DORSET MEDICINES ADVISORY GROUP

SHARED CARE GUIDELINES FOR THE USE OF DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

INDICATIONS FOR USE

NICE Technology Appraisal TA 217 recommends the use of the three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as options for managing mild to moderate Alzheimer's disease. Memantine 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.

NICE (partial review in May 2016) states that treatment should be under the following conditions

- non-specialists can now prescribe donezepil, galantamine, rivastigmine and memantine, as long as they have taken advice from 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 with specialist expertise in diagnosing and treating Alzheimer's disease
- Treatment should be continued when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. It is important to recognise that stability of symptoms is considered an effective treatment
- local arrangements for prescribing, supply, and treatment review should follow the NICE guideline on medicines optimisation (NICE guideline NG5).

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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.

Donepezil is the AChE inhibitor of choice with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). An alternative AChE inhibitor should only be prescribed if there is evidence of Lewy Body Dementia or Parkinsonian features when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles. Alternatively memantine may be selected when a patient has moderate to severe Alzheimer's Disease and is presenting with challenging behaviours.

N.B. TA 217 states that "combination treatment with memantine and AChE inhibitors could not be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy". The Dorset Medicines Advisory Group have stated that combination treatment with memantine and AChE inhibitors is outside the recommendations of this shared care guideline and all prescribing and monitoring of this combination should be the sole responsibility of secondary care.

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 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 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 a more complex dementia or Alzheimer's Disease receiving these drugs would not be discharged from their CMHT and an annual medication review will be undertaken by the CMHT.

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	Prior to referral to carry out a physical examination and baseline screening of of FBC, calcium, glucose, renal and liver function, thyroid function tests, serum vitamin B12 and folate levels up to 6 months before referral.
2	Refer patient via the Memory Gateway referral form.

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 (excluding 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	Donepezil is the AChE inhibitor of choice, an alternative AChEI should only be considered if there is evidence of Lewy Body dementia or Parkinsonian symptoms. This must be documented in the notes.
5	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.
6	Consider discontinuing treatment or a switch to memantine if the patient is intolerant of the AChE inhibitor or the patient develops severe Alzheimer's Disease. Discontinue treatment where there has not been benefit or where there has been a deterioration of the condition.
7	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.
8	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.
9	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.
10	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.
11	Ensure that clear backup arrangements exist for GPs to obtain advice and support.
12	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 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 pulse, weight as agreed with the specialist.
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

Refer to Summary of Product Characteristics for full prescribing information.

Medication choice
When the decision has been made to prescribe an acetylcholinesterase inhibitor or memantine, 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. **[NICE TA 217]** ACEIs can be stopped when patient is deemed not to be benefitting from the medication; however there is a risk of significant decline in the cognitive and daily functions on stopping the medication.
Memantine 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. Memantine may be selected when a patient has moderate to severe Alzheimer's Disease and is presenting with challenging behaviours

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.

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 pregnancy and breast-feeding;
- 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 severe liver impairment. It should not be used while breast-feeding and should be used with caution in pregnancy.

Side Effects
Most common adverse effects include diarrhoea, nausea, vomiting, muscle cramps, dyspepsia, fatigue, insomnia, anorexia, weight loss, dizziness, headache and somnolence.

Other side effects include confusion, fall, injury, syncope, upper respiratory tract infection and urinary tract infection.

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

Common adverse effects of memantine are constipation, hypertension, dyspnoea, headache, dizziness and drowsiness. Less commonly vomiting, thrombosis, heart failure, confusion, fatigue, hallucinations and abnormal gait

Drug Interactions
Acetylcholinesterase inhibitors should **not** be administered with anticholinergic medication due to the antagonism of effect (e.g. hyoscine, dicycloverine, orphenadrine, procyclidine, propantheline) or drugs with anticholinergic properties (e.g. antipsychotics, tricyclics).

The summary of product characteristics for Galantamine states that during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine, fluoxetine or fluvoxamine) or CYP3A4 (e.g. ketoconazole, ritonavir), patients may experience an increased incidence of cholinergic side effects, mainly nausea and vomiting and a reduction in the dose of the acetylcholinesterase inhibitor may be considered.

Drug interaction studies performed in vitro show that ketoconazole and quinidine inhibit Donepezil metabolism. Other drugs that could also inhibit the metabolism of Donepezil are itraconazole, erythromycin and fluoxetine. Enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of Donepezil

Memantine enhances the effects of dopaminergics, anticholinergics and selegiline. Memantine possibly enhances the effects of warfarin and antimuscarinics and possibly reduces the effects of barbiturates and primidone. The manufacturer advises avoiding concomitant use of memantine with amantadine.

Drug Costs

Drug	Strength	Quantity	Cost
Donepezil[3]	5mg	28	1.07
	10mg	28	1.35
Donepezil orodispersible[3]	5mg	28	6.79
	10mg	28	8.61
Aricept Evess®[2]	5mg	28	59.85
	10mg	28	83.89
Galantamine[3]	8mg	56	61.13
	12mg	56	74.10
	4mg/ml	100ml	437.00
Galantamine XL[3]	8mg	28	51.88
	16mg	28	64.90
	24mg	28	79.80
Rivastigmine[3]	1.5mg	28	2.56
	3mg	28	2.85
	4.5mg	28	14.57
	6mg	28	15.58
	4.6mg/24hr	30	77.97 (72.77 for 28 days)
	9.5mg/24hr	30	24.96 (23.30 for 28 days)
	13.3mg/24hr	30	77.97 (72.77 For 28 Days)
	2mg/ml	120ml	96.82
Memantine[3]	10mg	28	1.35
	20mg	28	1.68

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 July 2016
3. Drug Tariff online accessed July 2016
4. Summary of Product Characteristics for AChEIs and memantine

REVIEW

This Shared Care Guideline should be reviewed every two years unless new guidance or legislation dictates a review any sooner. Date of review: July 2018