Donepezil, Rivastigmine, Galantamine and Memantine
(AMBER with shared care)
(Donepezil Green in Wiltshire)

Shared Care Guideline for the Treatment of Alzheimer's Disease

This shared care guideline is intended to apply to patients who have been initiated on treatment and who have been assessed as benefiting by specialist services experienced in the care of people with dementia. This is in accordance with the guidance from the National Institute for Health & Clinical Excellence - **NICE guideline NG97**, **Dementia: assessment, management and support for people living with dementia and their carers (Published: 20 June 2018 nice.org.uk/guidance/ng97) - Technology appraisal guidance TA217, Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Published date: 23 March 2011, Updated: 20 June 2018)**

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

GPs should refer appropriate patients for assessment within a secondary care specialist service using the agreed local referral pathway. Where indicated treatment should be initiated in secondary care. Secondary care services **should continue to prescribe for the first three months** while response is assessed. After referral GPs will be asked to continue prescribing after the first three months as part of a shared care arrangement for those patients who have been assessed as benefiting.

Drug treatment for Alzheimer's disease should form part of a wider package of support and information for the patient and their carer. Treatment with dementia medication should only be initiated if reasonable steps are taken to ensure adequate compliance.

Sharing of care assumes communication between secondary care services, the GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment plans and are in agreement with it. Patients with the Alzheimer's disease are open to regular specialist follow-up, providing an ongoing opportunity to discuss drug therapy. **The doctor who prescribes the medication legally assumes clinical responsibility for the drug, its monitoring and the consequences of its use.**

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Diagnosis of probable or possible Alzheimer's disease (excluding other forms of dementia) and any appropriate assessments required.
2	Discuss the benefits and potential side effects of treatment with the patient and carer and provide information including the action to be taken should side effects occur.
3	Confirm the patient's understanding and consent to treatment (discuss with carers where patient lacks capacity).
4	Explain to patients and carers the normal course of the disease and if and when they should expect to be re-referred.
5	Initiate treatment for patients with Alzheimer's disease in accordance with the NICE guideline NG97 / NICE TA217 and make any dose adjustments.
6	Provide a minimum 3 months supply of medication (3 x one monthly supply) or any additional duration required to stabilise the patient.
7	Assess the patient after a minimum of three months (earlier review at 10 weeks may sometimes be necessary to ensure adequate medication supply for transfer to GP) to confirm stable on medication and approach the GP (with a shared care agreement) providing advice to continue prescribing if there is evidence of benefit. When needed, this may include the use of cognitive, global, functional and behavioural assessments. This review may take place by telephone, where appropriate.
8	Discontinue treatment after 3 months where there been no benefit, intolerable side effects or no slowing in the deterioration of the condition. If discontinuing treatment, medication should be gradually reduced with monitoring for any potentially significant deterioration of patient functioning or a worsening of behavioural symptoms. The specialist will liaise closely with the GP about the planned course of action. The specialist will consider a trial of an alternative cognitive enhancer where appropriate.
9	When treatment is continued under the shared care agreement, a member of the secondary care services specialist team will review patients where appropriate when requested to do so by the GP.
10	Give advice to the GP on when and how to adjust treatment doses, switch medication or stop treatment.
11	Ensure that clear backup arrangements are in place for GPs to obtain advice and support from the secondary care services specialist team.

	General Practitioner responsibilities
1	Pre-referral assessment should include a physical examination and baseline blood tests (FBC, U&Es, LFTs, glucose, TFTs, B12, folate, calcium, renal function eGFR and where possible/appropriate a CT Brain scan) to exclude non-dementia causes of cognitive decline, in accordance with the local memory assessment pathway for primary care. Non-dementia causes of cognitive decline including depression should be treated and monitored before referral.
2	Refer appropriate patients to secondary care specialist services using the agreed local referral pathway (PATIENTS or carer MUST GIVE CONSENT TO REFERRAL). Effective use of the mental capacity act (MCA) should be made for those patients who cannot consent to an assessment so as to prevent any delay in referral. Secondary care specialist services will provide advice and support.
3	Reply to the request as soon as practicable if they are **unable** to support shared care (in writing or via secure email).
4	Continue the prescribing of dementia medication at the recommended dose after the first three months for those patients assessed as benefiting and stable on treatment after a minimum of three months.
5	The recommended monitoring: • Donepezil, Rivastigmine and Galantamine - Pulse every 6-12 months • Memantine - Renal function (eGFR) regular monitoring for patients with significant renal impairment (a dose reduction may be needed in renal impairment) • Side effect screening - asking about GI disturbance, faints, blackouts headache, dizziness, drowsiness and breathing difficulties.
6	Refer to secondary care services specialist team if intolerable side effects develop, there is no slowing in the deterioration of the condition or there is significant worsening of disease-related symptoms.
7	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP
8	Undertake an annual medication review for those patients that have been discharged from the memory service and remain on medication. The review should be based on the following questions: • How is your memory? Any improvement or decline? • Is there any evidence of behavioural problems, or behavioural and psychological symptoms related to dementia (BPSD)? • Is there any carer stress? • Any side-effects of medication, dizziness, diarrhoea? A decline in cognitive function year on year is to be expected with a diagnosis of dementia so this on its own would not warrant re-referral or review by the memory service. If the GP has concerns regarding increasing behavioural disturbance or the development of new symptoms they should contact the local agreed secondary care service point of contact for access to further prescribing or treatment advice from a Memory Service clinician. The advice may be provided by telephone/letter and may not require a referral.
9	Stop treatment in conjunction with the specialist. Where appropriate, phase out the medication gradually and monitor for a potentially significant deterioration of patient functioning or a worsening of behavioural symptoms.
10	Report adverse events to the specialist and MHRA.

	Patient's role
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	To attend secondary care specialist services and GP clinic appointments (Failure to attend may result in medication being reviewed and possibly stopped on specialist advice).
3	Have regular blood tests to monitor renal function (eGFR) 6 to 12 monthly (for Memantine)
4	Have regular pulse check every 6 – 12 months (for Donepezil, Rivastigmine, and Galantamine).
5	Share any concerns in relation to treatment with medicine.
6	Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Email address:
Specialist: Dr Jill Mann	01225 476420	info@rice.org.uk www.rice.org
Specialist: Prof Roy Jones		RICE – The RICE Centre Building 8, Royal United Hospital, Combe Park, Bath, BA1 3NG
Specialist: Dr Roz Ward	01225 396799	rosalind.ward@nhs.net AWP Consultant Psychiatrist for Older People BANES Complex Intervention & Treatment Team (Later Life SBU), The Hollies CMHT, High Street, Midsomer Norton, Radstock, BA3 2DP
WWKDYD and NEW Primary Care Liaison Service Green Lane Hospital Marshall Road Devizes SN10 5DS	01380 737840	awp.PCLNorthWiltsAdminTeam@nhs.net
SARUM Primary Care Liaison Service Fountain Way Hospital, Wilton Road, Salisbury SP2 7FD	01722 820372	awp.AC-PCL-Swilts@nhs.net
Swindon Memory Service Victoria Centre 53 Downs Way Swindon, Wilts SN3 6BW	01793 327894/888 (memory service admin) 327800 (Victoria centre reception)	awp.swindonmemoryserviceadmin@ nhs.net
Great Western Hospital, Swindon	Geriatrician of the day hotline: 01793 607383 (weekdays 9-5pm)	
Salisbury Hospital	Consultants Dr Hugo Powell Dr Jonny Drayson	hugo.powell@nhs.net jonny.drayson@nhs.net
Royal United Hospital, Bath		ruh-tr.olderpeople@nhs.net

SUPPORTING INFORMATION

Summary of condition and licensed indications:

Donepezil, Rivastigmine and Galantamine
Donepezil, Rivastigmine and Galantamine are recommended as options in the management of cognitive impairment in mild to moderate Alzheimer's disease. The acetylcholinesterase (AChE) inhibitors are not recommended for vascular dementia.

Memantine
Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or severe Alzheimer's disease. For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor:

- Consider memantine in addition to an AChE inhibitor if they have moderate disease
- Offer memantine in addition to an AChE inhibitor if they have severe disease.

- According to this SCG this would be done by secondary care specialist services. Consideration of memantine in addition to an AChE inhibitor should be done when the patient begins to show some signs of progression/ deterioration. Advice may be provided by telephone/letter and may not require a referral.

Memantine is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. There is evidence for memantine providing benefit for patients who are developing behaviour disturbances, moderate or emerging agitation/ aggression (neuropsychiatric symptoms) in dementia.

This SCA should be read in conjunction with the Summary of Product Characteristics (SPC). Originally prepared by Ray Gray. Approved by AWP MOG July 2020 & BSW APC September 2020. V3 approved BSW APC June 2022. Review June 2024.

NICE recommendations: Donepezil, Rivastigmine and Galantamine

NICE (NG97, June 2018) states that treatment should be under the following conditions

- Non-specialists can prescribe donepezil, galantamine and rivastigmine as long as they have taken advice from a clinician who has the necessary knowledge and skills (not applicable for GPs in Wiltshire who can initiate donepezil without specialist advice via the Wiltshire dementia LES). This includes:
- Secondary care medical specialists such as psychiatrists, geriatricians and neurologists
- Other healthcare professionals such as GPs, nurse consultants and advanced nurse practitioners with specialist expertise in diagnosing and treating Alzheimer's disease
- Treatment should be continued when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. It is important to recognise that stability of symptoms is considered an effective treatment.

Choice of medication:

Donepezil is the AChE inhibitor of choice with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). An alternative AChE inhibitor should only be prescribed if there is evidence of Lewy Body Dementia or Parkinsonian features and when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles. Alternatively memantine may be selected when a patient has moderate to severe Alzheimer's disease and is presenting with challenging behaviours.

Non-Cognitive Symptoms and Behaviour that Challenges:

Acetylcholinesterase inhibitors may be considered to treat:

- People with Lewy Body Dementia who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges
- People with mild, moderate or severe Alzheimer's disease who have non-cognitive symptoms and/or behaviour that challenges causing significant distress or potential harm to the individual if:
    1. A non-pharmacological approach is inappropriate or has been ineffective, and
    2. Memantine/antipsychotic are inappropriate or have been ineffective.

DO NOT USE acetylcholinesterase inhibitors to treat non-cognitive symptoms or behaviour that challenges in people with vascular dementia

NICE recommendations: *Memantine*

Memantine is recommended by NICE (NG97, 2018), within its licensed indication as an option for managing Alzheimer's disease for people with:

- Moderate Alzheimer's disease who are intolerant of, or have a contraindication to cholinesterase inhibitors.
- Severe Alzheimer's disease.

For people with an established diagnosis of Alzheimer's disease who are already taking an inhibitor of acetylcholinesterase (AChE):

- consider memantine in addition to an AChE inhibitor if they have moderate disease
- Offer memantine in addition to an AChE inhibitor if they have severe disease.

- According to this SCG, this would be done by secondary care specialist services or advice may be provided by telephone/ letter and may not require a referral.

Treatment should be under the following conditions:

NICE (NG97, June 2018) states that treatment should be under the following conditions

- Non-specialists can now prescribe memantine as long as they have taken advice from a clinician who has the necessary knowledge and skills. This includes:
- secondary care medical specialists such as psychiatrists, geriatricians and neurologists
- Other healthcare professionals such as GPs, nurse consultants and advanced nurse practitioners with specialist expertise in diagnosing and treating Alzheimer's disease.
- Once a decision has been made to start an AChE inhibitor or memantine, the first prescription may be made in primary care

- **According to this SCG, this would be in urgent circumstances on advice from specialist services and in non-urgent circumstances advice may be provided by telephone/letter and may not require a referral.**

- For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, primary care prescribers may start treatment with memantine (as recommended above) without taking advice from a specialist clinician.

- According to this SCG, this would be in urgent circumstances on advice from specialist services and in non-urgent circumstances advice may be provided by telephone/letter and may not require a referral.

- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional and behavioural symptoms.
- It is important to recognise that stability of symptoms is considered an effective treatment.
- Patients who continue on the drug should be reviewed regularly (at least annually once stable) using where appropriate cognitive, global, functional and behavioural assessments.
- Carers' views on the patient's condition at follow-up should be sought.

SAFETY ISSUES: Donepezil, Rivastigmine and Galantamine

Dose

Usual maintenance doses are:

- Donepezil, initiated at 5mg daily for 1 month then increased to daily 10mg daily (consider maintaining a dose of 5mg daily for the more frail patient, to reduce the risk of side effects), taken as a single dose in the evening just prior to retiring (the dose can be taken in the morning if more appropriate for the patient).
- Rivastigmine, 3-6mg twice a day with meals, swallowed whole
- Galantamine, 8-12mg twice a day with meals (or Galantamine XL 16-24mg as a single dose once daily with meals, swallowed whole). Prescribe brand with lowest drug tariff price.
- Rivastigmine patch 9.5mg/24 hours. The patch should be applied once a day.
  (Patches should be reserved for patients with a particular clinical need such as poor compliance or swallowing difficulties).

The manufacturers' summaries of product characteristics should be referred to for full prescribing information.

Contra-indications

The summaries of product characteristics includes the following contra-indications:

- Patients with hypersensitivity to Donepezil (or piperidine derivatives), Rivastigmine (or carbamate derivatives), Galantamine or the excipients;
- Galantamine is contra-indicated in patients with severe renal and/or hepatic impairment, and in patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency.

Special warnings and precautions

The acetylcholinesterase inhibitors should be given with caution in:

- Cardiovascular conditions - the potential for vagotonic actions may be particularly important for patients with "sick sinus syndrome," patients with conduction defects, those who take drugs that significantly reduce heart rate, or those who have uncorrected electrolyte imbalance;
- Gastrointestinal conditions - patients at increased risk of developing ulcers should be monitored for symptoms;
- Neurological conditions - the drugs are believed to have some potential to cause generalised convulsions (seizure activity may also be a manifestation of Alzheimer's disease);
- Patients with a history of asthma or obstructive pulmonary disease;
- Patients with urinary outflow obstruction or recovering from bladder surgery.

Side-effects

The most common adverse effects include diarrhoea, nausea, vomiting, muscle cramps, dyspepsia, fatigue, insomnia, anorexia, weight loss, dizziness, headache and somnolence.

Other side-effects include confusion, fall, injury, syncope, upper respiratory tract infection and urinary tract infection.

Weight loss is also associated with Alzheimer's disease itself and therefore patients' weight should be monitored during therapy (if clinically appropriate).

Drug interactions

Acetylcholinesterase inhibitors should **not** be administered with anticholinergic medication due to the antagonism of effect (e.g. hyoscine, dicycloverine, orphenadrine, procyclidine, propantheline). When the patient is taking a drug with anticholinergic properties (e.g. antipsychotics, tricyclics) the relative benefits of taking acetylcholinesterase inhibitors alongside these should be assessed.

Acetylcholinesterase inhibitors are likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

The summary of product characteristics for galantamine states that during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine, fluoxetine or fluvoxamine) or CYP3A4 (e.g. ketoconazole, ritonavir), patients may experience an increased incidence of cholinergic side-effects, mainly nausea and vomiting and a reduction in the dose of the acetylcholinesterase inhibitor may be considered.

Drug interaction studies performed in vitro show that ketoconazole and quinidine inhibit donepezil metabolism. Other drugs that could also inhibit the metabolism of donepezil are itraconazole, erythromycin and fluoxetine. Enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil.
Any suspected serious adverse reaction to an established drug should be reported to MHRA via the 'yellow card scheme' http://yellowcard.mhra.gov.uk/

SAFETY ISSUES: Memantine
Dose
Starting dose: Memantine is initially given as 5mg once daily and then increased in steps of 5mg at weekly intervals to a maximum of 20mg daily. Usually best taken as a single dose in the evening just prior to retiring.

Usual maintenance dose (adult): 20mg once daily Maximum dose: 20mg once daily

Dosing using Memantine Oral Solution (10mg/ml) Pump Pack or Pipette is complex, patient and carers may need additional counselling/advice – **Memantine orodispersible tablets may provide a more cost effective alternative to oral solution.**

Duration of treatment: Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional and behavioural symptoms. Evidence of continued benefit may be demonstrated through clinical assessment, use of rating scales (e.g. **NPI** - Neuropsychiatric Inventory rating scale for evaluating the psychological impact of neuropsychiatric symptoms, **CMAI** - Cohen-Mansfield Agitation Inventory a 29-item scale to systematically assess agitation)

Contra-indications and precautions for use:
- No contradictions listed
- Cautions – history of convulsions
- Hepatic impairment – avoid in severe impairment
- **Renal Impairment** – Memantine Only

eGFR	
30-49mL/minute/1.73m²	Reduce to 10mg daily, if well tolerated after 7 days, increase in steps to 20mg daily
5-29mL/minute/1.73m²	Reduce dose to 10mg daily
Less than 5mL/minute/1.73m²	Avoid

Initiation of memantine – patients with mildly impaired renal function (eGFR 50-80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (eGFR 30-49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme.
Patients established on memantine – dose for patients with severe renal impairment (eGFR 5-29 ml/min) should be 10mg per day.

Side-effects
List the most common side-effects and any management of them. Provide guidance on when the GP should refer back to hospital. Refer to the SPC for a full list of adverse effects.

Clinical condition (reported frequency)	*Management*
Common (10-15%) constipation, hypertension, dyspnoea, headache, dizziness, drowsiness	**Reduce dose initially, stop drug if persistent**
Less commonly – vomiting, thrombosis, heart failure, confusion, fatigue, hallucinations and abnormal gait	**Stop drug and discuss**
Very rarely – seizures, pancreatitis, psychosis, depression and suicidal ideation also reported	**Stop drug and seek urgent attention**

Drug Interactions
Check BNF Appendix 1 *Before* Co-Prescribing Any Other Drug
- **Amantadine** – Increased risk of CNS toxicity when Memantine given with Amantadine (manufacturer of Memantine advises avoid concomitant use)
- **Antimuscarinics** – Memantine possibly enhances side effects of antimuscarinics
- **Antipsychotics** – Memantine possibly reduces effects of antipsychotics
- **Baclofen** – Memantine possibly modifies effects of Baclofen
- **Barbiturates** – Memantine possibly reduces effects of barbiturates
- **Dantrolene** – Memantine possibly modifies effects of Dantrolene
- **Dopaminergics** – Memantine possibly enhances effects of dopaminergics

- **Ketamine** – Increased risk of CNS toxicity when Memantine given with Ketamine (manufacturer of Memantine advises avoid concomitant use)
- **Primidone** – Memantine possibly reduces effects of Primidone
- **Selegiline** – Memantine possibly enhances effects of Selegiline
- **Warfarin** – Memantine possibly enhances anticoagulant effect of Warfarin

Any suspected serious adverse reaction to an established drug should be reported to MHRA via the 'yellow card scheme' http://yellowcard.mhra.gov.uk/

MONITORING:

Baseline investigations

To be undertaken by general practice, prior to referral for memory or psychiatric assessment in accordance with the local memory assessment pathway.
This includes a physical examination and baseline blood tests (FBC, viscosity (or ESR or CRP) B12, red cell folate, C&E, TSH, LFT glucose, calcium), Baseline brief cognitive examination.
Consideration of other underlying causes e.g. depression, alcohol, medication, and other medical problems.
Confirm any hearing and eyesight aids have been reviewed recently as appropriate.
Lipids, syphilis serology and HIV testing as appropriate. MSU/Urinalysis if delirium a possibility. ECG if appropriate / Chest x-ray if appropriate. Ongoing physical health monitoring and management and monitoring for adverse effects

Cost

The use of any other pharmaceutical form, other than solid oral tablets or capsules (including modified release forms), should be clinically justified by compliance issues. Alternative forms include orodispersible tablets, liquid preparations and transdermal patches. Prescribe generically unless directed to cost-effective branded generics (primary care, see *'prescribe well spend less'*).
At current prices, one year's treatment with these medicines is as follows:

Drug	Dose	Annual Cost eBNF Drug Tariff Price (July 2022)
Donepezil tablets	10mg daily	£13.92
Galantamine MR capsules	24mg daily	£957.60
Rivastigmine capsules	6mg twice daily	£654
Rivastigmine patch	9.5mg daily	£239.64
Memantine tablets	20mg daily	£16.56
Memantine orodispersible tablets	20mg daily	£599.76
Memantine 10mg/ml oral solution	20mg daily	£13.94

References:

NICE guideline NG97, Dementia: assessment, management and support for people living with dementia and their carers (Published: 20 June 2018 nice.org.uk/guidance/ng97)
https://www.nice.org.uk/guidance/ng97

NICE - Technology appraisal guidance TA217, Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Published date: 23 March 2011, Updated: 20 June 2018)
https://www.nice.org.uk/guidance/ta217

Summary of Product Characteristics at eMC
https://www.medicines.org.uk/emc

Version number	Author	Purpose/change	Date
3.0	AWP/ Rachel Hobson	• Change TLS for Swindon area from RED to AMBER	30/06/22