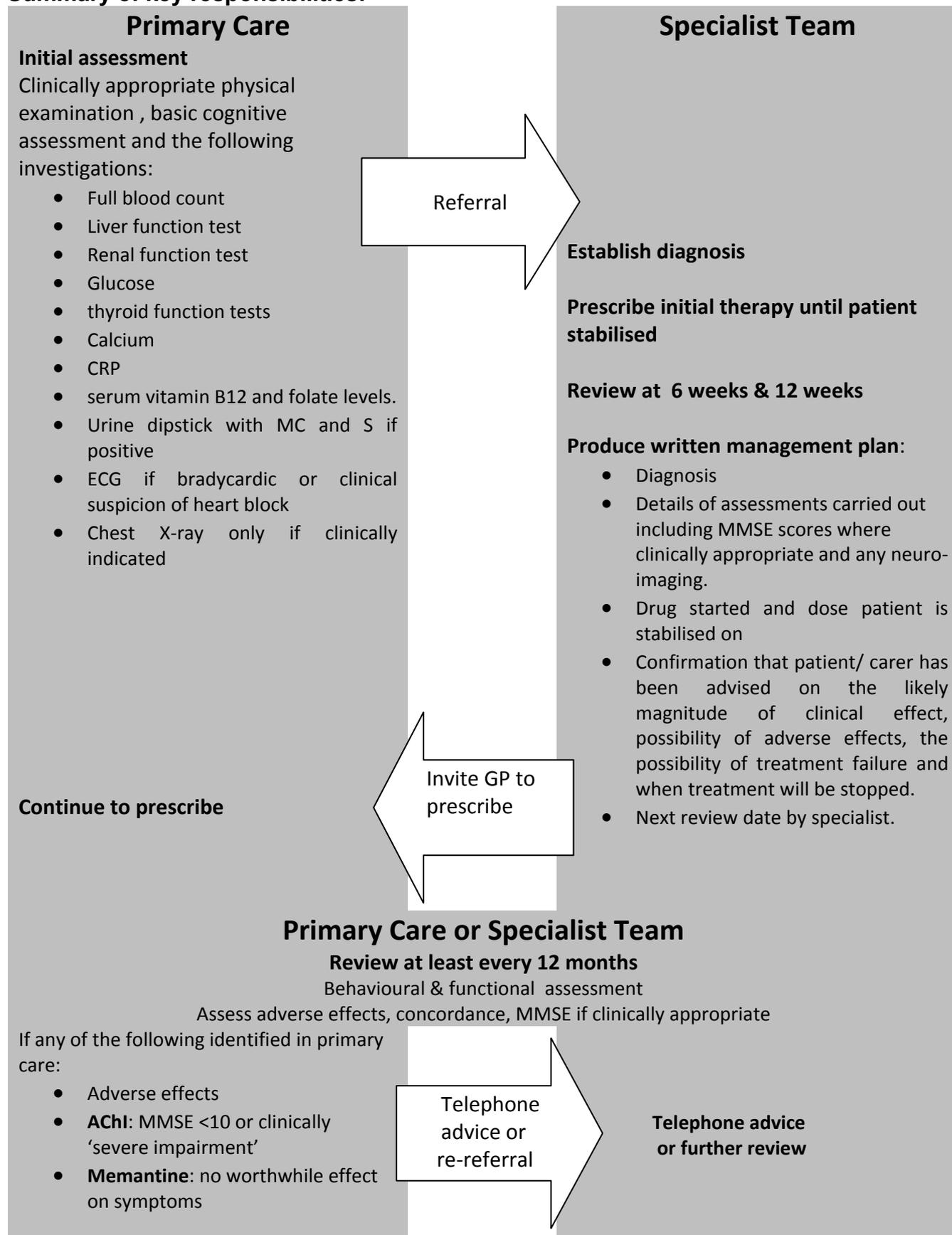
- Attend appointments and cooperate with assessments.
- Report any adverse effects to the prescriber whilst taking treatment.
- Report to the prescriber if the patient misses several days' doses (as dose re-titration may be needed) or if the patient has taken too many tablets.
- Report to the prescriber any concerns about their treatment.

Monitoring

- After initiation, the specialist team should review the patient at around six weeks to assess concordance and tolerance to the drug. A further review should be undertaken at around twelve weeks to assess benefit and decide whether long term treatment should continue.
- Thereafter regular assessments, at least annually should include:
 - Folstein MMSE (if clinically appropriate).
 - Behavioural and functional assessment using a recognised rating scale or by forming a clinical impression.
- The annual review may take place in primary or secondary care as clinically appropriate.

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Summary of key responsibilities:



Appendix 1- Prescribing Information

AChE Inhibitors	Usual maintenance dose	Formulations	Adverse effects / contraindications
Donepezil	5-10mg once daily usually at night	tablets orodispersible tablets	Can cause unwanted dose-related cholinergic effects and should be started at a low dose. The dose should be increased incrementally according to response and tolerability. Adverse effects are usually more pronounced at higher doses and during rapid dose titration. Prescribe with care in patients with asthma and chronic obstructive airways disease, severe hepatic or renal failure, cardiovascular conditions, e.g. heart block or SVT, urinary outflow obstruction, or history of peptic ulceration. All drugs with anticholinergic effects (i.e. drugs for urinary incontinence, tricyclic antidepressants) should be avoided wherever possible in people with AD as they exacerbate symptoms and reduce the efficacy of the AChI.
Rivastigmine	3-6mg twice daily 4.6mg/24hours (5cm ²) 9.5mg/24hours (10cm ²)	capsules liquid transdermal patches*	
Galantamine	8-12mg twice daily 16-24mg m/r once daily	tablets liquid m/r capsules	
Glutamate modulators	Usual maintenance dose	Formulations	Adverse effects / contraindications
Memantine	20mg daily	tablets liquid in pump dispenser 5mg/actuation	Most common side effects headache, somnolence and constipation. In severe renal impairment administer half dose (10mg daily). May exacerbate effects of anticholinergic agents and dopamine promoting agents used in treatment of Parkinson's disease. Use with caution in people with a history of seizures.

Choosing a First Line AChI

- NICE advocates using the drug with the lowest acquisition cost. Generic versions of AChI tablets are expected to become available soon. Donepezil is likely to be the most cost effective first line option at a once daily dose.
- Liquid preparations may provide more flexible dose titration when starting treatment.
- *Reserve patches for use when oral formulations cannot be swallowed or cannot be tolerated due to serious side effects. Ensure patients are familiar with instructions as incorrect use has been associated with overdose. (e.g not removing patch/ applying more than one patch at the same time).

Changing to an alternative AChI

- Tolerability to individual AChI varies and may be influenced by titration options: e.g. adverse effects associated with the starting dose of donepezil may be avoided by a slower introduction of galantamine or rivastigmine.
- If a patient fails to respond to an AChI despite a therapeutic dose and adequate time frame there is no rationale for changing to an alternative AChI.