

Drugs for Dementia: information for primary care

Cholinesterase inhibitors and Memantine are now classified as Amber Initiated drugs by the Pan Mersey Area Prescribing Committee, allowing:

- The initial transfer of prescribing to primary care after successful initiation and;
- Ultimate discharge from secondary care services where both secondary and primary care agree it is appropriate to do so.

This document aims to provide pragmatic primary care information to support both activities.

Who will diagnose and decide who is suitable for which drug?

Specialists will continue to diagnose, assess suitability and safety of drug treatment for patients referred to Memory Services. Specialists will counsel and inform patients of their diagnosis and treatment options. Specialists will then follow up the patients until the patient is stable on the maximum tolerated dose of medication; this is usually for a period of one to three months.

Who will increase the dose?

Patients are likely to be on the maximum tolerated dose of medication when the request for primary care to continue prescribing is made.

When will the patient be suitable for discharge?

Specialist services will seek to discharge patients who remain settled for six months after stabilisation.

Who will follow up the patients?

Once the patient is stable on the maximum tolerated dose of medication, specialists will request to transfer prescribing to primary care. After a further six months of stability, specialists will request to discharge patients back to primary care.

Prior to discharge, specialists will follow up patients. Specialists will also identify patients with complex needs and refer onto other services. The memory service will continue to follow up for longer periods on a case by case basis, as need dictates. Should further information be required, the locality memory services can be contacted.

Related NICE guidance [NICE TAG 217, NICE NG97, NICE Clinical Knowledge Summaries]

NICE recognises that acetylcholinesterase (AChE) inhibitors are clinically cost effective and has recommended their use in mild to moderate Alzheimer's Disease. NICE recommends memantine as an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and as an option, in addition to an AChE inhibitor, for managing severe Alzheimer's disease.

NICE recommends that AChE inhibitors or memantine may be considered for people with dementia with Lewy bodies (DLB) and patients with Alzheimer's disease, irrespective of severity, who have non cognitive symptoms and/or behavioural challenges causing significant distress or potential harm to the individual. Dementia in Parkinson's disease shares a number of similarities with DLB; the recommendations for DLB may therefore be useful when considering treatments for dementia associated with Parkinson's disease.

NICE recognises that many cases of dementia may have mixed pathology (for example, Alzheimer's disease and vascular dementia or Alzheimer's disease and DLB). Unless otherwise stated by NICE, such cases should be managed according to the condition that is thought to be the predominant cause of dementia.

Licensed Indication and Mode of Action

Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer's disease, specifically for mild to moderate disease. Rivastigmine is also used for mild to moderate dementia associated with Parkinson's disease. Donepezil, galantamine and rivastigmine reversibly antagonise the action of acetylcholinesterase increasing the concentration of acetylcholine released by functionally intact cholinergic neurones to facilitate cholinergic transmission. Galantamine also exhibits nicotinic receptor agonist properties.

Memantine is a glutamate receptor antagonist licensed for the treatment of moderate to severe Alzheimer's disease.

Dosage and Administration

- Donepezil:** The dose is initially at 5 mg once daily. After 1 month the treatment should be assessed, and the dose can be increased to a maximum of 10 mg once daily if necessary. It is recommended that the dose is given at bedtime to minimise likelihood of gastrointestinal (GI) symptoms. However if sleep disturbances are noted, particularly vivid nightmares, then a shift to morning dosing can resolve this.
- Galantamine:** The dose is initially 4mg twice daily for a minimum period of 4 weeks with a maintenance dose 8mg twice daily for a minimum of 4 weeks. This can be increased to 12mg twice daily after appropriate assessment of benefit & tolerability. If no response to the higher dose or unable to tolerate, reduce to 8mg twice daily.
Where appropriate, the total daily dose may be converted to once daily administration using modified release formulations.
Galantamine should be taken after food to reduce the risk of cholinergic side effects (e.g. nausea, vomiting, diarrhoea). Administration with food slows rate of absorption but has no effect on total absorption. Modified release forms must be swallowed whole and not chewed.
- Rivastigmine :** The dose is initially 1.5 mg twice daily and may be increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to tolerance, up to a maximum dose of 6 mg twice daily.
Rivastigmine increases gastric acid secretion and should be taken with food to minimise the effects of this.
Alternatively rivastigmine patches are available, initially using a 4.6-mg patch per day. This can be increased to a 9.5-mg patch per day after at least 4 weeks.
- Memantine:** Initially 5mg daily for a minimum of seven days. Increase by 5mg in weekly intervals to a maximum daily dose of 20mg. Tablets should be administered once a day and should be taken at the same time every day.

What are the contraindications/ cautions for initiating these drugs?

Cholinesterase inhibitors are contraindicated in heart block and sick-sinus syndrome. They should be used with caution in those with other supraventricular conduction problems and arrhythmias, e.g. atrial fibrillation, where an ECG is indicated prior to initiation. An ECG is also required if patients develop bradycardia, syncope or palpitations during treatment to exclude heart block. Memantine is used as an alternative in these situations.

Oral cholinesterase inhibitors are used with caution in people with a history of upper GI ulceration and bleeding: Memantine, additional Proton Pump Inhibitor cover or Rivastigmine patches may be used as an alternative. Caution is also advised in those with history of epilepsy or a pre-disposition to seizures.

Cholinesterase inhibitors should be used with caution in people with asthma and COPD. Galantamine is contraindicated in those with an eGFR of < 9 ml/min and in severe hepatic impairment (Child-Pugh score >9). The maximum dose of Memantine should be 10mg per day in patients with severe renal impairment (creatinine clearance 5-29 ml/min); however, GPs are encouraged to discuss the finding with the mental health specialist before changing the dose.

What are the main side-effects?

The most common side-effects of cholinesterase inhibitors are nausea, mild anorexia, fatigue, diarrhoea, muscle cramps and sometimes poor sleep.

The most common side effect of memantine is constipation.

Patients should be advised to take the medicine with food to minimise side effects. Side effects usually decrease with time.

Please refer to the BNF for further details

Co-prescription / Misuse issues

Individuals taking drugs affecting cognitive function will require review as below before initiation of these drugs.

Alcohol misuse	Patients currently drinking unsafe amounts of alcohol will not be treated with cholinesterase inhibitors or memantine, but may be considered for treatment if they have Alzheimer's disease or Lewy Body Disease and their alcohol intake is reduced to be within safe limits.
Benzodiazepines	Consideration must be given to whether the benzodiazepines may be affecting cognitive function especially in large doses, if so they must be reduced gradually and stopped.
Non Steroidal Anti Inflammatory Drugs (NSAID)	Increased risk of acid production with Cholinesterase inhibitors review need for NSAID. Patients may need increased monitoring for gastric complications if using NSAID. See NB below
Drugs that may cause bradycardia e.g. digoxin, beta blockers	There is an increased risk of potentiation of bradycardia with cholinesterase inhibitors. This is particularly important in 'sick sinus syndrome' or AV block. Increased monitoring is required.
Tricyclic antidepressants as an antidepressant / anxiolytic.	Tricyclic antidepressants have strong anticholinergic effects and may be affecting cognitive function; particularly at the relatively high doses used for these indications. Consider changing to an SSRI/ SNRI or mirtazapine if still requiring treatment. Individual drugs vary in their capacity to interact so check before prescribing an antidepressant. For example there is an interaction between paroxetine and galantamine, which may increase the levels of the cholinesterase inhibitor.
Tricyclic antidepressants as an adjunct to pain control	If prescribed for pain in small dosage, and still required after review, continue with caution.
Other anticholinergic drugs	Review the need for these drugs as they may oppose the effect of cholinesterase inhibitors.
Drugs with cholinomimetic properties:	Peripherally Acting Cholinesterase inhibitors: e.g. neostigmine or pyridostigmine. Cholinergic drugs e.g. pilocarpine.

NB: If patients are prescribed medication which increases the risk of gastric irritation, such as aspirin, NSAID, SSRI a proton pump inhibitor or equivalent should be prescribed concomitantly.

Drug Interactions - Memantine

Avoid concomitant use of ketamine, dextromethorphan and amantadine.

Memantine possibly enhances the anticoagulant effect of warfarin so if these drugs are to be used concurrently additional INR monitoring should be carried out and dose adjusted accordingly.

Drugs that increase the pH of the urine (e.g. sodium bicarbonate, carbonic anhydrase inhibitors) may reduce the elimination of memantine.

L-dopa, dopaminergic agonists and anticholinergics may be enhanced. Effects of barbiturates and antipsychotics may be reduced. Concomitant administration with antispasmodics, dantrolene or baclofen can modify their effects and dosage adjustment may be necessary.

Increased plasma levels possible with cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine.

Drug Interactions - Acetylcholinesterase Inhibitors

There are no specific dose changes which need to be made in relation to acetylcholinesterase inhibitors however it would be useful for prescribers to be aware of the following:

Potent inhibitors of CYP3A4 (including ritonavir, clarithromycin and itraconazole) may raise donepezil and galantamine levels.

Inducers of CYP3A4 (including carbamazepine, phenytoin, and rifampicin) may lower donepezil levels.

Smoking tobacco increases the clearance of rivastigmine.

The risk of adverse effects, including bradycardia, may be increased if an acetylcholinesterase inhibitor is given with amiodarone or other antihypertensive/antiarrhythmic drugs. Acetylcholinesterase inhibitors may antagonise effects of anticholinergic drugs and worsen Parkinsonian symptoms; this may induce or exacerbate extrapyramidal side effects.

Monitoring

- **Adverse effects:** Most common side effects are gastrointestinal disturbance (nausea, vomiting, and diarrhoea).
- **Concurrent medication:** Medication should be reviewed at each visit in order to identify potential drug interactions.
- **Renal and hepatic function:** GPs are encouraged to seek mental health specialist telephone advice to consider dose changes should the patient suffer significant worsening of:
 - renal function (creatinine clearance falls below 30ml/min in patients taking memantine)
 - hepatic function (galantamine only).
- **Weight / BMI:** Weight loss is associated with Alzheimer's disease but acetylcholinesterase inhibitors are also reported to cause weight loss. Patients weighing <50kg may experience more adverse effects and are more likely to discontinue treatment as a result.
- **Cardiovascular health:** Acetylcholinesterase inhibitors may have vagotonic effects so baseline cardiovascular function must be monitored before starting treatment and repeated when indicated, for example, when additional drugs with vagotonic effects are added or in the event of emerging cardiovascular problems.
- **Cognitive, global functional and behavioural assessment:** Patients who continue on treatment should be reviewed at least annually by the GP. If any concerns regarding cognition, functioning or behaviour are noted, the GP is encouraged to contact the memory service to discuss possible referral. Specialist services may perform a cognition test but, especially in more advanced dementia where benefits of cholinesterase inhibitors may cease to outweigh risks of continued treatment, an assessment of well-being and functioning may be more important. Carers' views on the patient's condition at follow-up should be sought.

When should the drug be stopped?

Drugs should be stopped if a patient develops an allergy or contra-indication to the medication.

The duration of treatment benefit will vary significantly between individuals; therefore, if a patient no longer appears to be gaining any benefit from the drug it may be an indication for stopping. However, in addition to treating the cognitive aspects of dementia, cholinesterase inhibitors and memantine have a role in behavioural and psychiatric changes in dementia and therefore, patients who are scoring low on cognitive testing may still benefit. Specialist advice may be sought from the locality memory treatment services in this situation.

What happens if my patient's needs change or become more complex following discharge?

You may wish to seek telephone advice in this situation. However, if the GP wishes to re-refer, the specialist service will accept the re-referral and will see the patient as a priority in acute situations. Contact details for the locality memory services are:

5 Boroughs Partnership Mon – Fri (excluding Bank Holidays)

Halton:	01928 753162
Knowsley:	0151 676 5262
St Helens:	01744 646 833
Warrington:	01925 664041

Mersey Care NHS Trust

For urgent referrals, contact the individual consultant or community mental health team directly using the contact details provided on the dementia support documentation or via Mersey Care switchboard on [0151 473 0303](tel:01514730303) or follow the following link <http://www.merseycare.nhs.uk/gps-and-referrers/>.

Alternatively, contact the relevant memory service as follows:

Liverpool: Phone - [0151 250 3000](tel:01512503000) (ask for relevant consultant secretary);

Fax - [0151 250 6115](tel:01512506115)

North Liverpool and Kirby: Phone - [0151 479 3818](tel:01514793818) or 0151 479 3819; Fax - [0151 737 4870](tel:01517374870)

South Sefton: Phone - [0151 330 8511](tel:01513308511) or 8512; Fax - [0151 330 8513](tel:01513308513)

Southport: Fax - [01704 383074](tel:01704383074)

When to seek Specialist advice / review

You can get advice regarding patients taking drug treatments for dementia from the locality memory treatment services in addition to the CCG medicines management team.

In the majority of cases treatment will be initiated by a specialist in the care of people with dementia in line with NICE guidance. Following dose titration the specialist will recommend continuation treatment on the basis of tolerability and patient preference.

Tolerability may change over time consequent upon the ageing process and the emergence of medical co-morbidities and frailty. In this situation it may be appropriate to reduce the dose or discontinue treatment and/or consider an alternative drug. It may be appropriate to make such decisions in consultation with the specialist who initiated treatment.

You may wish to seek telephone advice in the following circumstances:

- Emergent concerns regarding tolerability
- Emergent significant deterioration in hepatic and/or renal function
- To consider whether to discontinue treatment with a cholinesterase inhibitor at an advanced stage of the illness as outlined above.

NB. Re-referral may not always be necessary

Guidance for GPs prescribing

The GP will monitor for on-going side effects and discuss with the Memory Service if any arise for advice on dose reduction, discontinuation etc. If a patient's cardiac health changes, appropriateness of prescription will need to be discussed with the memory service and consideration for referral to cardiology.

- Provide regular prescriptions for cholinesterase inhibitors and / or memantine as per this guidance.
- Be aware of side effects and common drug interactions as documented in this guideline.
- Provide regular health checks including where relevant the review of patients with vascular dementia or mixed dementia and provision of advice about lifestyle.
- Inform specialist services of any relevant physical health problems at the earliest opportunity for those still open to specialist services or re-refer if necessary.
- If patient suffers any adverse reaction, GP should liaise with secondary care/specialist services.
- If patient develops bradycardia with symptoms on cholinesterase inhibitors, such as light-headedness or syncope, review any medication which may cause bradycardia, stop the drug if appropriate and notify Memory Service. If patient develops bradycardia without symptoms and if the rate is persistently less than 50, stop the cholinesterase inhibitor and notify Memory Service, if rate is 50-60, continue drug and notify the Memory Service. In all cases the Memory Service will consider if treatment remains appropriate or if changes are required
- If patient develops second or third degree AV block, stop cholinesterase inhibitor, consider referral to cardiology and notify Memory Service.

Any patient who is currently prescribed an AChE and develops any cardiac disease or peptic ulcer disease (that the Specialists at the memory service are not aware of) please contact the memory service to discuss on going appropriateness of drug treatment.

Acknowledgement: This guideline is an amended version of a document developed by the Greater Manchester Area Prescribing Committee