NHS
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Lincolnshire Partnership NHS Foundation Trust and NHS Lincolnshire-Wide Clinical Commissioning Groups

Acetyl Cholinesterase Inhibitors and Memantine Prescribing Arrangements Traffic Light Category: Amber 1

At the time of diagnosis, clinicians in specialist mental health services in LPFT 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 LPFT "choice and medication" website: www.choiceandmedication.org.uk/LPFT
Or can be accessed via the LPFT intranet Sharon site at http://sharon/lpft/pharmacy/default.aspx

Memory clinic contact details:
To discuss a patient or to request specialist advice, GPs can call their local Memory Service using the following numbers and ask for the CMHT Co-ordinator/team manager, or alternately use the listed secure e-mail:

Lincoln/Gainsborough Fen Lane, Nth Hykeham, Lincoln	Tel: 01522 508332 E-mail: Lpn-tr.OlderAdultsCMHTLincolnandGainsborough@nhs.net Fax: 01522 508325
Grantham/Sleaford Manthorpe Centre, Manthorpe Rd, Grantham	Tel: 01476 591676 E-mail: Lpn-tr.GranthamOlderAdultsCMHT@nhs.net Fax: 01476 572142
Boston Dept. of Psychiatry, Pilgrim Hospital, Boston	Tel: 01205 445750 E-mail:lpn-tr.BostonOlderAdultsCMHT@nhs.net Fax: 01205 445152
Stamford St. Georges Avenue, Stamford	Tel: 01780 757142 E-mail: lpn-tr.StamfordOlderAdultsCMHT@nhs.net Fax: 01780 767030
Skegness Holly Lodge, 9 The Meadows, Skegness	Tel: 01754 800200 E-mail: SkegnessResourceCentre-Olderadults@nhs.net Fax: 01754 765719
Louth Windsor House, Windsor Road, Louth	Tel: 01507 608319 E-mail: Lpntr.LouthOlderAdultsCMHT@nhs.net Fax: 01507 601264
Spalding Johnson Hospital, Pinchbeck Rd, Spalding	Tel: 01775 652300 E-mail: lpn-trJohnsonOlderAdultsCMHT@nhs.net Fax: 01775 652366

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

Area	Locality Manager	Contact Number
County wide.	Community Service Manager Witham Court, Fen Lane, Nth Hykeham, Lincoln, LN6 8UZ	01522 500690

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Reviewed & Agreed by: LPFT Drug and Therapeutics Committee, Date: Nov 2018
Approved by: PACEF, Date: March 2019
Review date: March 2022 (or sooner, if there are relevant changes to national guidance)

1. Introduction and Purpose

This Prescribing Arrangement document is written in line with the recommendations from the updated NICE guidelines on dementia which was updated in June 2018 (NG97). Subsequently, the previous technology appraisal TA217 has now been partially replaced by this updated guideline entitled Dementia: assessment, management and support for people living with dementia and their carers.

The purpose of these prescribing arrangements is to clarify the roles and responsibilities of both secondary and primary care clinicians in supporting both the initial diagnosis, initiation of treatment and maintenance. It also supports the referral and communication channels between primary and secondary care services.

Summary of NICE guideline on Pharmacological interventions for Dementia (NG97)

Alzheimer's Dementia (including mixed Vascular and Alzheimer's Dementia)
The three acetylcholinesterase inhibitors (AChEI) donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease.

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 the AchEI for moderate disease and offer memantine in addition to the AChEI for severe disease.

Lewy Body Dementia (including Parkinson's disease Dementia)
Donepezil or rivastigmine should be offered to people with mild, moderate and severe dementia with Lewy Bodies. Galantamine should only be considered in mild to moderate disease if donepezil and rivastigmine are not tolerated. Memantine should be considered if AChEI are not tolerated or contraindicated.

Vascular Dementia, Frontotemporal Dementia or cognitive impairment caused by multiple sclerosis
AChEI or memantine should not be offered to people with Vascular Dementia, Frontotemporal Dementia or cognitive impairment caused by multiple sclerosis

Treatment should be offered under the following conditions:

- Prescribers should only start treatment for new patients with these treatments on the advice of 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 if they have specialist expertise in diagnosing and treating Alzheimer's disease.

- Once a decision has been made to start an AChEI or memantine, the first prescription can be made in primary care.

- For people with an established diagnosis of Alzheimer's disease who are already taking an AChEI, primary care prescribers may start treatment with without taking advice from a specialist clinician. They may consider memantine in addition to an AChEI if they have moderate disease or offer memantine in addition to an AChEI if they have severe disease.

- If prescribing an AChEI (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost. However, an alternative AChEI could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

- Do not stop AChEI in people with Alzheimer's disease because of disease severity alone.

2. Responsibilities under shared prescribing arrangements

2.1 GP/Primary Care Specialist responsibilities before referral to LPFT for assessment:

The GP/Primary Care Specialist should be agreeable to providing the recommended prescriptions for treatment after the referral.

Initial referral to secondary care to include (as recommended by NG97):

- Cognitive testing using a validated brief structured instrument (e.g. 6CIT or Mini-Cog).
- Full GP Medical summary records
- History relevant to cognitive, behavioural and psychological symptoms and the impact the symptoms have on patient's daily life.
- Blood screening – FBC, U&E (including e-GFR), LFTs, calcium, glucose, thyroid function, B12 & folate, lipid profile.
- Urine screening.
- Investigate and review medication that may cause cognitive impairment.
- Physical examination.
- Cardiac history and history of complications including syncope, arrhythmias and bradycardia, unexplained falls and blackouts.

2.2 Secondary Care Specialist Team's responsibilities:

Initial Consultation

1. From details in GP/Primary Care Specialist referral letter, check medical history.
2. Check co-morbidities for contraindications.
3. Check medications for interactions and/or cautions.
4. Assess patient's cardiovascular risk factors.
5. Ensure baseline detailed cognitive assessments are performed along with a psychiatric assessment using appropriate rating scales plus any additional relevant investigations.
6. Provide confirmation of a diagnosis and sub-diagnosis or not as the case may be, of

dementia illness.
7. Provide written and verbal information to newly diagnosed patients and/or their carers about their condition, treatment and support options in their local area.
8. Recommend the appropriate dementia medication according to type or severity of illness.
9. Provide written confirmation of the diagnosis and initial treatment, titration and ongoing maintenance plan to GP within 1 working day of patient being informed of diagnosis. **See Appendix 1.** Refer to specific medicine SPC if further information is required.

2.3 Subsequent Consultations with Memory Clinics

1. To send correspondence to the GP/Primary Care Specialist after the initial assessment, following each further appointment and when any change in the medication regimen is recommended.
2. To notify the GP/Primary Care Specialist of any delay in service provision/delivery or patient's failure to attend appointments. In the case of a failure to attend, a second appointment will be made/offered. If there is a failure to attend two appointments the patient will be contacted to confirm if they still want the appointment and referred back to the care and management of the GP if not.
3. To advise, educate and support patients and their carer's in relation to any aspect of their care related to diagnosis and treatment.
4. To carry out the ongoing medication review of patients for whom secondary care specialists staff has recommended treatment for dementia.
5. The patient will be reviewed at least annually and the GP will be informed of the review outcomes.
6. In between annual medication review, to respond to any patient's dementia diagnostic or medication related issue(s) and see/support the patient accordingly.

2.4 GP/Primary Care Specialist responsibilities

1. To provide prescriptions for the recommended treatment.
2. To report adverse drug reactions to the specialist.
3. To notify the specialist team of significant medical changes or cognitive decline identified/reported to them.
4. To liaise directly with the specialist team (see front sheet for contact numbers) if advice is needed about continuation or stopping.
5. To ensure all relevant staff within the practice are aware of these prescribing arrangements and guidelines.

Provision of information.

- For recommended template of letter to GP/Patient/Carer, see **Appendix 1.**

It is important for GP/ Primary Care Specialist 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.

2.5 Patient/carer responsibilities

- To attend appointments.
- To understand that they can inform the secondary-care specialist if any dementia-related problem arises or recurs.
- To ensure correct medication is taken/administration.
- To be aware of side effects, and report any relevant symptoms such as severe nausea or syncope and to bring these to the attention of the specialist team.
- To be aware that any medication may be swapped or even discontinued depending on clinical review or if there are unacceptable adverse effects.

3 Baseline data and routine review

Parameter	Responsibility
Cognitive screen (pre-referral); physical examination; appropriate blood and urine tests Diagnosis including subtype, physical health screen (including frailty) mood screen.	GP/ Primary Care Specialist Secondary Care Specialist team
Annual medication review (or at interval indicated/agreed)	Secondary Care Specialist team
Dementia Review Checklist (see Appendix A)	GP /Practice Nurse **optional**

4 Interruptions in drug treatment

The following guidance 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 manufacturer's 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 Aricept ® tablets; Reminyl XL® tablets; Exelon® capsules, patches & oral solution; Ebixa® tablets and Ebixa® 5mg/pump oral solution www.medicines.org.uk
2. NICE Technology Appraisal Number TA217, Alzheimer's disease – donepezil, rivastigmine, galantamine and memantine (March 2011)
3. Dementia: assessment, management and support for people living with dementia and their carers (NICE guideline [NG97]) [June 2018]
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. 2013;Article ID925702, 8 pages htt://dx.doi.org/10.1155/2013/925702.
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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 1: Suggested Letter Template

Please see link below to access the latest letter template:

http://www.lpft.nhs.uk/assets/files/older-adults/example-mams-care-review-letter.pdf

Appendix 2:

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 under the relevant drug name.

Common (frequency estimate 1% to 10%) side effects include
For the acetylcholinesterase 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 black triangle drugs all adverse reactions should be reported
For established drugs only serious adverse reactions should be reported

Note none of the products covered by these guidelines have "black triangle" status

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.

APPENDIX 3: Patients from out of area (and/or prescribed by a non-LPFT prescriber)

Patients arriving from out of area (and/or prescribed by a non-LPFT prescriber) and already established on a Acetyl cholinesterase 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. This would be considered a new referral and the above arrangements would apply. Prescribing arrangements would remain the GPs responsibility.

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 would be referred to the Older Adult Services Clinical Director. If independent arbitration is required, the case can be referred to the relevant CCG's case review committee.

APPENDIX 4: 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.

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

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