THE SHEFFIELD AREA PRESCRIBING GROUP

Shared Care / Prescribing Guideline

For

the Prescribing of Cognitive Enhancers in Dementia.

Shared Care Guideline developed by:

Karen O'Connor, GP, Sheffield CCG
Heidi Taylor, Clinical Effectiveness Pharmacist, Sheffield CCG
Peter Bowie, Consultant in Old Age Psychiatry and Clinical Director, Specialist Directorate, SHSC(FT).

Updated November 2018 by:
Heidi Taylor, Peter Bowie and Sarah Jones, GP

Date approved: April 2019
Review Date: 3 years from approval

Shared Care / Prescribing Guideline for the Prescribing of Cognitive Enhancers in Dementia.

Statement of Purpose

This shared care prescribing guideline has been written to enable the initiation of prescribing and continuation of care by primary care clinicians of cognitive enhancers for patients who have the following diagnosis of dementia, diagnosed by a *clinician with the necessary knowledge and skills:

- Alzheimer's disease or
- Lewy bodies dementia or
- comorbid vascular dementia (i.e. only if mixed with Alzheimers dementia, Parkinsons Disease or Lewy bodies)

Primary care will only be requested to prescribe cognitive enhancing drugs within licensed indications or NICE guidelines (where use if off-label, this is indicated below).

For Parkinson's disease dementia – See the Parkinson's shared care guideline

The use of acetylcholinesterase (AChE) inhibitors or memantine for other indications such as the management of behavioural disturbance is beyond the scope of this protocol.

The use of cognitive enhancer medication should be part of a package to support patients with Alzheimer's disease. Non-pharmacological treatment such as social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes should also be in place as needed as the disease progresses. Dementia is a progressive disease and consideration should be given as to how care will be coordinated and the patient supported to navigate health and social care support as requirements change.
See below for useful links.

*This would generally be a specialist within the memory service at SHSC, but could be any specialist who has the appropriate knowledge and skills with specialist expertise in assessing and diagnosing dementia.
If a patient cannot or chooses not to attend the specialist service, advice can be sought from the specialist service regarding assessment and treatment options. For care home patients see link.

Responsibilities of secondary care service

- To confirm diagnosis, and communicate to GP regarding starting acetylcholinesterase inhibitors or memantine in appropriate patients
- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent. This is particularly important for off label use of products (see below).
- Undertake a cardiac assessment, which may involve carrying out an ECG
- To report any adverse reaction to the MHRA – See yellow card.
- To contact patient's GP to request prescribing under shared care arrangements and send a link to or copy of the shared care guideline/ prescribing guideline.
- To conduct reviews to assess efficacy and tolerance; and once stabilised to determine and follow agreed case management pathway.
- As requested, to support primary care clinicians around when to consider adding in memantine as cognitive function decline worsens
- To discuss any concerns with the GP regarding the patient's therapy

- The patient to remain under / have access to the consultant /specialist service whilst ever the patient is being prescribed any medication within this guide (unless individual arrangements agreed).

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe for patients in line with the shared care / prescribing guideline
- To report any adverse reaction to the MHRA and the referring consultant – See yellow card.
- To initiate / continue to prescribe for the patient as advised by the consultant
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant / specialist if any concerns with the patient's therapy (see contact details below)
- To conduct an annual face to face medication review or more frequent if required.
- Monitor patient in line with recommendations below
- To review severity of dementia as appropriate, but at least annually and consider adding memantine as per below (under selection of patients). Cognitive decline alone should not be a reason to stop cognitive enhancing medication as evidence suggests cognitive function can worsen upon stopping treatment – see below for more information around this.
- In the event that the GP is not able to prescribe, or where shared care is agreed but the consultant is still prescribing certain items e.g. hospital only product; the GP will provide the consultant with full details of existing therapy promptly by fax on request.
- For medication supplied from another provider GPs are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems: http://www.intranet.sheffieldccg.nhs.uk/Downloads/Medicines%20Management/Practice%20resources%20and%20PGDs/Recording_SIDs_on_practice_clinical_systems%20.pdf

Responsibilities of patient / carer

- To attend hospital and GP clinic appointments. Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the GP or specialist should their clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or GP whilst taking cognitive enhancing medication
- To read the medicines information given to them
- To take medication as prescribed
- Inform the specialist, GP or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Indication

This guideline covers the use of donepezil, galantamine, rivastigmine and memantine in patients diagnosed with Alzheimer's disease, Lewy bodies dementia (off label) and comorbid vascular dementia (vascular dementia with Alzheimer's disease, Parkinson's Disease or Lewy bodies – off label).

Note – See Parkinson's SCP for use in PD dementias.

Alzheimer's dementia

The three AChE inhibitors; **donepezil (generally first line based on cost)**, galantamine and rivastigmine, 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 an AChE inhibitor if they have moderate disease
- offer memantine in addition to an AChE inhibitor if they have severe disease.

Lewy bodies dementia
Mild to moderate - Donepezil and rivastigmine are generally offered first line (galantamine may be offered in mild to moderate disease if first line options not tolerated). Memantine can be used if AChE inhibitors are not tolerated or contraindicated. (Note, there is no current evidence to support combination therapy of an AChE inhibitor and memantine in Lewy bodies dementia).
Severe - donepezil or rivastigmine may be considered. Memantine can be considered if AChE inhibitors are not tolerated or they are contraindicated.

Comorbid vascular dementia
AChE inhibitors or memantine are only considered for use in people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies. (Note, there is no current evidence to support combination therapy of an AChE inhibitor and memantine in comorbid vascular dementia).

Selection of patients

If a GP suspects that a patient is developing significant cognitive impairment they should, after initial assessment, be referred to Older Adults Secondary Mental Health Services using the Dementia Protocol (under review). For patients with LD see link.

The specialist services will determine (where possible) the dementia subtype. They will discuss treatment options with the patient where indicated. Where prescribing is agreed with the patient, the GP will be asked to participate in the shared care, including initiating prescribing and review of ongoing medication.

Adding memantine to patients already taking AChE - considerations
For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, the adding in of memantine may improve cognitive function and global functioning:

- ***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.

In clinical trials staging of dementia has tended to be defined by Mini Mental State score (out of 30). Scores above 18 defined as “mild”, 10 to 18 defined as “moderate” and below 10 “severe”. These cut off scores have not been established with other cognitive scales although combining a score from another scale with an appraisal of the person’s functional capability could give a global impression of disease severity.

The prospects of maintaining a reasonable quality of life and the views of the patient and their carer should be taken into account before adding memantine to existing therapy.

* NICE use the term 'consider' to reflect a recommendation for which the evidence of benefit is less certain. This should be borne in mind when having discussions with the patient / family and carer.

** NICE use the term 'offer' to reflect a strong recommendation, usually where there is clearer evidence of benefit.

Dosage

All dosing should be in line with licensed indications and BNF dosing recommendations. Note all the doses below are licensed doses for Alzheimer's disease. Use in Lewy bodies and comorbid vascular dementia is off label but the doses below (from the BNF) can be used as a guide.

Donepezil:

- Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime.
- Tablets should be used first line. If a liquid preparation is needed then the orodispersible tablets are the most cost effective)

Galantamine:

- Immediate release preparation. Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for at least 4 weeks; maintenance 8–12 mg twice daily.
- Modified release preparations - Initially 8 mg once daily for 4 weeks, increased to 16 mg once daily for at least 4 weeks; maintenance 16–24 mg daily. Prescribe cost effective galantamine brand.
- Dose adjustments are required if moderate hepatic impairment. See BNF. Avoid in severe hepatic impairment.
- Avoid if eGFR less than 9 mL/minute/1.73 m^2

Rivastigmine:

- Oral - Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitrate from 1.5 mg twice daily.
- Transdermal - Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increase to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated; use caution in patients with body-weight less than 50 kg, if treatment interrupted for more than 3 days, re-titrate from 4.6 mg/24 hours patch. Prescribe cost effective rivastigmine brand.
- Use with caution in severe hepatic impairment

Memantine:

- Initially 5 mg once daily, then increased in steps of 5 mg every week; usual maintenance 20 mg daily; maximum 20 mg per day
- Renal impairment:
    - Reduce dose to 10 mg daily if eGFR 30–49 mL/minute/1.73 m^2, if well tolerated after at least 7 days dose can be increased in steps to 20 mg daily
    - Reduce dose to 10 mg daily if eGFR 5–29 mL/minute/1.73 m^2.
    - Avoid/stop if eGFR less than 5 mL/minute/1.73 m^2.

If prescribing an AChE inhibitor, treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose). There is no evidence to support one AChE inhibitor being more clinically effective than another, however an alternative AChE inhibitor may 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. Based on cost **donepezil tablets would generally be first line**. Other formulations, such as the orodispersible form, or alternative AChE inhibitors should only be used where there is

clinical need or due to patient choice
See table for examples of costs (correct at time of publication – November 2018)

Contra-indications

The details below are not a complete list and the BNF and the SPC remain authoritative

Applicable to all - Known hypersensitivity to the active ingredients or any of the excipients.

Donepezil – patients with a known hypersensitivity to piperidine derivatives

Galantamine – Severe hepatic (Child-Pugh score greater than 9) and severe renal impairment (creatinine clearance less than 9 ml/min).

Rivastigmine – Hypersensitivity to other carbamate derivatives. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch.

Side–effects and precautions

The details below are not a complete list and the BNF and the SPC remain authoritative

Acetylcholinesterase inhibitors

Side effects
Common: diarrhoea, muscle cramps, fatigue, nausea, vomiting, insomnia.
Rarely reported: syncope, bradycardia, sinoatrial block, atrioventricular block, psychiatric disturbances

Precautions
Anaesthesia, cardiac conduction problems, bladder outflow obstruction, seizures, asthma or obstructive pulmonary disease

Memantine

Side effects
Hypersensitivity, Hypertension, hallucinations, confusion, dizziness, balance disorders, somnolence, dyspnea, constipation, raised LFTs, headache and tiredness

Precautions
Epilepsy, sudden change to a vegetarian diet, recent myocardial infarction, uncompensated congestive heart failure. See above re renal impairment.

Monitoring

Following a 6 month trial of treatment the Memory Services will review the efficacy and tolerance to the AChE inhibitor. Those who are benefiting from treatment will be assessed for future care pathway management taking into account the needs, complexity and existing support of each patient. Three broad aftercare pathways are

- Level 1 - Patient assessed to have minimal need. Patient and carer given contact information (see appendix) and patient put on Memory Service case register. Patients will not routinely be seen unless specifically requested by patient/carer or third party (e.g. GP, social worker, voluntary sector)
- Level 2 - Patient assessed to have low level needs. Patient monitored by Memory Service via patient / carer telephone contact and, where available, via SystmOne.
- Level 3 - Patients assessed as having active mental health needs and are seen by Memory Service or another Mental Health team.

All patients will require an annual (medication) review in primary care. The following should also be considered at each review;

Symptom control and side effects
Stopping or continuing treatment?
When considering benefits of treatment cognitive, functional and behavioral symptoms should be taken into account as well as considering side effects and interactions with other medicines. **Decline of cognitive function alone should not be a reason to stop cognitive enhancers. Studies have shown clear evidence of harm from discontinuing cholinesterase inhibitors in people with moderate Alzheimer's disease, with a substantial worsening in cognitive function upon cessation.**

At review consider the patient holistically and factors such as;

- quality of life,
- global and daily functions,
- life expectancy and
- treatment goals
- evidence on behavioural symptoms, in particular agitation (there is evidence memantine monotherapy may have positive effects on agitation, and some evidence that cholinesterase inhibitors may worsen agitation in some individuals.)
- discussing benefits / side effects with the patient / carer and
- the potential that functioning may worsen if stopped.

If at the review there is a shared decision to stop cognitive medication, the GP can discontinue treatment. However, if needed, advice can be sought from the specialist service, contact details below. Wherever possible ensure patient, carers and relatives are all involved fully in decision making, and all discussions documented

These potential effects are also important to consider.

The GP should inform the specialist services of significant side effects, such as:

- Bradycardia
- Acute asthmatic exacerbations
- Persistent new gastrointestinal symptom, particularly bleeding e.g melaena

Bradycardia and acute asthmatic exacerbations would be reasons to discontinue treatment.

Renal or hepatic function
If either decline doses may need altering. See above under dosage.
Patients on memantine should have an annual renal function checked (see advice under dosage).

Other medication
As well as tolerance / side effects to current cognitive medication the impact of other medication on cognitive function and potential interactions should also be considered. Examples of medication that may effective cognitive functioning are below, see link for more details on drugs that can increase anticholinergic cognitive burden (ACB):

- Antipsychotics
- Anticholinergic medication (See link – consider prescribed and OTC)
- Diuretics – watch for electrolyte disturbance
- Benzodiazepines
- Opioids (consider prescribed and OTC)
- Dopaminergic medication has been reported to both enhance and reduce cognitive impairment – discuss with PD specialist

Other considerations:
Non-cognitive symptoms
Agitation, aggression, distress and psychosis

Only offer antipsychotics if either;

- Patient is at risk of harming themselves or others **or**
- They are experiencing agitation, hallucinations or delusions that are causing them severe distress

Before starting treatment discuss the benefits and harms with the person, their family or carers, consider using a decision support tool for this discussion (See link). Prescribing should be part of a care plan that includes psychosocial and environmental interventions.

Sleep problems

Do not offer melatonin to help with sleep in Alzheimer's disease.
Evidence does not show significant benefit from using melatonin to treat insomnia in people with Alzheimer's disease. There is a lack of studies in other dementia subtypes Although it is not appropriate to extrapolate this evidence to other subtypes of dementia, the use of melatonin in any form of dementia is not covered by this guideline.
Non pharmacological support / sleep hygiene advice should be considered.

Note, melatonin may be considered to treat rapid eye movement sleep behaviour disorder in patients with Parkinson's disease, however this is not within the remit of this guideline.

If the specialist discontinues treatment the GP should be informed in a timely manner.

Interactions

The details below are not a complete list and the current BNF and the SPC remain authoritative.

Common to all acetylcholinesterase inhibitors
Antimuscarinic drugs, neuromuscular blocking agents, cholinergic drugs, beta blocking agents

Galantamine
Paroxetine, ketoconazole, erythromycin (plasma concentration of galantamine increased with concomitant use). Galantamine should not be given concomitantly with other cholinomimetics (such as donepezil, neostigmine, pyridostigmine or rivastigmine).

Rivastigmine
Rivastigmine should not be given concomitantly with other cholinomimetic substances and rivastigmine might interfere with the activity of anticholinergic medicinal products (e.g. oxybutynin, tolterodine).

Memantine
Amantadine, ketamine and dextromethorphan (avoid concomitant use).
L-dopa, dopamine agonists, anticholinergics (effects of these may be enhanced).
Barbiturates and neuroleptics (effects of these may be reduced).
Cimetidine, ranitidine, procainamide, quinine and nicotine (potential risk of increased levels of either drug).
Warfarin - enhance effect possible, closer monitoring of INR advisable.
Baclofen and dantrolene – effects of these may be modified.

Re-Referral guidelines

All patients will be on the case register at the Memory Service, if there are any concerns at any point regarding treatment / patient or carer safety then the service can be contacted for advice or possible intervention.

Financial implications

The table below lists the current (November 2018) costs of preparations if prescribed generically. Wherever clinically appropriate, donepezil tablets should be considered first line.

If galantamine, rivastigmine or memantine are prescribed, then prescribers are encouraged to use the most cost effective preparation of the appropriate formulation indicated.

Medication / formulation / strength	**Cost/28 days treatment (from November 2018 Drug Tariff)**
Donepezil 5mg/10mg tablets	74p /£1.04
Donepezil 5mg/10mg orodispersible tablets S/F	£7.12/£8.46
Donepezil 1mg/ml oral solution (S/F)	£52.25/150ml (based on a 5mg dose)
Galantamine 8mg / 12mg tablets	£61.13/£74.10 / 56 (based on BD dosing)
Galantamine 8mg/16mg/24/mg MR capsules **Branded generics are much more cost effective. Examples prices - 8/16/24 mg respectively**	£51.88/£64.90/£79.80 **£19.05/£23.84/£29.32**
Rivastigmine 1.5mg/3mg/4.5mg/6mg capsules	£4.56/£5.80/£47.06/£58.32 (based on BD dosing)
Rivastigmine 4.6mg/24hours and 9.5mg/24 hours patches **Branded generics are much more cost effective. Examples prices 4.6/9.5mg/24 hours**	£77.97/£30.02 **£35.10/£19.75**
Memantine 10mg/20mg tablets	£1.49/£1.24
Memantine 10mg/20mg orodispersible s/f tablets	£24.99/£49.98
Memantine 10mg/ml oral solution (S/F)	£54.52/50ml

Ordering information

All medication listed in this guideline are licensed preparations available from all main wholesalers.

Support, education and information

- Nurses help line: 0114 2718585
- Consultants in Old Age Psychiatry are contactable via Sheffield Health and Social Care Trust switchboard Tel: 0114 271 6310
- Main memory clinic number: 0114 2716015
- Sheffield Health and Social Care Trust Pharmacy department. Tel: 0114 271 8630

Other useful resources;

- Sheffield Directory
- Age UK
- Alzheimer's Society
- Sheffield Mind
- Sheffield Dementia Information pack
- Age better in Sheffield
- Samaritans
- Safe guarding
- Mental capacity
- Sheffield Carers
- Diagnosing dementia in Care homes
- Dementia Friends

References

NICE technology appraisal guidance TA217 - Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease

NICE NG97 - Dementia: assessment, management and support for people living with dementia and their carers

Electronic BNF

Electronic Medicines Compendium (EMC)

Quality and Outcomes Framework **-** https://www.nhsemployers.org/-/media/Employers/Documents/Primary-care-contracts/QOF/2018-19/2018-19-QOF-guidance-for-stakeholders.PDF?la=en&hash=6A53571FC0F7A63FA7354951C733B9E6011EC2CD

Appendix – sample letter to patient

Sheffield Health and Social Care
NHS Foundation Trust

Sheffield Memory Service
The Longley Centre
Norwood Grange Drive
SHEFFIELD
S5 7JT

Fax: 0114 2716016

Our ref: sb/kt/serdev

Date:

Dear

The Sheffield Memory Service is currently reviewing the service it provides to make the experience more user friendly.

We currently find that people would prefer to attend the service for follow up appointments when they are experiencing changes or difficulties to their memory, and/or, their day to day activities of daily living skills, rather than attend when all is well.

To ensure that you receive the service when you want and need it we are planning on providing appointments at your request, rather than sending you routine follow up appointments.

Your next appointment was due in the next 2 – 6 weeks, however, we will be relying on you to contact us if you need to be seen. Again, to reiterate, we feel that this service will offer you access when you need it.

We would like to reassure you that this does not mean that you have been discharged from our service. You will continue to remain with our service and we will send you a bi-monthly news letter and information of drop in sessions and events that we are running.

Should you, at any time, wish to speak with a nurse you can call our

Nurse Help Line on 0114 2718585
(the help line is open 0900-1100hrs and 1300-1500hrs Monday to Friday)
or e mail us on
sheffmemoryservice@shsc.nhs.uk

We would be happy to hear your thoughts or concerns on this new way of providing a service which is bespoke to your needs.

Yours sincerely

Appendix – sample letter to relative or supporter

Sheffield Health and Social Care
NHS Foundation Trust

Sheffield Memory Service
The Longley Centre
Norwood Grange Drive
SHEFFIELD
S5 7JT

Fax: 0114 2716016

Our ref: sb/kt/serdev

Date:

Dear

The Sheffield Memory Service is currently reviewing the service it provides to make the experience more user friendly.

We currently find that people would prefer to attend the service for follow up appointments when they are experiencing changes or difficulties with their memory, and/or, their day to day activities of daily living skills, rather than attend when all is well.
To ensure that you receive the service when you or your relative want and need it we are planning on providing appointments at your request, rather than sending out routine follow up appointments.

Your relatives next appointment was due in the next 2 – 6 weeks, however, we will be relying on you or your relative to contact us if you need support or advice. Again, to reiterate, we feel that this service will offer you access when you need it.

We would like to reassure you that this does not mean that your relative has been discharged from our service. They will continue to remain with our service and we will send a monthly news letter and information of drop in sessions and events that we are running.

Should you, at any time, wish to speak with a nurse you can call our

Nurse Help Line on 0114 2718585
(the help line is open 0900-1100hrs and 1300-1500hrs Monday to Friday)
or e mail us on
sheffmemoryservice@shsc.nhs.uk

We would be happy to hear your thoughts or concerns on this new way of providing a service which is bespoke to your needs.

Yours sincerely