DORSET MEDICINES ADVISORY GROUP

SHARED CARE GUIDELINES FOR THE USE OF ACETYLCHOLINESTERASE INHIBITORS AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIA

INDICATIONS FOR USE

NICE Technology Appraisal TA 217 recommends the use of the three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapy options for managing mild to moderate Alzheimer's disease. Memantine as monotherapy is recommended as an option for managing moderate Alzheimer's disease for those who are intolerant of or have a contraindication to AChE inhibitors **or** have severe Alzheimer's disease.

Updates to the NICE guidelines on dementia (NG97) were incorporated into TA217 in June 2018:

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.

Treatment should be under the following conditions:

For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include:

- 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 AChE inhibitor or memantine, the first prescription may be made in primary care.

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

The NICE guidelines do not define the severity of dementia but local experts in Alzheimer's suggest the following as a guide to support GPs, from ICD-10:

- **Mild** – New learning mainly affected. Impaired performance in daily living but not to a degree it makes the individual dependent on others.

- **Moderate** – Degree of memory loss represents a serious handicap to independent living. Unable to function without assistance of another in daily living.

- **Severe** – Complete inability to retain new information, failure to recognise close relatives. Absence of intelligible ideation.

While this predominantly refers to the stages of dementia in Alzheimer's there are no clear stage criteria for dementia with Lewy Bodies or Parkinson's disease dementia.

Ensure that local arrangements for prescribing, supply and treatment review follow the NICE guideline on medicines optimisation.

Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone.

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This shared care guideline reflects the locally agreed protocol for shared care and should be followed in conjunction with the local Memory Assessment Gateway Referral form and algorithm.

AREAS OF RESPONSIBILITY OF SHARED CARE

This shared care agreement outlines ways in which the responsibilities for managing the prescribing for the treatment of Alzheimer's disease and other dementia can be shared between the specialist and general practitioner (GP). GPs are invited to participate. The commissioned pathway for non complex patients mean that they will be discharged from the Memory Assessment Service (MAS) for ongoing annual medication review by their GP. Where a GP.is not confident to undertake this review the support of the Memory Assessment Service clinicians should be sought. Patients with more complex needs can still be reviewed by CMHT where appropriate.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients and/or carer(s) are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Pre-diagnosis and in conjunction with the Memory Gateway referral form General Practitioner Responsibilities	
1	At the initial assessment take a history (including cognitive, behavioural and psychological symptoms, and the impact symptoms have on their daily life) from the person with suspected dementia and if possible, from someone who knows the person well (such as a family member).
2.	If dementia is still suspected after initial assessment conduct a physical examination and undertake appropriate blood and urine tests to exclude reversible causes of cognitive decline and use cognitive testing.
3	When using cognitive testing, use a validated brief structured cognitive instrument such as the 6-Item Screener (6 CIT);10-point cognitive screener (10-CS); the Memory Impairment Screen (MIS) or Test Your Memory (TYM). The MMSE is no longer recommended by NICE.
4	Do not rule out dementia solely because the person has a normal score on a cognitive instrument.
5	When taking a history from someone who knows the person with suspected dementia, consider supplementing this with a structured instrument such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ).
6	Refer patient via the Memory Gateway referral form if: • reversible causes of cognitive decline (including delirium, depression, sensory impairment [such as sight or hearing loss] or cognitive impairment from medicines associated with increased anticholinergic burden) have been investigated and • dementia is still suspected.
Post diagnosis and in conjunction with Memory Gateway algorithm Specialist Responsibilities (Specialist services in the care of patients with dementia)	
1	Confirmation of diagnosis of Alzheimer's disease and other forms of dementia and assessment including tests of cognitive, global and behavioural functioning and of activities of daily living. Assessment must be appropriate to the needs of the patient (e.g. language skills and cognitive deficit).
2	Ensure that the patient has access to an overall programme of care and support through the multidisciplinary team.
3	Assess the patient's suitability for therapy with an acetylcholinesterase inhibitor or memantine if appropriate. This should include checking for any potential drug interactions and ensuring that a carer or care-worker is in sufficient contact with the patient to ensure compliance.
4	Where indicated, to initiate treatment and to continue to prescribe and assess the patient during the first three months. Review patient at 3 months to assess benefit of treatment.
5	Consider: • switching to memantine if the patient is intolerant of the AChE inhibitor • adding memantine to an AChE if the patient develops moderate Alzheimer's Disease. Offer memantine in addition to an AChE if the patient develops severe Alzheimer's Disease
6	Where there is benefit after 3 months, the GP should be requested to continue prescribing treatment. It is important to recognise that stability should be considered as effective treatment. Prescribing can be transferred once a patient has been stabilised on the treatment for 3 months.
7	In accordance with the memory assessment algorithm, review the patient twelve months following the end of the 3 month trial (i.e. following at least 15 months of therapy) and contact the GP with regard to discharging from service if there has been improvement or no deterioration in cognitive function, together with evidence of global improvement on the basis of behavioural and/or

	functional assessment. Requests to GPs should be made in writing and must include appropriate information to allow an informed decision to be made. On agreement from the GP, to provide the GP with appropriate information, including relevant clinical assessment information to support the transfer of clinical responsibility. Also describing the mechanism to receive re-referral of a patient from the GP in the event of deteriorating clinical condition, directly back to MAS.
8	Ensure the patient and/or carer have been fully informed with comprehensive advice and information with regards to their treatment and consent has been discussed and documented.
9	To communicate promptly with the GP when treatment is changed, stopped or adjusted and to communicate changes in response to treatment or the condition itself.
10	Ensure that clear backup arrangements exist for GPs to obtain advice and support.
11	To ensure the patient has sufficient supply of medication until such time as is appropriate for the GP to assume prescribing responsibility. This may include times to cover initial transfer of responsibility.

Post diagnosis and in conjunction with Memory Gateway algorithm General Practitioner Responsibilities	
1	Prescribe after the first three months of a successful trial for those patients who have been initiated on treatment with an AChE inhibitor and/or memantine and who have been assessed as benefitting from treatment. Reply to the request for shared care as soon as practicable. Transfer of care is assumed if the specialist is not contacted within 14 days of the request.
2	Following specialist assessment, with patient stabilised on medication ready for discharge, (this would normally be around 15 months for majority of patients if stable), to receive the clinical responsibility for annual medication review and care of patient from the MAS service. Reply to this request for transfer of care as soon as practicable. Following discharge from the memory service, if the patient is stable on their treatment then a referral back to secondary care should be at the discretion of the GP for review if there has been deterioration or are concerns in respect of continuing the prescription. The MAS service will provide appropriate contact details on discharge.
3	To complete yearly ongoing medication reviews of clients who have been discharged from the Memory Service but remain on medication. The initial annual medication review required by the GP after discharge will be after at least 27 months of receiving the medication. The review should be based on the following questions: • How is your memory? Any improvement or decline? • Is there any evidence of behavioural problems, BPSD (behavioural and psychological symptoms related to dementia) • Is there any carer stress • Any side effects from the medication, dizziness, diarrhoea. A steady decline in cognitive function year on year is to be expected so this on its own would not necessarily need a re-referral and review by the MAS. However if there are GP, patient or carers concerns they can be referred for review. Patients suffering a significant deterioration, whose general wellbeing is deteriorating, showing signs of another MH problem e.g. depression, hallucinations or developing behavioural problems should be referred back to the MAS routinely or CMHT urgently depending on the presentation and severity of symptoms.
4	To consider any side effects reported by the patient and to discuss with the specialist if necessary
5	To undertake any necessary monitoring including e.g. pulse, weight and others where appropriate as agreed with the specialist. Dementia monitoring in line with the GP Contract Plus (basket)
6	Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
7	Report adverse events to the specialist.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Share any concerns in relation to treatment.
3	Report any adverse effects to the specialist or GP.

SUPPORTING INFORMATION

Medication choice

When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative

acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions, and dosing profiles.

Locally the agreed first-line AChE inhibitor is donepezil film-coated tablets.

In addition, the use of any other pharmaceutical form, other than solid oral tablets or capsules (including modified release forms), should be clinically justified by compliance issues and should be initiated by or discussed with the specialist. Alternative forms include oro-dispersible tablets, liquid preparations and transdermal patches but these may be considerably more expensive – see Drug Costs table.

Treatment Choices for Non-Alzheimer's dementia

According to the NICE dementia guidelines updates in 2018:

- Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies. Only consider galantamine 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 cognitive impairment caused by multiple sclerosis.

For guidance on pharmacological management of Parkinson's disease dementia, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease

Refer to Summary of Product Characteristics for full prescribing information https://www.medicines.org.uk/emc

Contraindications
The summaries of product characteristics include the following contra-indications:

- Patients with hypersensitivity to donepezil, rivastigmine, galantamine, memantine or the excipients;
- Donepezil is contra-indicated in patients with hypersensitivity to piperidine derivatives. It should not be used while breast-feeding and should be used with caution in pregnancy.
- Since no data are available on the use of galantamine in patients with severe hepatic (Child-Pugh score greater than 9) and severe renal (creatinine clearance less than 9 ml/min) impairment, galantamine is contraindicated in these populations. Galantamine is contra-indicated in patients who have both significant renal and hepatic dysfunction. It should not be used while breast-feeding and should be used with caution in pregnancy;
- Rivastigmine is contra-indicated in patients with hypersensitivity to other carbamate derivatives or in patients with severe liver impairment. It should not be used while breast-feeding and should be used with caution in pregnancy.
- Rivastigmine patches are contran-indicated where there is a previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch,
- Memantine**:** manufacturer advises avoid in severe impairment'

Side Effects

AChE inhibitors

Common (occurs between 1 in 10 and 1 in 100) or Very Common (occurs more frequently than 1 in 10), according to the BNF

Common to all the AChE inhibitors: Appetite decreased; diarrhoea; dizziness; headache; nausea; skin reactions; syncope; vomiting

Specific to individual AChE inhibitors:

Donepezil
Aggression; agitation; common cold; fatigue; gastrointestinal disorders; hallucination; injury; muscle cramps; pain; sleep disorders; urinary incontinence;

Rivastigmine,
Anxiety; arrhythmias; asthenia; dehydration; depression; drowsiness; fall; gastrointestinal discomfort; hyperhidrosis; hypersalivation; hypertension; movement disorders; tremor; urinary incontinence; urinary tract infection; weight decreased
Specific to oral use: Confusion; gait abnormal; hallucinations; malaise; parkinsonism; sleep disorders

Galantamine,
arrhythmias; asthenia; depression; drowsiness; fall; gastrointestinal discomfort; hallucinations; hypertension; malaise; muscle spasms; tremor; weight decreased

Memantine
Common or very common adverse effects of memantine are balance impaired; constipation; dizziness; drowsiness; dyspnoea; headache; hypersensitivity and hypertension.

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

Drug Interactions

From the SPCs, seek further advice and information from specific drug interaction resources, if necessary

Acetylcholinesterase inhibitors should not be administered with anticholinergic medication due to the antagonism of effect (e.g. hyoscine, oxybutynin, solifenacin) or drugs with anticholinergic properties (e.g. antipsychotics, tricyclics, sedating antihistamines).

Galantamine:

- Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. The possibility of clinically relevant interactions is low.

- Formal drug interaction studies showed an increase in galantamine bioavailability of about 40% during co-administration of paroxetine (a potent CYP2D6 inhibitor) and of 30% and 12% during co-treatment with ketoconazole and erythromycin (both CYP3A4 inhibitors). Therefore, during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine, or fluoxetine) or CYP3A4 (e.g. ketoconazole or ritonavir) patients may experience an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting

Donepezil:

- In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil.

Rivastigmine:

- Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardiovascular beta- blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers. Therefore, caution should be exercised when rivastigmine is combined with beta-blockers and also other bradycardia agents

Memantine:

- The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as 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 should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan (see also section 4.4). There is one published case report on a possible risk also for the combination of memantine and phenytoin.

- Other active 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.

Drug Costs

At November 2018, costs may change, consult the latest Drug Tariff for more information

Drug	Strength	Quantity	Cost
Donepezil[3]	5mg	28	0.74
	10mg	28	1.02
Donepezil orodispersible[3]	5mg	28	7.12
	10mg	28	8.46
Galantamine[3]	8mg	56	61.13
	12mg	56	74.10
	4mg/ml	100ml	120.00
Galantamine XL[3]	8mg	28	51.88
	16mg	28	64.90
	24mg	28	79.80
Rivastigmine[3]	1.5mg	28	2.28
	3mg	28	2.90
	4.5mg	28	23.53
	6mg	28	29.16
	4.6mg/24hr	30	77.97
	9.5mg/24hr	30	30.02
	13.3mg/24hr	30	77.97
	2mg/ml	120ml	96.82
Memantine[3]	10mg	28	1.24
	20mg	28	1.49
Memantine orodispersible[3]	10mg	28	24.99
	20mg	28	49.98
Memantine soluble tablets[3]	10mg	28	29.09
	20mg	28	58.18
Memantine oral solution sugar-free[3]	10mg/ml	50ml	54.39
Memantine starter pack[3]	5mg/10mg/15mg/20mg	28	43.13

REFERENCES

1. NICE TA217 Donepezil, Galantamine, Rivastigmine and Memantine for The Treatment of Alzheimer's Disease https://www.nice.org.uk/guidance/ta217
2. BNF online accessed November 2018
3. Drug Tariff online accessed November 2018
4. Summary of Product Characteristics for AChEIs and memantine via emc.org.uk

REVIEW

This Shared Care Guideline should be reviewed every two years unless new guidance or legislation dictates a review any sooner.

Updated by	Mental Health working group (sub-group)	November 2018
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