Donepezil, Rivastigmine and Galantamine
(TLS Amber with shared care)
Donepezil (TLS green Wilts)

Shared Care Guidelines: For the treatment of Alzheimer's disease
It is intended to apply to patients who have been initiated on treatment, (and who have been assessed as benefiting) by specialist services experienced in the care of people with dementia in accordance with the guidance from the National Institute for Health & Clinical Excellence (NICE TA 217 and NICE Dementia Clinical Guideline 42)

GPs should refer appropriate patients to RICE (BaNES) or AWP (Wilts) (see referral pathway for BaNES in Appendix A & B on BCAP website) for assessment within a specialist service. Where indicated, treatment should be initiated in secondary care. Secondary care services **should continue to prescribe for the first three months** while response is assessed. After referral GPs will be asked to continue prescribing after the first three months as part of a shared care arrangement for those patients who have been assessed as benefiting.
Drug treatment for Alzheimer's disease should form part of a wider package of support and information for the patient and their carer. Treatment with an acetylcholinesterase inhibitor should only be initiated if reasonable steps are taken to ensure adequate compliance.
Sharing of care assumes communication between the specialist, GP and patient. GPs are invited to participate. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with the Alzheimer's disease are under regular specialist follow-up, which provides an opportunity to discuss drug therapy. **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Diagnosis of probable or possible Alzheimer's disease (excluding other forms of dementia) and any appropriate assessments required.
2	Discuss the benefits and potential side effects of treatment with the patient and carer and provide information including the action to be taken should side effects occur
3	Confirm the patient's understanding & consent to treatment (discuss with carers' where patient lacks capacity)
4	Explain to patients and carers the normal course of the disease and if and when they should expect to be re-referred
5	Initiate treatment for patients with mild to moderate Alzheimer's Disease in accordance with the NICE TA217 and make any dose adjustments.
6	Provide at least 3 months supply or sufficient to stabilise patient.
7	Assess the patient after three months on stable medication and approach the GP (with a shared care agreement) with regard to continued prescribing if there is evidence of stabilisation using cognitive, global, functional and behavioural assessment and no significant side-effects. If the patient is stable on the medication, their care can be discharged back to the GP.
8	Discontinue treatment after 3 months where there has not been benefit or where there has been a deterioration of the condition. If discontinuing treatment, care should be taken to phase out the medication gradually and monitor for a potentially significant deterioration of patient functioning or a worsening of behavioural symptoms. The specialist will liaise closely with the GP about this. Specialist will consider a trial of alternative cognitive enhancer prescription when appropriate.
9	When treatment is to be continued after first assessment, a member of the specialist team will undertake a review of the patient if requested to do so by the GP.
10	Ensure that clear backup arrangements exist for GPs to obtain advice and support

	General Practitioner responsibilities
1	It is recommended good practice for there to be a pre-referral assessment including physical examination and baseline blood tests (FBC, C&E's, LFT's, glucose, TFT's, B12, folate and calcium) up to 6 months pre-referral, in accordance with the "Memory assessment pathway" for primary care.
2	Refer appropriate patients to RICE or AWP Community Mental Health Teams (according to the referral pathway)
3	Reply to the request for shared care as soon as practicable.
4	Prescribe medicine at the dose recommended after the first three months for those patients who have been initiated on treatment with an acetylcholinesterase inhibitor and who have been assessed as benefiting from treatment
5	The only monitoring that would be recommended would be a check of pulse and side effect screening, asking about GI disturbance, faints/blackouts and breathing difficulties annually. No blood testing is carried out routinely.
6	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. sudden unexpected worsening of disease-

	related symptoms) or intolerance to therapy occurs. GPs would not be expected to alter dose unless advised by specialist.
7	Report to & seek advice from the specialist on any aspect of patient care that is of concern to the GP
8	Undertake an annual medication review for those patients that have been discharged from the memory service and remain on 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, or behavioural and psychological symptoms related to dementia (BPSD)? • Is there any carer stress? • Any side-effects of medication, dizziness, diarrhoea? A decline in cognitive function year on year is to be expected with a diagnosis of dementia so this on its own would not warrant re-referral or review by the memory service. If the GP has concerns regarding increasing behavioural disturbance or the development of new symptoms they should contact the Primary Care Liaison Service for access to further prescribing or treatment advice from a Memory Service clinician.
9	Stop treatment in conjunction with the specialist.
10	Report adverse events to the specialist and MHRA.

Patient's/Carer's role	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	To attend hospital & GP clinic appointments (Failure to attend may result in medication being reviewed and possibly stopped on specialist advice)
3	Share any concerns in relation to treatment with medicine.
4	Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Specialist: Dr Jill Mann	01225 476420		Fax 01225 463403	info@rice.org.uk www.rice.org
Specialist: Prof Roy Jones				RICE - The RICE Centre Building 8 Royal United Hospital Combe Park Bath BA1 3NG
Dr Fiona Harrison	01225 731460			fiona.harrison4@nhs.net Complex Intervention & Treatment Team, Bath NHS House
Specialist: Dr Roz Ward	01225 396799		Fax: 01225 396557	rosalind.ward@nhs.net AWP Consultant Psychiatrist for Older People BANES Complex Intervention & Treatment Team (Later Life SBU), The Hollies CMHT, High Street, Midsomer Norton, Radstock BA3 2DP
WWKDYD and NEW Primary Care Liaison Service Green Lane Hospital Marshall Road Devizes SN10 5DS	01380 737840			awp.PCLNorthWiltsAdminTeam@nhs.net
SARUM Primary Care Liaison Service Fountain Way Hospital, Wilton Road, Salisbury SP2 7FD	01722 820372			awp.AC-PCL-SWilts@nhs.net

SUPPORTING INFORMATION

Summary of condition and licensed indications.

Donepezil, Rivastigmine and Galantamine are recommended as options in the management of cognitive impairment in mild to moderate Alzheimer's disease.

The acetylcholinesterase inhibitors are not recommended for vascular dementia.

NICE recommendations:

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

- non-specialists can now prescribe donezepil, galantamine and rivastigmine 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.

Choice of medication:

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) and is the first-line choice locally. 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, but this drug is not as yet included in the shared care agreement.

N.B. NICE TA217 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". 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 specialist services/secondary care.

Non-Cognitive Symptoms and Behaviour that Challenges

Acetylcholinesterase inhibitors may be considered to treat:

- people with Lewy Body Dementia who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges
- people with mild, moderate or severe Alzheimer's disease who have non-cognitive symptoms and/or behaviour that challenges causing significant distress or potential harm to the individual if:
  - a non-pharmacological approach is inappropriate or has been ineffective, and
  - antipsychotic drugs are inappropriate or have been ineffective

DO NOT USE acetylcholinesterase inhibitors to treat non-cognitive symptoms or behaviour that challenges in people with vascular dementia

Dose

Usual maintenance doses are:

- Donepezil 5-10mg daily, taken as a single dose in the evening, just prior to retiring;
- Rivastigmine, 3-6mg twice a day with meals, swallowed whole;
- Galantamine, 8-12mg twice a day with meals (or Galantamine XL 16-24mg as a single dose once daily with meals, swallowed whole); Prescribe as **Gatalin XL** brand
- Rivastigmine patch 9.5mg/24 hours. The patch should be applied once a day.
  (Patches should be reserved for patients with a particular clinical need)

The manufacturers' summaries of product characteristics should be referred to for full prescribing information.

SAFETY ISSUES

Contra-indications

The summaries of product characteristics includes the following contra-indications:

- patients with hypersensitivity to Donepezil (or piperidine derivatives), Rivastigmine (or carbamate derivatives), Galantamine or the excipients;
- Galantamine is contra-indicated in patients with severe renal and/or hepatic impairment, and in patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency.

Special warnings and precautions

The acetylcholinesterase inhibitors should be given with caution in:

- cardiovascular conditions - the potential for vagotonic actions may be particularly important for patients with "sick sinus syndrome," patients with conduction defects, those who take drugs that significantly reduce heart rate, or those who have uncorrected electrolyte imbalance;

- gastrointestinal conditions - patients at increased risk of developing ulcers should be monitored for symptoms;
- neurological conditions - the drugs are believed to have some potential to cause generalised convulsions (seizure activity may also be a manifestation of Alzheimer's disease);
- patients with a history of asthma or obstructive pulmonary disease;
- patients with urinary outflow obstruction or recovering from bladder surgery.

Side-effects

The 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 (if clinically appropriate).

Drug interactions

Acetylcholinesterase inhibitors should **not** be administered with anticholinergic medication due to the antagonism of effect (e.g. hyoscine, dicycloverine, orphenadrine, procyclidine, propantheline). When the patient is taking a drug with anticholinergic properties (e.g. antipsychotics, tricyclics) the relative benefits of taking acetylcholinesterase inhibitors alongside these should be assessed.

Acetylcholinesterase inhibitors are likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

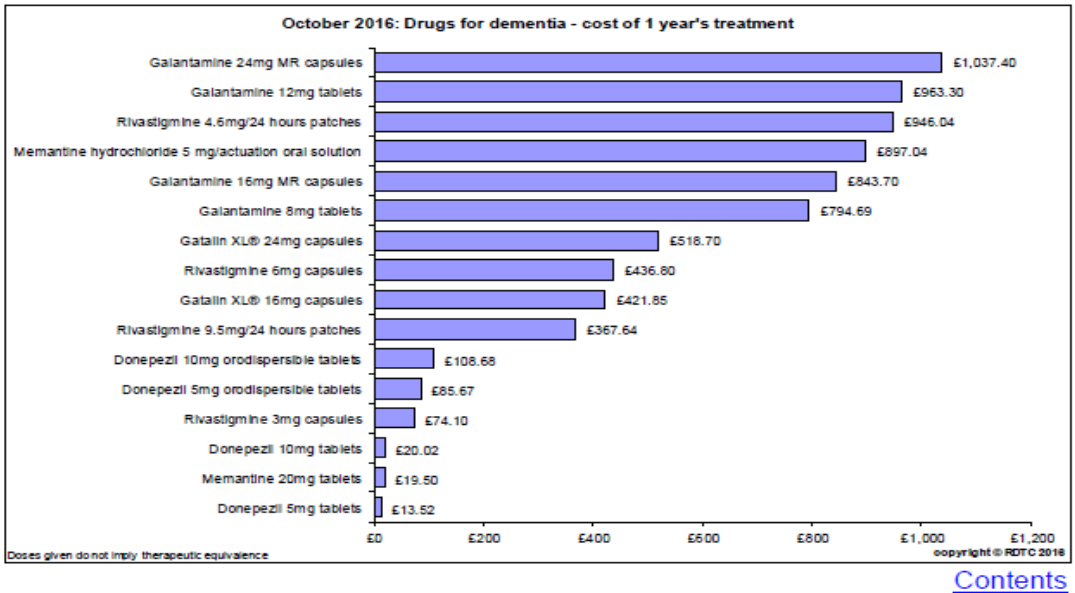
The summary of product characteristics for Galantamine states that during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine, fluoxetine or fluvoxamine) or CYP3A4 (e.g. ketoconazole, ritonavir), patients may experience an increased incidence of cholinergic side-effects, 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.

Cost

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. At current prices, one year's treatment with these medicines is as follows:

4.11 Drugs for dementia



Contents

Appendix A – RICE Guidance on Memory Assessment Referral Pathway for Primary Care (for BaNES patients)

Appendix B – RICE Memory Assessment Referral Pathway for Primary Care (for BaNES patients)

References

NICE TA 217 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (May 2016 update) https://www.nice.org.uk/guidance/ta217

NICE CG 42 Dementia: supporting people with dementia and their carers in health and social care (revised September 2016) https://www.nice.org.uk/guidance/cg42