Berkshire West Integrated Care System
Representing
Berkshire West Clinical Commisioning Group
Royal Berkshire NHS Foundation Trust
Berkshire Healthcare NHS Foundation Trust
Berkshire West Primary Care Alliance

Prescribing Guidelines

*Prescribing arrangement for the management of patients transferring from **Secondary Care to Primary Care***

Cholinesterase Inhibitors / Memantine Prescribing Arrangements

[APC PG 015a]

For the latest information on interactions and adverse effects, always consult the latest version of the Summary of Product Characteristics (SPC), which can be found at: http://www.medicines.org.uk/

Approval and Authorisation

Approved by	Job Title	Date
BHFT Drug and Therapeutics Committee,	DTC Chair	January 2018.
BW Area Prescribing Committee	G Braham, Chair	January 2019
GP Medicines Optimisation Committee	W Beecham, Chair	January 2019

Change History

Version	Date	Author	Reason
v.2.2	**January 2019**		**Updated document**

This prescribing guideline remains open to review considering any new evidence.

This guideline should only be viewed online and will no longer be valid if printed off or saved locally

Author	Unknown	Date of production:	Jnauary 2018
Job Title	Unknown	Review Date	January 2020
Protocol Lead	Unknown	Version	v.2.2

Healthcare from the heart of your community

Berkshire Healthcare NHS
NHS Foundation Trust

Berkshire Healthcare NHS Foundation Trust and NHS Berkshire East and West Clinical Commissioning Groups

Cholinesterase Inhibitors / Memantine Prescribing Arrangements

At the time of diagnosis, clinicians in specialist mental health services in BHFT will give patients and carers written information about the comprehensive management of Dementia. They will be advised that more useful information about Dementia and other mental health conditions can be found at the BHFT "choice and medication" website:
www.choiceandmedication.org.uk/berkshirehealthcare

BHFTs Medicines Information Service, Prospect Park Hospital - Tel: 0118 960 5075
Email: medicines.information@berkshire.nhs.uk

Memory clinic contact details:
To discuss a patient or to request specialist advice, GPs can call their local Memory Service using the following numbers:

Slough: Tel: Fax:	 01753 635075 01753 634204	**Reading:** Tel: Fax: email	 0118 960 5959 0118 960 5720
		readingmemoryservice@berkshire.nhs.uk or julianmason@nhs.net	
Bracknell: Tel: Fax:	 01344 823 220 01344 823 222	**Wokingham**: Tel: Fax:	 0118 949 5101 0118 949 5104
Windsor & Maidenhead: Tel: Fax:	 01628 640 350 01628 640 351	**Newbury**: Tel: Fax:	 01635 292 070 01635 292 087

Should you have difficulty contacting your local OPMH Service directly, please call the Locality Manager for your area:

Area	Locality Manager	Contact Number
Newbury	Alexandra.Luke@berkshire.nhs.uk	01635 292020
Reading	Heather.Eadie@berkshire.nhs.uk	0118 960 5158
Wokingham	Christine.Dale@wokingham.gov.uk	0118 989 0707
Bracknell	Tony.Dwyer@berkshire.nhs.uk	01344 823333
Windsor & Maidenhead	Eugene.Jones@berkshire.nhs.uk	01628 640200
Slough	Susanna.Yeoman@berkshire.nhs.uk	01735 690950

Authorised by: BHFT Drug and Therapeutics Committee, January 2018.
Approved by:
APC (Berks West) Date:
EPC Berks East Date:
Review date: January 2020 (or sooner, if there are relevant changes to national guidance)

1.1 Introduction and Purpose

In May 2016, the NICE Guidelines for Dementia were updated with a Technology Appraisal (TA) which recommended that donepezil, rivastigmine, galantamine could now be prescribed to treat mild as well as moderate Alzheimer's disease and that memantine could be prescribed those with severe Alzheimer's disease if appropriate (in some cases, mild to moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors).

The TA states that treatment should be offered under the following conditions:

- Only specialists in the care of patients with dementia.
- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.

Carers' views on the patient's condition at follow-up should be sought and documented.

The purpose of this Shared Care Guideline is to clarify the roles and responsibilities of both Secondary and Primary Care Clinicians in supporting both the initiation of treatment and maintenance, i.e., handover to GP care once the patient is stabilised.

1.2 Unlicensed Prescribing of High Dose Cholinesterase Inhibitors and use of combination therapy with memantine

Old Age Consultant Psychiatrists across the trust have had requests from carers and GPs for combined prescribing of Memantine and Cholinesterase Inhibitors (ChEIs) and high doses of Cholinesterase Inhibitors (ChEIs) for patients diagnosed with Alzheimer's dementia.

Since the NICE guidelines were last reviewed, there have been more recent studies and reviews investigating the efficacy and tolerability of high dose cholinesterase inhibitors and use of memantine as an adjunct.

There are benefits **albeit modest** shown for both high dose Cholinesterase inhibitors (donepezil and rivastigmine) and use of adjunctive memantine, with few significant adverse effects reported [4-15].

Unlicensed use of Dementia medications would only be considered within BHFT Specialist Memory Services for particular patients i.e. those who are declining despite having had an adequate trial of licensed doses of medication. Also, combination therapy would only be considered for patients who had exhausted monotherapy options. For these patients, modest improvements gained by having the opportunity to try higher doses or combination therapy would have a positive impact on their care. In terms of numbers, the Trust does not anticipate treating more than 6 patients in this manner at any one time.

Further details are noted below in section 2.2.2.

2. Responsibilities under shared care

2.1 GP responsibilities

1. Initial referral to secondary care to include:
   - cognitive screen
   - medical history
   - blood screening – FBC, U&E (including e-GFR),LFTs, Calcium, Glucose, thyroid Function, B12 & Folate
   - physical examination
   - cardiac history including syncope, arrhythmias and bradycardia.
   - If pulse rate 60 or below or there is significant cardiac history, to provide recent ECG
2. To provide repeat prescriptions after stabilisation.
3. To undertake an annual review of patient's physical health including weight and blood screening as clinically indicated.
4. To enquire at annual review about worsening cognition and/or new or distressing symptoms.
5. To report adverse drug reactions to the specialist
6. To act upon results communicated by specialist
7. To notify the specialist team of significant medical changes or cognitive decline
8. To liaise directly with the specialist team (see front sheet for contact numbers) if advice is needed about continuation or stopping
9. To assess ongoing benefit and consider a trial discontinuation, in discussion with the specialist team, if there has been rapid clinical deterioration or impairment has become severe.
10. To seek advice from the specialist team about discontinuation of treatment
11. To ensure all relevant staff within the practice are aware of the shared care guidelines
12. To ensure compliance with NICE Quality Standards for Dementia (QS – see Appendix D)

2.2 Secondary Care Specialist Team's responsibilities:

2.2.1 Initial Consultation (within 6 weeks of referral):

- Check medical history
- Check co-morbidities for contraindications
- Check medications for interactions and/or cautions
- Assess patients cardiovascular risk factors and request ECG *if considered clinically appropriate*
- To ensure baseline monitoring of MMSE or alternative cognitive scale if appropriate is performed and psychiatric assessment using appropriate rating scales plus any additional relevant investigations e.g. CT and MRI scan.
- To confirm baseline diagnosis of dementia subtype
- To provide written and verbal information to newly diagnosed patients and/or their carers about their condition, treatment and support options in their local area (see Appendix E for patient leaflets)

- A discussion about the Carer's view about the patient and their presentation
- Discuss and agree with the patient/carer if they would like to receive copies of their blood test results.
- To offer acetylcholinesterase inhibitors to those with mild to moderate Alzheimer's disease and mixed dementia.
- Patients with severe dementia can be offered treatment with memantine
- In advance of starting treatment, patients/carers will be informed that medication will be discontinued from the point at which it is considered no longer clinically effective.

2.2.2 Subsequent Consultations with Memory Clinics

- To send correspondence to the GP after the initial assessment, following each further appointment and when any change in the medication regimen is recommended
- To notify the GP of patient's failure to attend appointments
- To advise, educate and support patients and their carers
- To provide support for GPs / Practice nurses carrying out reviews, on a when required basis
- For patients arriving from out of area and already established on medication for Dementia see Appendix C
- To ensure compliance with NICE Quality standards for dementia (QS) see Appendix D
- Patient to have annual review with Memory Clinic Teams to be arranged 6 months after GP annual review (i.e. alternating every 6 months between GP and Memory Clinic).

Mild to Moderate Alzheimer's disease or Mixed Dementia

- To monitor adverse effects of treatment with an AChEI or memantine (where indicated) and titrate until optimal dose reached
- *NB; Memantine would be considered for patients with mild, moderate, mixed or severe Alzheimer's disease or Mixed Dementia*
- To review patient 3 months after a maintenance dose is established and every 12 months *thereafter or sooner if indicated or requested by GP.*
- Rivastigmine is licensed to treat mild to moderate dementia in **Parkinson's disease.**

Severe Alzheimer's Dementia

- To provide telephone advice for GP/ practice nurse/ carer/ patient when needed via Memory Clinic Team.
- To assess ongoing benefit and consider a trial discontinuation if there has been rapid clinical deterioration after a trial of appropriate doses or combinations of anti-dementia drugs. A MMSE score less than 10 is some guide to clinical decision making but should not be the only indication for stopping medication. This would be done in discussion with the Carer and GP.

- To initiate prescribing of memantine according to NICE guidance as clinically appropriate. Where memantine has been prescribed for mild or moderate Dementia, monitoring will be as described above under Shared

Care. This includes using memantine for behavioural symptoms in any subtype of dementia. A clear record of the indications for memantine should be recorded in the notes.

- Where memantine has been prescribed for severe Dementia, ongoing prescription and monitoring will be handed to GP 3 months after initiating medication.

Off-License use of AChEi's and memantine

- In patients who are declining despite medication consultant psychiatrists may consider the use of higher than BNF doses of acetylcholinesterase inhibitors and/or combination with memantine. It is the responsibility of the consultant psychiatrist to ensure that the patient is appropriately monitored in terms of cardiac side effects. This may include ECG or consultations with cardiologist. Higher than BNF doses should be discussed with GP on **a case by case** basis.
- Before handing over to the GP to continue management of patient, the Psychiatrist should ensure that the GP is willing to accept this responsibility for unlicensed prescribing.
- To provide telephone advice for GP/ practice nurse/ carer/ patient
- To assess ongoing benefit and consider a trial discontinuation if there has been rapid clinical deterioration after a trial of appropriate doses or combinations of anti-dementia drugs. A MMSE score less than 10 is some guide to clinical decision making but should not be the only indication for stopping medication. This would be done in discussion with the Carer and GP.

2.2.3 Provision of information.

- For suggested template of letter to GP/Patient/Carer, see **Appendix A**

It is important for GP to be supplied with a more detailed letter from the Consultant Psychiatrist detailing; diagnosis, relevant examinations and findings and any pertinent information specific to the patient/family.

2.3 Patient/carer responsibilities

- To attend appointments
- To inform the GP if new health problems occur
- To ensure correct medication administration
- To be aware of side effects, and report any relevant symptoms such as severe nausea or syncope
- To accept that treatment with these drugs will only continue as long as they are effective
- To be aware that any medication will be discontinued if there are unacceptable adverse effects

3. Baseline data and routine monitoring

Parameter	Responsibility
Cognitive screen	Initially and annually by Specialist

	team GP annually - optional
Annual Physical Health Review	GP/Practice nurse
Dementia Review Checklist (see Appendix A)	GP /Practice Nurse **optional**

Unlicensed Prescribing of High Dose Cholinesterase Inhibitors

Acetylcholinesterase inhibitor doses above BNF limits can be prescribed by consultant psychiatrists for adults where there is a clinical indication and the potential benefits outweigh the risks. There needs to be careful liaison between the psychiatrist and the GP to ensure there is appropriate follow up. The psychiatrist should take responsibility for the prescribing until the patient is **fully established** on the above BNF limits dose/combination with memantine (as mentioned above in 1.2).

MEDICATION CHECK

In cases where people are not able to self-medicate or are living alone – or no relative/carer to prompt patient to take their medication then a medication check may need to be arranged or it may be necessary to consider stopping the medication

INTERRUPTIONS IN DRUG TREATMENT

There is little published information about restarting dementia medicines after intentional or unintentional treatment breaks.

The following guidance, based on a pragmatic evaluation[1] of half-life and limited information from manufacturers' is suggested:

a) Rivastigmine patch and capsules should be re-titrated if there is a gap in treatment of 3 days or more back up to the previously stabilised maintenance dose i.e. :

- restart at 1.5mg twice daily (with food) for at least two weeks. Increase in steps of 1.5mg twice daily at intervals of at least two weeks until the previous dose is reached (oral) or
- restart at 4.6mg per 24 hours by patch increasing if needed after a minimum of 4 weeks to 9.5mg in 24 hours

This can be done safely by the GP – contact the memory clinic if further advice is needed.

b) Donepezil

- If the patient has only taken this for up to 3 weeks, then any treatment break would have to be discussed with specialist clinician. Although, the 5mg dose is usually prescribed for four weeks before reviewing dose.
- If the patient has been prescribed and has taken donepezil 10mg daily for more than three weeks then a break of less than 7 days would not significantly affect plasma levels and the patient can be restarted on the same 10mg daily dose. Breaks of more than 7 days would need the patient to be retitrated (by restarting at a daily dose of 5mg donepezil at night and increased after 28 days to 10mg). With donepezil, however, it should be noted that 5mg is a treatment dose in itself.

c) Galantamine (ordinary and 'XL') –

- Although there is no formal guidance, the manufacturers state that for treatment breaks longer than 7 days, the dose should be retitrated. (For XL preparation, this means restarting at 8mg daily (with food) for 28 days then increasing to 16mg daily for 28 days and (if previously stabilised on 24mg) increasing to 24mg daily.

d) Memantine - The manufacturers state that:

- Break of 1-2 days - the patient can restart at their original dose.
- Break of 3-7 days - dose would be titrated starting from 10mg daily for 7 days then increasing to 15mg daily for 7 days then increasing to 20mg
- Break of more than 7 days - retitrate from 5mg daily (i.e. by prescribing the memantine treatment initiation pack)

References

1. Summary of product characteristics all accessed online November 2017: www.medicines.org.uk
- Aricept Tablets Last Updated on eMC 28-Nov-2016
- Gatalin XL 24mg prolonged release capsules, hard Last Updated on eMC 16-Dec-2016 View changes | Aspire Pharma Ltd
- Ebixa film-coated tablets Last Updated on eMC 06-Mar-2017 View changes | Lundbeck Limited
- Rivastigmine Actavis 1.5mg, 3mg, 4.5mg, 6mg hard capsules Last Updated on eMC 18-Jan-2016 View changes | Actavis UK Ltd
- Details of literature search under BHFT MI Databank ref: 10370
2. NICE Technology Appraisal Number TA217, Alzheimer's disease – donepezil, rivastigmine, galantamine and memantine (March 2011, last updated May 2016)
3. NICE Clinical Guidelines CG42, Dementia (Nov 2006, last updated September 2016)
4. **Muayqil T.,** Camicoli R. Systemic Review and Meta-Analysis of Combination Therapy with CHEIs and Memantine in AD and Other Dementias. *Dement Geriart Cogn Disorder Extra*. **2012**;2: 546-572.
5. **Howard R et al**. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease. *N Eng J Med.* **2012**; 366:893-903.
6. **Farrimont LE**., Roberts E., McShane R. Memantine and Cholinesterase Inhibitor combination therapy for Alzheimer's disease: systematic review. BMJ Open **2012**; 2: e000917. Doi:10.1136/bmjopen-2012-000917.
7. **Tariot at al**. Memantine treatment in patients with moderate to severe AD already receiving Donepezil: RCT. *JAMA.* **2004**; 291:317-324.
8. **Doody RS., et al.** Efficacy and Safety of Donepezil 23 mg v 10 mg for moderate to severe AD: subgroup analysis in patients already taking or not taking concomitant Memantine. *Dement Ger Cogn Disord.* **2012**; 33: 164-173.
9. **Molino I., et al.** Efficacy of Memantine, Donepezil, or Their Association in Moderate – Severe Alzheimer's Disease: A Review of Clinical Trials. Review Article. The Scientific Word Journal. 2**013**;Article ID925702, 8 pages htt://dx.doi.org/10.1155/2013/925702.
10. **Zhu at al.** Long term association between cholinesterase inhibitors and Memantine use and health outcomes among patients with Alzheimer's disease. *Alzheimer's &Dementia.* **2013** (1-8). In press.
11. **Cummings J, et al.** Double-blind, Parallel-Group, 48-Week Study for Efficacy and Safety of a Higher-Dose Rivastigmine Patch (15 vs. 10 cm^2) in AD. *Dement Geriatr Cogn* Disord. **2012**;33:341-353.
12. **Doody, R. S., Corey-Bloom, J., Zhang, R., Li, H., Ieni, J., Schindler, R.,** (2008). Safety and Tolerability of Donepezil at Dozes up to 20 mg/day. Results from a Pilot Study in Patients with Alzheimer's disease. *Drugs Aging, 25 (2): 163-174.*
13. **Farlow, M. R., Salloway S., Tarioot, P. M., Yardley J., Moine, M. L., Wang, Q., Brand-Schieber E., Zou, H., Hsu, T., Satin, A.,** (2010). Effectiveness and tolerability of high-dose (23 mg/d) versus standard- dose (10 mg) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. *Clin Ther, 32(7): 1234-1251.*

14. **Sabbagh M, et al**. Evaluating the cognitive effects of donepezil 23 mg/d in moderate and sever Alzheimer's disease: analysis of effects of baseline features on treatment response. BMC Geriatrics 2013; http://www.biomedcentral.com/1471-2318/13/56.
15. **Christensen DD.** High dose (23 mg/day) Donepezil formulation for the treatment of patients with moderate-to-severe Alzheimer's disease*. Postgrad Med,* (2012) Nov;124(6): 110-6.

Appendix A: Suggested Letter Template

GP ADDRESS

Community (older adults) Mental Health Service
Barkham Day Hospital · Wokingham Hospital
41 Barkham Road · Wokingham · RG41 2RE
t: 0118 949 5101
f: 0118 949 5104

Ref:

Dear

Re: Name – DOB:
Address

Diagnosis:
ICD Code:
READ Code: Eu
Please add this to your GP QOF Dementia Register

Date of Review			
Summary of Assessment			
Cognitive Testing			
MMSE:	MOCA:	Clock:	BADLS:
Current Medication			
Care Plan			
1.			
2.			
3.	**This patient has been prescribed and supplied**; *(insert drug name)* and will require a review in 6 months e.g. weight, BP, pulse, FBC, U&E,C, glucose, lipids and LFTs. (please delete if not required)		
4.	**This patient falls within shared care guidelines (copy enclosed) and we would be pleased if you could take over prescribing.** They commenced on …… on dd/mm/yyyy and are now taking xx mg daily. They are stable on this. The last prescription was written on …… and they were given a …. month supply. **Please can you issue a new prescription from ……..** (please delete this point if not required) Please note that your patient may receive varied brands of the same medicines.		

	As these may differ in appearance, please ensure your patient knows to finish one preparation before starting the next.
5.	This patient will next be reviewed (insert) (please delete if not relevant). This patient will now be discharged to your care. (please delete if not relevant).

If you require any additional information or if we can be of any assistance prior to the next review, please do not hesitate to contact the team.

Yours sincerely

Name
Job Title

Dr
Memory Clinic Consultant

Enc (if enclosing shared care guidelines)

cc Patient
(Memory Clinic Administrator)

Appendix B

For detailed information about dose, adverse effects, cautions/ contraindications, please refer to the product Summary of Product Characteristics which can be accessed via:

www.medicines.org.uk

Common (frequency estimate 1% to 10%) side effects include
For AChE inhibitors:
Diarrhoea, nausea, vomiting, dyspepsia, anorexia, dizziness, fatigue, insomnia, headache, agitation, hallucinations and tremor
There is a reduced incidence of nausea using the rivastigmine patch compared to the oral formulation.
For Memantine:
Headache, constipation, hypertension; dyspnoea; dizziness; drowsiness

Suspected adverse drug reactions
If an adverse reaction to the drug is suspected, a Yellow card should be completed:
For established drugs only serious adverse reactions should be reported

Main Cautions
AChE inhibitors should be used with caution in patients with sick sinus syndrome or other cardiac conduction abnormalities as they may have vagotonic effects on heart rate e.g. bradycardia. Their use is also cautioned in patients with susceptibility to peptic ulcers, asthma, chronic obstructive pulmonary disease, renal and hepatic impairment. Contra-indicated in sever hepatic impairment.

Memantine is contra-indicated in severe hepatic impairment. Caution is recommended in patients suffering from epilepsy, former history of convulsions or predisposing factors for epilepsy. Caution in renal and hepatic impairment. Memantine is also known to cause bradycardia.

Further specialist advice can be sought if necessary from BHFT Medicines Information Service (For BHFT telephone: 0118 960 5075) or Southampton Regional Medicines Information Centre (02381206908)

APPENDIX C: Patients from out of area (and/or prescribed by a non-BHFT prescriber)

- Patients arriving from out of area (and/or prescribed by a non-BHFT prescriber) and already established on a AChE inhibitor or memantine can be reviewed by the specialist team with regard to continuing benefit or whether the drug should be discontinued, if the GP requires this.
- The specialist team will not be able to advise on prescribing until an assessment of the patient has been made – the patient should be asked to obtain at least 3 months supply from their previous (eg out of area) prescriber to ensure sufficient time for an appointment and assessment to be made.
- If a patient is unable to obtain a supply from their previous prescriber, then it will be the responsibility of the patient's new GP to decide whether to continue prescribing the AChE Inhibitor or memantine until such time as the patient can be assessed by BHFT.
- In the event of dispute with the family about stopping acetylcholinesterase inhibitors or memantine in those who are outside of the NICE guidelines and no other clinical indication for continuation can be found, these patients can be referred to the GP and/or original prescriber. If independent arbitration is required the case can be referred to the relevant CCG's case review committee

Appendix D

COST OF MONTHLY TREATMENT

Please refer to the electronic Drug Tariff for the current FP10 price. - http://www.ppa.org.uk/ppa/edt_intro.htm
The Drug tariff is updated monthly.

Acknowledgment: Sussex Partnership NHS Foundation Trust and West Sussex PCT

Please click on following link for medicines information leaflets for patients and carers:
http://www.choiceandmedication.org/berkshirehealthcare/

Medicines Information enquiries for healthcare professionals: 0118 960 5075 (Prospect Park Hospital- Pharmacy)
Medicines Information enquiries for patients and carers : 0118 960 5059 (Prospect Park Hospital- Pharmacy)