Donepezil, Galantamine, Rivastigmine and Memantine for the treatment of Dementia – Information for Primary Care

Formulary Status – Green Plus

Introduction

This guideline is developed in accordance with NICE guideline 97 and NICE Technology Appraisal 217. NICE (TAG 217) concluded that Acetylcholinesterase inhibitors (AChEi) are clinically cost effective compared with best supportive care.
• AChEi are recommended options for managing mild to moderate Alzheimer's Disease
• Memantine monotherapy is recommended as an option for:
  ○ people with **moderate Alzheimer's disease** in whom AChEi are contraindicated or not tolerated
  ○ people with **severe Alzheimer's disease**
• For people already taking an AChEi, **memantine** should be:
  ○ **Offered** to those with **severe** Alzheimer's disease
  ○ **Considered** for those with **moderate** Alzheimer's disease
• **Offer donepezil** or **rivastigmine** to people with **mild to moderate** dementia with Lewy bodies
• **Galantamine** should only be considered if donepezil and rivastigmine are not tolerated
• **Consider donepezil** or **rivastigmine** for people with **severe** dementia with Lewy Bodies
• Consider **memantine** for people with dementia with Lewy bodies if AChEi are contraindicated or not tolerated

Medication – For full details see NICE NG97, individual SPCs and current edition of BNF
Acetylcholinesterase Inhibitors - *Donepezil, Galantamine and Rivastigmine* *All licensed for mild to moderate dementia in Alzheimer's dementia* *Rivastigmine also licensed for use in dementia in Parkinson's disease*
Dosage and administration

Donepezil (First line formulary preference)	Initially 5mg once daily for one month, increasing to 10mg once daily if tolerated. Doses can be given at bedtime to minimise gastrointestinal (GI) symptoms If sleep disturbance is noted (particularly vivid nightmares) consider morning dosing instead.
Galantamine	**Immediate-release formulations** Initially 4mg **twice** daily for 4 weeks, increasing to 8mg **twice** daily for at least 4 weeks; usual maintenance dose 8–12mg **twice** daily. **Modified release (MR) formulations** Initially 8mg **once** daily for 4 weeks, increasing to 16mg once daily for at least 4 weeks usual maintenance dose 16–24mg daily. • Use of the modified release formulation Gatalin XL is preferred due to lower acquisition cost compared to the immediate release formulation which is administered twice daily • If dose is not tolerated, reduce to maximum tolerated dose • Oral solution is only approved for short-term use in the management of hospital patients who are unable to swallow tablets/capsules, not for those unable to swallow tablets due to severe dementia

Rivastigmine	**By mouth** Initially 1.5mg **twice** daily, increasing by 1.5mg **twice** daily at fortnightly intervals according to tolerance and response; usual dose 3–6mg **twice** daily (max 6mg **twice** daily). If treatment is interrupted for more than several days, re-titrate from 1.5mg **twice** daily.
	
	By transdermal application using patches
	Apply **one** 4.6 mg/24 hours patch **daily** for at least 4 weeks, increasing to **one** 9.5mg/24 hours patch **daily** if tolerated for a further 6 months. **After 6 months** increasing to **one** 13.3mg/24 hours patch daily, can be considered if well tolerated and evidence of cognitive or functional deterioration.
	• Use with caution in patients with body weight **less than 50kg**
	• If treatment interrupted for **more than 3 days**, re-titrate from 4.6mg/24 hours patch
	• Rivastigmine patches are formulary approved for patients:
	  ○ unable to tolerate **oral** rivastigmine due to nausea and vomiting and
	  ○ requiring AchEi treatment but are unable to take orally (e.g. swallowing difficulties or 'nil by mouth' prior to surgery).

Glutamate receptor antagonists – *Memantine* *Licensed for moderate to severe dementia in Alzheimer's disease*	
Dosage and administration	
Memantine	Initially 5 mg once daily, increasing weekly in steps of 5 mg to maximum tolerated dose; usual maintenance dose 20mg daily; maximum 20 mg per day. • Administer once daily at roughly the same time every day. This is usually taken in the morning but may be given at night if drowsiness is evident. • The absorption of memantine is not affected by food • Avoid concurrent use with **amantadine**
Common adverse effects – See SPC and BNFC for full details	
Acetylcholinesterase inhibitors	GI disturbance (nausea, vomiting, and diarrhoea), reduced appetite, weight loss, dizziness, headache, tiredness/fatigue, agitation/anxiety, urinary incontinence, sleep disturbance, syncope, muscle cramps. Patients <50kg are more likely to experience adverse effects and discontinue treatment
Memantine	Dizziness, light-headedness, headache, constipation, hypertension, breathlessness, somnolence and elevated liver function tests. Less commonly: vomiting, thrombosis, worsening heart failure, confusion, fatigue, hallucinations, seizures and abnormal gait.
Potentially serious drug interactions – See SPC and BNFC for full details	
Acetylcholinesterase inhibitors	Concurrent use with drugs that cause GI irritation or bleeding (e.g. NSAIDs or SSRIs (cumulative effect)). 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**. Concurrent use of AChEi with amiodarone or other antihypertensive/antiarrhythmic drugs may increase the risk of adverse effects, including bradycardia. AChEi may antagonise the effects of anticholinergic drugs when used concurrently; this may precipitate extrapyramidal side effects such as Parkinsonian symptoms.

Memantine	Avoid concomitant use of ketamine, dextromethorphan and amantadine. Memantine **enhances** the anticoagulant effect of **warfarin**; additional INR monitoring is necessary and warfarin dose may need adjusted. Drugs that increase the pH of the urine (e.g. sodium bicarbonate, carbonic anhydrase inhibitors) may **reduce the elimination of memantine**.
Contraindications/Cautions – See SPC and BNFC for full details	
Acetylcholinesterase inhibitors	Asthma and COPD Sick sinus syndrome Supraventricular conduction abnormalities Susceptibility to peptic ulcers
Memantine	Epilepsy, history of convulsions, risk factors for epilepsy
Medication choice	
Initial drug treatment should be with the drug with lowest acquisition cost; an alternative AChEi may be suitable considering adverse event profile, adherence, comorbidities, potential drug interactions and dosing profiles. **Do not stop AChEi** in people with Alzheimer's disease because of disease severity alone. Only consider AChEi or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies. Do not offer AChEi inhibitors or memantine to people with frontotemporal dementia.	
Baseline assessment	Before initiating patients on medicines for dementia, undertake a full assessment in line with NICE guidance.
Prescribing	Treatment for dementia should usually be started on the advice of a Secondary Care Specialist and can be safely prescribed and maintained in primary care without on-going specialist monitoring. A patient should be established on a stable dose of medication and a minimum of one month supply should be given to patients by the Specialist Prescriber when transferring responsibility to primary care. If a patient uses compliance aids, consider the best interests of the patient when deciding the length of the supply.
Maintenance and monitoring	Monitor for adverse effects associated with medications for dementia and document in the patient's notes. Encourage people taking medicines for dementia, their family and carers to monitor and report adverse effects. It cannot be accurately determined how much benefit is obtained by taking medicines for dementia and the condition will continue to progress despite treatment. Continuing therapy should primarily be decided on tolerability and patient preference These medicines are effective in maintaining cognitive and general functioning even in moderate to severe illness and may delay placement into long-term care.
Physical health monitoring for all cognitive enhancing medication	The initiating clinician must ensure baseline monitoring is carried out before prescribing. On-going monitoring is the responsibility of the GP. QoF requirements for dementia includes routine bloods. Renal function may decline with age/other factors, therefore memantine doses should be reviewed and reduced or stopped according to the degree of impairment. Contact the specialist team for advice if needed.

	Baseline / Initiation	**On-going**
Adverse effects (outlined above)	✓	✓
Weight / BMI: Weight loss is associated with Alzheimer's disease but AChEi may also cause reduced appetite and weight loss. Patients weighing <50kg may experience more adverse effects and are more likely to discontinue treatment.	✓	✓

	Concurrent medication: Review at each visit to identify the potential for drug interactions.	✓	✓
	Cardiovascular health: AChEi may have vagotonic effects. Baseline cardiovascular function including heart rate must be monitored **before** starting treatment and repeated when indicated (e.g. adding medicines with vagotonic effects or emergent cardiovascular concerns.)	✓	When clinically indicated
	Renal and hepatic function: Measure baseline creatinine and LFTs. Titrate doses slowly in patients with renal or hepatic impairment monitor closely for adverse effects.	✓	Annual eGFR (memantine) When clinically indicated (AChEi)
Review of medication and discontinuation	Discontinuation of medicines for dementia should be considered in the event of: • Adverse reactions • Emergent tolerability issues (e.g. secondary to frailty or medical co-morbidities) • Poor adherence: if swallowing solid dose preparations becomes difficult assess whether switching to a topical patch, orodispersible tablet or liquid preparation would be in the best interest of the patient • The patient is on an end-of-life care pathway • Irreversible deterioration in global clinical presentation since last review (e.g. CVA)		

When to seek Specialist Advice/Review

A Secondary Care Specialist will make treatment recommendations regarding initiation and continuation of medicines for dementia in line with NICE guidance and taking patient preference and tolerability into consideration. Tolerability may change over time due to ageing, development of co-morbidities and frailty.
Dose reduction, treatment discontinuation and/or an alternative medicine (e.g. Memantine) may be appropriate strategies. A discussion with a Secondary Care Specialist may support this decision-making without the need for a formal re-referral to secondary care services.

Contact Details (Monday – Friday 9am – 5pm)

Northumberland

Northumberland Memory Service (NMS) – 01670 844 730
North Northumberland Community Treatment Team: Berwick – 01289 301 301Alnwick – 01665 608 000
West Northumberland Community Treatment Team – 01434 612 800
South Central Northumberland Older Adult Community Treatment Team – 01670 844 730

Newcastle

Memory Assessment and Management Service (MAMS) – 0191 246 8753

North Tyneside

Vacant post (Residential & Nursing Home Team) 0191 293 2749
Dr Christopher Davison (Memory Clinic) 0191 293 4010
Dr Gillian Encore (Wallsend and North Shields) 0191 293 2748
Dr Sarah Henry (Tynemouth and Whitley Bay) 0191 293 2567

Gateshead

Ellison Unit, Bensham Hospital, Gateshead 0191 445 6660

North Cumbria

Older Adult Community Mental Health Team – Carlisle Tel. 01228 602 100
Older Adult Community Mental Health Team – Allerdale Tel. 01900 705 850
Older Adult Community Mental Health Team – Eden Tel. 01768 245 530
Memory Matters and Later Life Service – Workington Tel. 01900 705 850

References

- eBNF accessed on 19 August 2022 via https://www.medicinescomplete.com/#/
- Summary of product characteristsics for drugs included accessed on 19 August 2022 via https://www.medicines.org.uk
- Dementia: assessment, management and support for people living with dementia and their carers
- NICE accessed on 19 August 2022 via https://www.nice.org.uk/guidance/ng97Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease NICE NTAG accessed on 19 August 2022 via https://www.nice.org.uk/guidance/TA217