Integrated Medication Guidelines for the use of Donepezil, Galantamine, Rivastigmine and Memantine in Dementia

Donepezil, Galantamine, Rivastigmine and Memantine for the treatment of Dementia NOTES to the GP

The information in the integrated medication guideline has been developed in consultation with CCGs in South East London

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing **Donepezil, Galantamine, Rivastigmine and Memantine** for the treatment of **Dementia .**

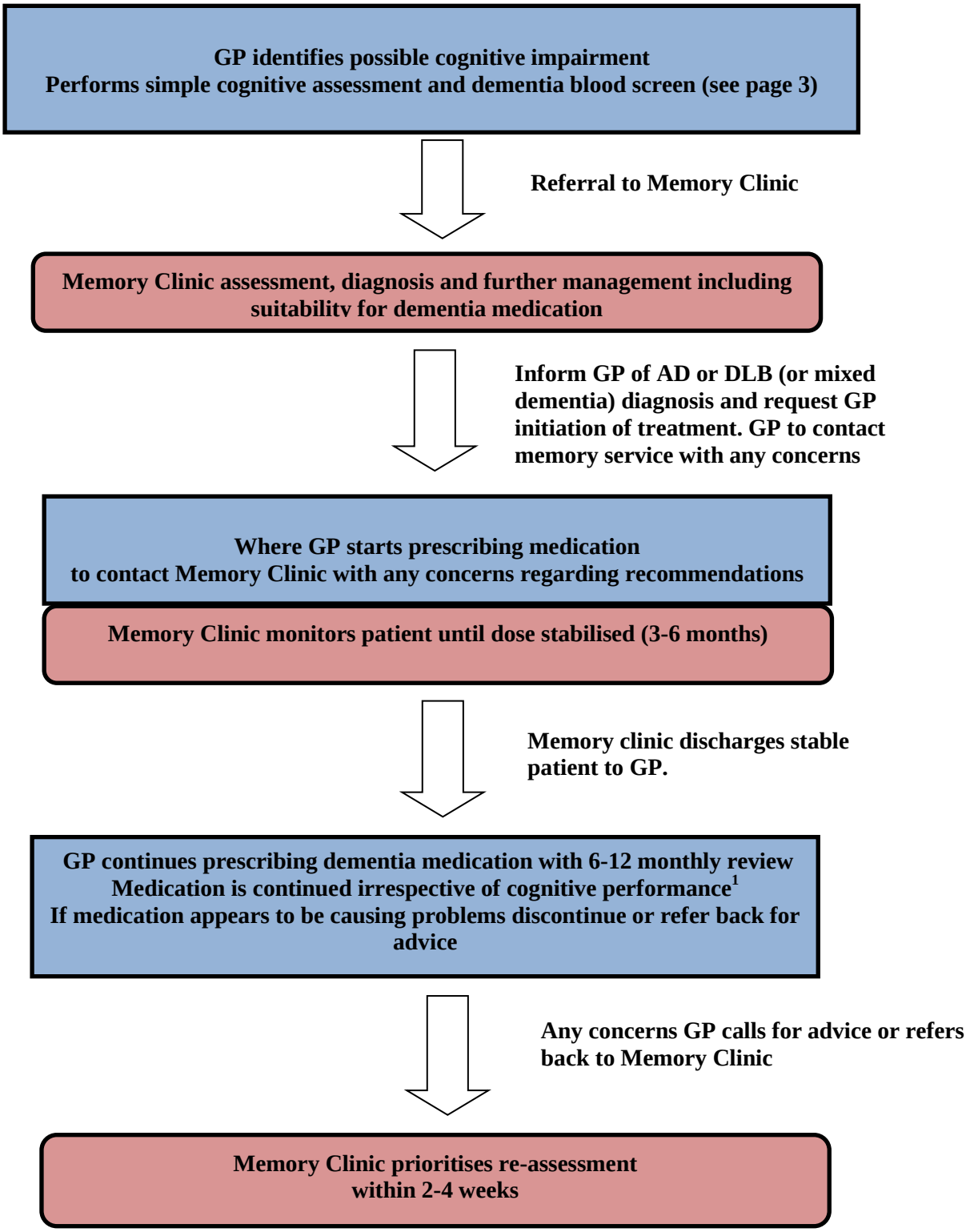
Prescribing should follow requirements in the South East London Interface Prescribing Policy.
The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount.

The objectives of these guideline include the following:

- **Safe Prescribing in Dementia**
- **Innovative thinking in dementia prescribing and care**
- **Prioritising patient and carer convenience**
- **Improving efficiencies and timely access to services**
- **Supporting primary care colleagues**
- **Rapid re-entry to services on discharge**

These integrated medication guidelines form part of a wider management pathway for patients with Alzheimer's disease. Healthcare professionals should also ensure that the patient's social care needs are taken into consideration and that they are referred to local services as and when appropriate.

1- DEMENTIA MEDICATION PATHWAY



*AD = Alzheimer's Disease
*DLB = Dementia with Lewy Bodies

[1] Howard R, McShane R, Lindesay J et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366:893-903.

Donepezil, Galantamine, Rivastigmine and Memantine for the treatment of Dementia

2. AREAS OF RESPONSIBILITY

Memory Clinic Consultant / Specialist team responsibilities

Investigations, assessments and blood tests

1. Confirm diagnosis & communicate cognitive score to the GP. The sMMSE, ACE or other validated tools may be appropriate.
2. Specialist assessment:
    - Tests of cognitive domain
    - Clinical evaluation of non-cognitive domains (e.g. hallucinations, delusions, agitation, behaviour that challenges)
    - Assessment of activities of daily living (ADLs)
    - Assessment of global function
    - Likely compliance with treatment before drug is prescribed.
    - The main therapeutic targets should be confirmed (Cognition, Psychosis, Behaviour that challenges, ADL)
3. When clinically appropriate request CT or MRI brain scan.

Supporting adherence and ongoing treatment

4. Discuss medication options with patient/carer and provide patient information leaflet (PIL) for drug prescribed.
5. Identify a carer who will undertake monitoring of adherence.
6. Seek agreement that treatment will be stopped if there are adverse effects.
7. Check for interactions with other medicines
8. Contact GP with plan or recommendation to initiate drug treatment.
9. Continue monitoring until patient stabilised on medication at optimum dose.
10. Review treatment at month one and again at month three before discharging patient to GP.
11. Seek carer's views on patient's condition at baseline & follow-up.

Adverse effects and deterioration

12. Stop treatment if any of the following occur:
    - Poor concordance
    - Major adverse effects
    - Patient asks to stop
13. Report serious adverse effects to the MHRA via 'yellow card system'.
14. Advise patient/carer on future care (for patient in their own home or nursing home) in situations where patient needs further care support.

Other

15. If patient is prescribed concomitant antipsychotic by specialist team, ensure indication (and preferably duration/need for regular review is communicated to GP. (see GP responsibilities below)
16. Review medication and cognitive burden with advice to GP.
17. Patients discharged to have easy and timely access back in to Memory Clinic/ alternative mental health service.

General Practitioner responsibilities

***Before referral**:*

1. Confirm history of cognitive decline from patient or independent informant.
2. Simple initial cognitive assessment
3. Initial dementia blood screening (HbA1c, FBC, U&E, Bone profile, B12, folate, TFTs, LFTs, CRP - HIV and syphilis if indicated)
4. Urinalysis, BP & heart rate.
5. Consider performing ECG if a cardiac caution to cholinesterase inhibitor treatment is suspected (e.g. sick sinus syndrome or other supraventricular conduction abnormalities); or where indicated. Use community ECG hub if available.
6. Ensure that the patient's social care needs are taken into consideration and that they are referred to local services as

and when appropriate.

7. Consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives when assessing whether to refer a person with suspected dementia for diagnosis and during medication reviews. The Anticholinergic Effect on Cognition (AEC) scale should be used to identify and assess the anticholinergic burden of drugs in patients (www.medichec.com).

After confirmation of diagnosis by Memory Clinic:

8. Initiate medication as recommended or continue prescribing treatment.
9. Check for interactions with other medicines
10. Highlight the importance of adherence to treatment.
11. Support & educate patients/carers

Monitoring of adverse effects and deterioration:

12. Review patients discharged from secondary care [stable on dementia medication] at least 12 monthly.
13. Monitor for adverse effects and report any serious reactions to the MHRA via the 'yellow card system'.
14. Call Memory Clinic for any concerns regarding memory or dementia medication.
15. Refer back to Memory Clinic if reassessment is required.
16. Stop treatment if urgent need arises.
17. If patient is prescribed concomitant antipsychotic drugs – ensure clear indication and duration of therapy is documented and that antipsychotic is reviewed at least every 6 weeks initially until the patient is clinically stable and tolerating it. Thereafter, antipsychotic review can be every 3-6 monthly but ensure there are procedures in place for regular reviews and reporting of adverse effects.

Other

18. Ensure patient is on the QOF dementia register.

Patient's / Carer's responsibilities

- Ensure adverse effects, deterioration and response to medicines is reported to Mental Health Team/ consultant and GP
- Report any changes in disease symptoms to the GP or specialist.
- Take medicines as agreed and do not share medicines.

Test Results/ Investigations

Results of all tests and investigations should be copied by/ to both consultant and GP.

3. CLINICAL INFORMATION

NOTE: The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for **Donepezil, Galantamine, Rivastigmine or Memantine** prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via www.medicines.org.uk)

Place in Therapy

Acetylcholinesterase inhibitors (donepezil) are recommended (and licensed) for the 1st line treatment of people with Alzheimer's Disease (AD) of mild to moderate severity (and treatment of Parkinson's Disease Dementia with rivastigmine only). Memantine monotherapy is recommended as an option (and licensed) for people with moderate AD where acetylcholinesterase inhibitors have not been tolerated or are contraindicated and for severe AD.

In line with NICE guidance[1]:
For people with established AD who are already taking an acetylcholinesterase inhibitor:

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

(GPs may start treatment with memantine without taking advice from specialist clinician)
See appendix 1 for guidance in the use of memantine in combination therapy.

For people with dementia with Lewy bodies:

- Offer donepezil or rivastigmine to people with mild to moderate 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 donepezil or rivastigmine for people with severe dementia with Lewy bodies
- Consider memantine for 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 or to people with cognitive impairment caused by multiple sclerosis.

Dose & route of administration

Medicine	Dosing	Titration week and dose (mg)					
		1	2	3	4	6	8
Donepezil (tablets, orodispersible tablets, oral solution)	Daily (oral)	5mg			10mg		
Galantamine (modified release capsules)	Daily (oral)	8mg			16mg		24mg
Galantamine (tablets, oral solution-)	Twice daily (oral)	4mg			8mg		12mg
Rivastigmine (oral capsules, oral solution)	Twice daily (oral)	1.5mg		3mg		4.5mg	6mg
Rivastigmine (patch)	Daily (clean dry skin)	4.6mg/ 24hrs			9.5mg/ 24hrs		
Memantine (scored tablets, oral solution)	Daily (oral)	5mg	10mg	15mg	20mg		

Duration of treatment

Medication is continued even with evidence of cognitive decline so long as it is tolerated and patient is able to take it regularly.

Criteria for stopping treatment and how to stop

If a patient does not tolerate one acetylcholinesterase inhibitor (e.g. due to diarrhoea), it may be reasonable to try another acetylcholinesterase inhibitor (see SPC for full details) prior to changing to memantine.

Stop treatment if any of the following occur:
- Poor concordance
- Major adverse effects
- Patient asks to stop

Do not stop acetylcholinesterase inhibitors in people with AD because of severity of disease alone.

If stopping treatment, a gradual withdrawal over 1-4 weeks (depending on drug, preparation and dose) is suggested where possible. Keep the patient under regular review. If serious adverse effects occur, stop immediately.

Contact specialist or Medicines Information for advice if needed.

Monitoring Requirements including frequency

Parameter	Frequency of monitoring	Action
Mini Mental State Examination (sMMSE) / global, functional and behavioural assessment	At diagnosis and review within three-six months after commencing treatment (specialist).	Continue acetylcholinesterase inhibitor (AChEI) treatment unless medication not tolerated Continue prescribing even where an sMMSE is less than 10, particularly where the medication is tolerated and the score does not represent severe dementia, e.g. patients with learning difficulties, speech problems or where English is not the first language.
Heart rate (HR)	By primary or secondary care before starting treatment and then as and when clinically indicated and annually during a patient medication review.	If HR is less than 50bpm do not initiate AChEI. If AChEI associated bradycardia occurs (less than 50bpm) stop treatment. Cardiology assessment/ opinion may be required.
Blood Pressure (BP)	By primary or secondary care before starting treatment and then as and when clinically indicated and annually during a patient medication review.	Review medication, adjust dose (consider discontinuing) and refer to secondary care for advice if: (a) syncope occurs (donepezil and galantamine) or (b) hypertension occurs (galantamine and memantine)
ECG (in patients with cardiac history)	By primary or secondary care before initiation of treatment where there are suspected cardiac cautions (e.g. sick sinus syndrome or other supraventricular conduction abnormalities); or where indicated. Where there is access to a community hub refer there for ECG.	If ECG abnormal, suitability for dementia medication will be considered in secondary care. Cardiac re-assessment/ opinion may be required.
Renal and liver function	By GP before starting treatment.	If deterioration in renal or liver function, follow recommendation for individual medicine. Liaise with

		specialist if required.
Side effects	Review regularly at start of treatment by specialist and GP. By GP annually, or as requested by patient/carer by appointment.	Persist with treatment if mild side effects are experienced during initiation or up-titration of treatment. Stop treatment if severe persistent gastro-intestinal side effects and refer to Memory Clinic specialist. Serious side effects should be reported to the MHRA through the yellow card scheme (yellowcard.mhra.gov.uk)

NB Teams will work together to make sure tests and monitoring are done in a patient-centred way

Summary of Adverse Effects

Reminder: this list is not exhaustive - for full details of adverse effects and all potential drug interactions refer to latest Summary of Product Characteristics (SPC) for the drug, available via www.medicines.org.uk.

	Adverse effect	Frequency	Management
Acetylcholinesterase inhibitors *(See Summary of Product Characteristics (SPC) for full list or BNF)* Very common: >1/10 Common: >1/100, <1/10 Uncommon: >1/1000, <1/100 Rare: >1/10,000, <1/1000	Gastro-intestinal symptoms (incl. anorexia, nausea, vomiting, diarrhoea)	Very common	Generally mild and transient and disappear within a few days of treatment. Can be minimised by taking drug after food. If symptoms persist discuss with/refer to specialist who may reduce dose or try an alternative acetylcholinesterase inhibitor or switch to memantine.
	Headache, fatigue, dizziness and muscle cramps	Common	Generally mild & transient. The ability of the patient to continue driving or operating complex machinery should be evaluated. Consult specialist if problematic for the patient. May need dose reduction/discontinuation.
	Agitation, confusion, insomnia, abnormal dreams and nightmares	Common	Consult specialist if problematic for the patient. May need dose reduction/discontinuation.
	Syncope	Common	Consult specialist. May need dose reduction/discontinuation. In investigating seizures, the possibility of heart block or long sinusal pauses should be considered.
	Bradycardia	Common/ Uncommon	Seek urgent review. Stop treatment and consult specialist. Caution in "sick sinus syndrome", sinoatrial or atrioventricular block or concomitant treatment with digoxin or beta-blockers.
	May enhance predisposition to peptic ulceration	Uncommon / rare	Care with active or predisposition to gastric or duodenal ulcers. Consult specialist to consider discontinuation of treatment. Patient should be regularly monitored for symptoms.
	May lower seizure threshold	Uncommon / rare	Extreme caution in epilepsy. Review treatment with specialist if seizures develop as may be caused by underlying disease. The possibility of heart block or long sinusal pauses should be considered.
	May cause bronchoconstriction	No data available	Caution in COPD or asthma, consult specialist to review treatment.

	May exacerbate bladder outflow problems	No data available	Caution if history of prostatic conditions, urinary retention. (Avoid galantamine in urinary retention or post bladder surgery).
	Hepatic impairment	No data available	Avoid in severe impairment, caution in mild/moderate impairment. See BNF guidance for each drug and seek advice from consultant hepatologist.
	Renal impairment (galantamine, rivastigmine)	No data available	Avoid in severe impairment (except donepezil which is not affected by renal impairment). Caution in mild/moderate impairment. See BNF guidance for each drug and seek advice from consultant nephrologist.
Memantine *(See Summary of Product Characteristics (SPC) for full list or BNF)* Common: >1/100, <1/10 Uncommon: >1/1000, <1/100	Somnolence Dizziness	Common	The ability of the patient to continue driving or operating complex machinery should be evaluated. Consult specialist if problematic for the patient.
	Hypertension	Common	Caution in those with uncontrolled hypertension or cardiac disease. Review treatment with a specialist if this develops. May need dose reduction/discontinuation
	Dyspnoea	Common	Caution in those with COPD or asthma, consult specialist to review treatment.
	Constipation	Common	Refer back to specialist if severe or is not self limiting. Consider prn or regular laxative.
	Headache	Common	Refer back to specialist if severe or is not self limiting
	Elevated liver function test	Common	Refer back to specialist for review
	Drug hypersensitivity	Common	Stop and refer back to specialist
	Fungal infections	Uncommon	Refer back to specialist if severe.
	Gait abnormal	Uncommon	Refer back to specialist if severe.
	Venous thrombosis/ thromboembolism	Uncommon	Refer for treatment of VTE, and review memantine with a specialist.
	Confusion, hallucinations, psychosis, fatigue	Uncommon	Refer back to specialist for review.
	Pancreatitis	Unknown	Stop if severe, refer back to specialist.
	Vomiting	Uncommon	Stop if severe, refer back to specialist.
	Cardiac failure	Uncommon	Stop and refer back to specialist
	May lower seizure threshold	Very rare	Extreme caution in epilepsy. Review treatment with specialist if seizures develop as may be caused by underlying disease.
	Hepatic impairment	No data available	Avoid in severe impairment. Stop treatment and consult hepatologist.
Memantine continued *(See Summary of Product Characteristics (SPC) for full list or BNF)* Common: >1/100, <1/10 Uncommon: >1/1000, <1/100	Renal impairment	No data available	See BNF guidance: Avoid if eGFR <5mL/min/1.73m^2; reduce dose to 10mg/day if eGFR 5-29mL/min/1.73m^2; reduce dose to 10mg/day if eGFR 30-49mL/min/1.73m^2 and if well tolerated after 7 days increase to 20mg in 5mg steps.

Drug-drug interactions[4]

The table below is reproduced from the Maudsley Prescribing Guidelines 13th edition. The list of drug interactions presented in the table is not exhaustive, prescribers should also refer to individual SPCs for the medicines concerned for further detail on potential drug interactions (via www.medicines.org.uk). Caution is advised with other drugs that are also inhibitors or enhancers of CYP 3A4 and 2D6 enzymes.

Drug	Metabolism	Plasma levels increased by	Plasma levels decreased by	Pharmacodynamic interactions
Donepezil (Aricept®)	Substrate at 3A4 and 2D6	**Ketoconazole** **Itraconazole** **Erythromycin** **Quinidine** **Fluoxetine** **Paroxetine**	**Rifampicin** **Phenytoin** **Carbamazepine** **Alcohol**	Antagonistic with **anticholinergic drugs** and **competitive neuromuscular blockers (**eg **tubocurarine)**. Potential for synergistic activity with **cholinomimetics** such as **depolarising neuro-muscular blocking agents** (e.g. **succinylcholine**), **cholinergic agonists** and **peripherally acting cholinesterase inhibitors eg neostigmine. Beta blockers, amiodarone or calcium channel blockers** may have additive effects on cardiac conduction. Caution with concomitant use of **drugs known to induce QT prolongation and/or torsade de pointes**. Movement disorders and Neuroleptic Malignant Syndrome have occurred with concomitant use of **antipsychotics** and cholinesterase inhibitors. Concurrent use with **seizure lowering agents** may result in reduced seizure threshold.
Rivastigmine (Exelon®)	Non-hepatic metabolism	Metabolic interactions appear unlikely. Rivastigmine may inhibit the butyryl-cholinesterase mediated metabolism of other substances e.g. **cocaine**. Smoking **tobacco** increases the clearance of rivastigmine		Antagonistic effects with **anticholinergic** and **competitive neuromuscular blockers (**eg **tubocurarine)**.Potential for synergistic activity with **cholinomimetics** such as **depolarising neuro-muscular blocking** agents (e.g. **succinylcholine) - cholinergic agonists** e.g. **bethanecol or peripherally acting cholinesterase inhibitors e.g. neostigmine**. Synergistic effects on cardiac conduction with **beta blockers**, **amiodarone, calcium channel blockers**. Caution with concomitant use of **drugs known to induce QT prolongation and/or torsade de pointes.** Movement disorders and Neuroleptic Malignant Syndrome have occurred with concomitant use of **antipsychotics** and cholinesterase inhibitors. Concurrent use with **metoclopramide** may result in increased risk of EPSEs.
Galantamine (Reminyl®)	Substrate at 3A4 and 2D6	**Ketoconazole** **Erythromycin** **Ritonavir** **Quinidine** **Paroxetine** **Fluoxetine** **Fluvoxamine** **Amitriptyline**	None known	Antagonistic effects with **anticholinergic** and **competitive neuromuscular blockers (**eg **tubocurarine)**. Potential for synergistic activity with **cholinomimetics** such as **depolarising neuro-muscular blocking** agents (e.g. **succinylcholine),- cholinergic agonists** and **peripherally acting cholinesterase inhibitors eg neostigmine**. Possible interaction with agents that significantly reduce heart rate e.g. **digoxin**, **β blockers**, **certain calcium-channel blockers** and **amiodarone**. Caution with concomitant use of drugs known to induce QT prolongation and/or torsade de pointes (manufacturer recommends ECG in such cases). Movement disorders and Neuroleptic Malignant Syndrome have occurred with concomitant use of **antipsychotics** and cholinesterase inhibitors.

Drug-drug interactions[4] continued

Drug	Metabolism	Plasma levels increased by	Plasma levels decreased by	Pharmacodynamic interactions
Memantine (Exiba®)	Primarily non-hepatic metabolism Renally eliminated	**Cimetidine** **Ranitidine** **Procainamide** **Quinidine** **Quinine** **Nicotine** **Trimethoprim** Isolated cases of INR increases reported with concomitant warfarin (close monitoring of prothrombin time or INR advisable). Drugs that alkalinize urine (PH ~8) may reduce renal elimination of memantine eg **carbonic anhydrase inhibitors**, **sodium bicarbonate.**	None known (Possibility of reduced serum level of **hydrochlorothiazide** when co administered with memantine).	Effects of **L-dopa**, **dopaminergic agonists, Selegiline** and **anticholinergics** may be enhanced. Effects of **barbiturates** and **antipsychotics** may be reduced. Avoid concomitant use with **amantadine**, **ketamine** and **dextromethorphan** -increased risk of CNS toxicity. One published case report on possible risk for **phenytoin** and memantine combination Dosage adjustment may be necessary for **antispasmodic agents, dantrolene** or **baclofen** when administered with memantine. A single case report of myoclonus and confusion when co-administered with **co-trimoxazole** or **trimethoprim**

Information provided to the patient

Patient information leaflets (from NHS Choices)

NHS Choices Dementia

Patient information leaflets for specific medicines available at www.medicines.org.uk (patient leaflet) for **memantine, rivastigmine, galantamine and donezepil**

Evidence Base for treatment and key references

1. NICE Clinical Guideline 42, Dementia: supporting people with dementia and their carers in health and social care (updated June 2018)
2. British National Formulary last updated 25 Jul 2018 or www.BNF.org
3. Summaries of Product Characteristics for Aricept®, Exelon®, Reminyl®, Ebixa® http://www.medicines.org.uk accessed 08/01/2019
4. Taylor D, Barnes T, Young A. The Maudsley Prescribing Guidelines in Psychiatry 13th ed. 2018. Wiley-Blackwell

4. COMMUNICATION AND SUPPORT

Memory Services

Southwark & Lambeth Memory Service (SLMS)	Bexley Memory Service	Bromley Memory Service	Greenwich Memory Service	Lewisham Memory Service
151 Blackfriars Road London SE1 8EL Tel: 020 3228 0570 slmsreferrals@slam.nhs.uk	Bexleyheath Centre 4 Emerton Close DA6 8DX Tel: 020 8301 7900	Bridgeways Turpington Lane BR2 8JA Tel: 020 8629 4900	Memorial Hospital Shooters Hill SE18 3RZ. Tel: 020 8836 8519	91 Granville Park Lewisham SE13 7DW Tel: 020 3228 0939

South London and Maudsley (SLAM)

Consultant/specialist team
Dr Justin Sauer, Consultant Psychiatrist
Tel: 020 3228 1640
Email: Justin.sauer@slam.nhs.uk

Medication-Prescribing advice, interactions etc
Delia Bishara, Consultant Pharmacist, MHOA
Tel: 020 3228 1624/ 1629
Email: delia.bishara@slam.nhs.uk (Tue, Thu & Fri)

Medicines Information: 020 3228 2317

Oxleas NHS Foundation Trust

Medicines information: 01322 625002 or
oxl-tr.medicinesinfo@nhs.net

Dementia Support Hubs

Greenwich Dementia information hub:
www.greenwichcommunitydirectory.org.uk
or call 020 8921 8533
Bromley Dementia support hub:
https://www.bromleydementiasupporthub.org.uk/

Links and Referral Options to other Services

These integrated medication guidelines form part of a wider management pathway for patients with dementia. Healthcare professionals should also ensure that the patient's social care needs are taken into consideration and that they are referred to local services as and when appropriate.

Social services: Lambeth Duty phone : 020 7926 5555
Southwark Duty phone: 020 7525 3324

Alzheimer's Society: http://www.alzheimers.org.uk/
Alzheimer's Society for Southwark & Lambeth Tel: 020 7735 5850 southwarkandlambeth@alzheimers.org.uk
Alzheimer's Society for Greenwich Tel : 01322524950/ 01322 559308 Email: dagreenwich@alzheimers.org.uk
You can request a dementia advisor at the society branch who can signpost and organise peer support, carer support and advice

Age UK : https://www.ageuk.org.uk/
Lambeth: https://www.ageuk.org.uk/lambeth Ring 020 7346 6800
Lewisham & Southwark: http://www.ageuk.org.uk/lewishamandsouthwark/ Ring 020 7701 9700

National dementia helpline: 0300 222 1122 can provide information, support, guidance and signposting to other appropriate organisations. The Helpline is usually open from:
9am - 8pm Monday to Wednesday
9am - 5pm on Thursday and Friday
10am - 4pm on Saturday and Sunday

Appendix 1

Guidance for healthcare professionals in primary care on the use of Memantine for Dementia – in line with updated Dementia NICE guidelines 2018

Monotherapy

Memantine monotherapy is recommended as an option for managing Alzheimer's disease (AD) in people with:

- moderate Alzheimer's disease who are intolerant of or have a contraindication to acetylcholinesterase inhibitors (AChEIs) or
- severe Alzheimer's disease. Prescribers should only start memantine (or an AChEI) on the advice of a specialist, but a GP can do so if they have specialist expertise in diagnosing and treating AD.

Memantine should also be considered:

- for people with dementia with Lewy bodies if AChE inhibitors are not tolerated or are contraindicated and
- for people with vascular dementia but only if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.

Once a decision has been made to start memantine (or AChEI), the first prescription may be made in primary care (in line with the local integrated care guideline for dementia).

Combination therapy

For people with an established diagnosis of AD 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

If a person has an established diagnosis of AD and is already taking an acetylcholinesterase inhibitor, primary care prescribers may start treatment with memantine without taking advice from a specialist.

What is memantine?

NMDA receptor antagonist which blocks the effects of glutamate. Glutamate is released in increased amounts in Alzheimer's disease and this excessive stimulation causes neuronal damage.

What are the therapeutic effects of memantine?

It can slow progression of symptoms, like disorientation. It may help with delusions, aggression and agitation.

Dosage and how to start?

Starting dose is 5mg daily. Increasing the dose weekly by 5mg until maximum dose of 20mg daily.

Precautions and contraindications?

Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy.

Renal impairment

In patients with mildly impaired renal function (creatinine clearance 50 – 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 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. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day. Avoid if eGFR less than 5 mL/minute/1.73 m^2

Hepatic impairment

In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B), no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of memantine is not recommended in patients with severe hepatic impairment.

What are the possible side effects of memantine?

In general, the observed side effects are mild to moderate.

Common (affects 1 to 10 users in 100):

• Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (affects 1 to 10 users in 1,000):
• Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait**,** heart failure and venous blood clotting (thrombosis/thromboembolism)

Very Rare (affects less than 1 user in 10,000):
• Seizures

Not known (frequency cannot be estimated from the available data):
• Inflammation of the pancreas, inflammation of the liver (hepatitis) and psychotic reactions

Drug interactions (prescribers should also refer to individual product information for specific drugs)
• L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dose adjustment may be necessary.
• Concomitant use of memantine and amantadine, ketamine or dextromethorphan should be avoided, owing to the risk of pharmacotoxic psychosis. There is one published case report on a possible risk also for the combination of memantine and phenytoin.
• Substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
• There may be a possibility of reduced serum level of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.
• In post-marketing experience, isolated cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

What needs to happen when the person is stable on treatment?
A person with dementia continues to benefit from a regular review of their condition and update of their care plan. This should also include a check of BP and pulse rate and assessment of changes in cognition and social needs. Review of care plan should be at least annually, and at any point when a significant change has occurred for the person with dementia.

When to stop treatment?
Memantine should not be stopped because of severity of illness alone; it should be continued even if there is evidence of cognitive decline, so long as it is tolerated and patient is able to take it regularly.

References:

- NICE Clinical Guideline 42, Dementia: supporting people with dementia and their carers in health and social care (June 2018)
- British National Formulary: www.BNF.org (last updated August 2018)
- Summary of Product Characteristics for Ebixa® http://www.medicines.org.uk/ accessed 09/11/2018