North of Tyne, Gateshead and North Cumbria Area Prescribing Committee

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 (AChEs) are clinically cost effective and recommends: • Using AChEs in mild to moderate Alzheimer's Disease • Consider prescribing in people with dementia with Lewy bodies 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 • Offer people with mild – moderate dementia with Lewy bodies donepezil or rivastigmine first line, with galantamine only to be considered if donepezil and rivastigmine are not tolerated. • Consider donepezil or rivastigmine for people with severe dementia with Lewy Bodies, or memantine if AChE inhibitors are not tolerated or contraindicated • Using memantine to manage moderate Alzheimer's disease for people who have non-cognitive symptoms and/or behaviour that challenges and cannot take AChE inhibitors, and for managing severe Alzheimer's disease. Treatment for dementia is usually initiated by a Secondary Care Specialist and can be safely 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 before 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	
Medication - For full details see NICE NG97, individual SPCs and current edition of BNF	
Acetylcholinesterase Inhibitors - *Donepezil, Galantamine and Rivastigmine* *All licensed for mild – moderate dementia in Alzheimer's dementia* *Rivastigmine also licensed for use in dementia in Parkinson's disease*	
Dosage and administration	
Donepezil (Formulary preferred first-line choice)	Initially 5 mg once daily for one month, then increased up to 10 mg once daily if tolerated. Doses to be given at bedtime to minimise gastrointestinal (GI) symptoms If sleep disturbance is noted (particularly vivid nightmares) morning dosing may resolve.
Galantamine	**Immediate-release formulations** Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for at least 4 weeks; maintenance 8–12 mg twice daily. **Modified-release formulations -** Initially 8 mg once daily for 4 weeks, increased to 16 mg once daily for at least 4 weeks; usual maintenance 16–24 mg 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 • Oral solution is only approved for short-term use in the management of hospital patients who are unable to swallow tablets/capsules. Not for use in patients who can no longer swallow tablets due to severe dementia

Rivastigmine	**By mouth -** Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, re-titrate from 1.5 mg twice daily.
	By transdermal application using patches
	Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increase to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated
	• Use with caution in patients with body-weight less than 50 kg
	• 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 treatment with oral rivastigmine due to nausea and vomiting and
	  ○ requiring treatment with an AChE who are unable to take oral medication (e.g. swallowing difficulties or 'nil by mouth' prior to surgery).

Glutamate receptor antagonists - *Memantine* *Licensed for moderate – severe dementia in Alzheimer's disease*	
Dosage and administration	
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. • Administer once a day at approximately the same time every day • The absorption of memantine is not affected by food • Usually taken in the morning but may be given at night if sedation is a problem • Do not give if patient is on 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 weighing <50kg are more likely to experience adverse effects and discontinue treatment
Memantine	Dizziness, constipation, hypertension, breathlessness, headache, somnolence and elevated LFTs. Less commonly vomiting, thrombosis, heart failure, confusion, fatigue, hallucinations, 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 with amiodarone or other antihypertensive/antiarrhythmic drugs may increase the risk of adverse effects, including bradycardia. May antagonise effects of anticholinergic drugs when used concurrently + this may induce/exacerbate extrapyramidal side effects including worsening Parkinsonian

	symptoms.
Memantine	Avoid concomitant use of ketamine, dextromethorphan and amantadine. Memantine enhances the anticoagulant effect of warfarin; additional INR monitoring should be carried out and warfarin dose adjusted accordingly. 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	
Donepezil, galantamine and rivastigmine as monotherapies are recommended treatment options for managing mild to moderate Alzheimer's disease. Start treatment with the drug with the lowest acquisition cost, an alternative AChE inhibitor could be prescribed depending on adverse event profile, expectations about adherence, comorbidity, potential drug interactions and dosing profiles. Memantine monotherapy is an option in moderately severe Alzheimer's disease in patients who are intolerant of or have a contraindication to AChE inhibitors and for people with severe Alzheimer's disease. Consider adding memantine in severe and moderate disease for patients with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone. Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies and consider use for people with severe dementia with Lewy bodies. Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated. Consider memantine in people with dementia with Lewy bodies if AChE inhibitors are not tolerated or are contraindicated. Only consider AChE inhibitors 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 AChE inhibitors or memantine to people with frontotemporal dementia.	
Baseline assessment	Before initiating patients on cognitive enhancing medication a full assessment in line with NICE guidance should be undertaken by the Specialist.
Prescribing	Treatment for dementia is usually initiated by a Secondary Care Specialist and can be safely 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 before 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 patient's taking medication for dementia and their family/carers to monitor and report and adverse effects. It is not possible to accurately determine whether somebody is deriving benefit from a cognitive enhancing medication decisions to continue therapy is made primarily on the basis of tolerability and patient preference. These medications are effective in maintaining cognitive and general functioning even in moderate to severe illness, and may delay placement into long-term care.

<table>
<tr><td rowspan="6">Physical health monitoring for all cognitive enhancing medication</td><td colspan="3">The initiating clinician must ensure that baseline monitoring has been carried out prior to prescribing.
On-going monitoring is the responsibility of the GP. QoF requirements for dementia include routine bloods. Renal function may decline with age/other factors. Therefore, the memantine dose should be reviewed and reduced or stopped depending on the degree of renal impairment. Contact the specialist team for advice if needed.</td></tr>
<tr><td></td><td>Baseline / Initiation</td><td>On-going</td></tr>
<tr><td>Adverse effects (outlined above)</td><td>✓</td><td>✓</td></tr>
<tr><td>Weight / BMI: Weight loss is associated with Alzheimer’s disease but AChEs may also cause weight loss. Patients weighing <50kg may experience more adverse effects and are more likely to discontinue treatment.</td><td>✓</td><td>✓</td></tr>
<tr><td>Concurrent medication: Medication should be reviewed at each visit in order to identify potential drug interactions.</td><td>✓</td><td>✓</td></tr>
<tr><td>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.</td><td>✓</td><td>When clinically indicated</td></tr>
<tr><td>Renal and hepatic function: Baseline creatinine and LFTs should be measured; Patients with renal or hepatic impairment should have doses titrated slowly and be monitored closely for adverse effects.</td><td>✓</td><td>Annual eGFR (memantine)

When clinically indicated (AChEi)</td></tr>
<tr><td>Review of medication and discontinuation</td><td colspan="3">Discuss discontinuing therapy with the carers, family, and with the patient wherever possible. Discontinuation should be considered in the event of:
Adverse reaction to the medication
Emergent tolerability issues e.g. secondary to frailty or medical co-morbidities
Lack of compliance with the medication - if swallowing solid dose preparations has become a problem an assessment should be made as to whether switching to a skin patch, orodispersable tablet or an liquid preparation would be in the best interest of the patient.
The patient is on the end of life care pathway
Irreversible deterioration in global clinical presentation since last review e.g. CVA</td></tr>
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When to seek Specialist Advice/Review

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 issues & 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 appropriate to reduce the dose or discontinue treatment &/or consider an alternative drug, for example Memantine.

It may be appropriate to make such decisions in consultation with the specialist who initiated treatment. Dementia Specialists, usually a Consultant Psychiatrist or Speciality Doctors are available to provide advice on such matters without the need for a formal re-referral. Seek advice:

- Emergent concerns regarding tolerability
- To consider stopping treatment with an AChE at an advanced stage of illness as outlined above.

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

Northumberland

Northumberland Memory Service (NMS) – 01670 844 730

North Northumberland Community Treatment Team:

- Berwick – 01289 301 301
- Alnwick – 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

Emma Terriere (Residential & Nursing Home Team) 0191 293 2749

Dr Christopher Davison (Memory Clinic) 0191 293 4010

Dr Greig Ramsay (Wallsend and North Shields) 0191 293 2748

Dr Simon Wilson (Tynemouth and Whitley Bay) 0191 293 2567

Gateshead

Ellison Unit – Bensham Hospital, Gateshead 0191 445 6660 (opening hours Mon-Fri 9am to 5pm)

North Cumbria – tbc

References

eBNF accessed on 27th June 2019 via https://www.medicinescomplete.com/#/

Dementia: assessment, management and support for people living with dementia and their carers NICE accessed on 27th June 2019 via https://www.nice.org.uk/guidance/ng97

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease NICE NTAG accessed on 27th June 2019 via https://www.nice.org.uk/guidance/TA217