

ACETYLCHOLINESTERASE INHIBITORS: INFORMATION FOR PRIMARY CARE

Shared Care Status – Green +

Should be initiated by a Secondary Care Specialist but can be safely maintained in primary care without on-going specialist monitoring. A patient should be established on a stable dose of medication and a minimum of one month supply should be given to patients by the Specialist Prescriber before transferring responsibility to primary care. If a patient uses compliance aids, consider the best interests of the patient when deciding the length of the supply

Related NICE guidance

NICE (TAG 217) has concluded that Acetylcholinesterase inhibitors are clinically cost effective and has recommended their use in mild to moderate Alzheimer’s Disease. NICE also recommends they be considered for people with dementia with Lewy bodies and patients with Alzheimer’s Disease irrespective of severity who have non cognitive symptoms and/or behavioural challenges causing significant distress or potential harm to the individual.

Licensed Indication

Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer's disease, specifically for mild to moderate disease. Rivastigmine is also used for mild to moderate dementia associated with Parkinson's disease. Donepezil, galantamine and rivastigmine reversibly antagonise the action of acetylcholinesterase increasing the concentration of acetylcholine released by functionally intact cholinergic neurones to facilitate cholinergic transmission. Galantamine also exhibits nicotinic receptor agonist properties.

Dosage and Administration

Donepezil (formulary preferred first line drug)	It is given initially at 5 mg once daily. After 1 month the treatment should be assessed, and the dose can be increased to a maximum of 10 mg once daily if necessary. It is recommended that the dose is given at bedtime to minimise likelihood of gastrointestinal (GI) symptoms, however if sleep disturbances are noted, particularly vivid nightmares, then a shift to morning dosing can resolve this.
Galantamine	The dose is initially 4mg twice daily for a minimum period of 4 weeks with a maintenance dose 8mg twice daily for a minimum of 4 weeks. This can be increased to 12mg twice daily after appropriate assessment of benefit & tolerability. If no response to the higher dose or unable to tolerate, reduce to 8mg twice daily. Where appropriate, the total daily dose may be converted to once daily administration using modified release formulations. Galantamine should be taken after food to reduce the risk of cholinergic side effects (e.g. nausea, vomiting, and diarrhoea). Ensure adequate fluid intake during treatment. Administration with food slows rate of absorption but has no effect on total absorption. Modified release forms must be swallowed whole and not chewed.
Rivastigmine	The dose is initially 1.5 mg twice daily and may be increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to tolerance up to a maximum dose of 6 mg twice daily. Rivastigmine increases gastric acid secretion and should be taken with food to minimise the effects of this. Alternatively rivastigmine patches are available, initially using a 4.6-mg patch per day. This can be increased to a 9.5-mg patch per day for at least 4 weeks. See the local formulary and summary of product characteristics for further information on using patches.

Cautions

Pre-existing cardiac disease, asthma, COPD, urinary retention/bladder outflow obstruction, history of seizures, history of peptic ulcers, low body weight.

Renal / Hepatic Impairment		
Use donepezil with caution in hepatic impairment. Use rivastigmine with caution in renal and hepatic impairment. Galantamine is contraindicated if eGFR <9 ml/min, if eGFR is >9ml/min no dosage adjustment is required. Maximum daily dose of 16mg galantamine in hepatic impairment. Avoid in severe hepatic impairment.		
Side Effects¹		
<p>Gastrointestinal disturbances are most commonly encountered. Peptic ulcers with donepezil have been reported in some patients; this should be monitored in patients on concurrent GI irritant medication (e.g. NSAIDs, antidepressants affecting serotonin) and those with a previous history of peptic ulceration</p> <p>Although not very common, vagotonic effects including bradycardia have been noted with use of acetylcholinesterase inhibitors in particular galantamine. This should be considered in patients receiving drugs to lower blood pressure/heart rate. Seizures can be associated with Alzheimer's disease but acetylcholinesterase inhibitors have been reported to induce seizures. Patients weighing <50kg are more likely to experience adverse effects and discontinue treatment as a result of this. Other side effects include hallucinations, depression, dizziness, drowsiness, abnormal dreams, anxiety, insomnia and urinary incontinence.</p>		
Drug Interactions²		
<p>There are no specific dose changes which need to be made in relation to acetylcholinesterase inhibitors however it would be useful for prescribers to be aware of the following:</p> <p>Potent inhibitors of CYP3A4 (including ritonavir, clarithromycin and itraconazole) may raise donepezil and galantamine levels.</p> <p>Inducers of CYP3A4 (including carbamazepine, phenytoin, and rifampicin) may lower donepezil levels.</p> <p>Smoking tobacco increases the clearance of rivastigmine.</p> <p>The risk of adverse effects, including bradycardia, may be increased if an acetylcholinesterase inhibitor is given with amiodarone or other antihypertensive/antiarrhythmic drugs. Acetylcholinesterase inhibitors may antagonise effects of anticholinergic drugs and worsen Parkinsonian symptoms this may induce or exacerbate extrapyramidal side effects.</p>		
Monitoring		
Baseline monitoring is the responsibility of the initiating clinician. Ongoing monitoring is the responsibility of the GP.	Baseline / Initiation	Ongoing
Adverse effects: Most common side effects are gastrointestinal disturbance (nausea, vomiting, and diarrhoea).	✓	✓
Weight / BMI: Weight loss is associated with Alzheimer's disease but acetylcholinesterase inhibitors are also reported to cause weight loss. Patients weighing <50kg may experience more adverse effects and are more likely to discontinue treatment as a result.	✓	✓
Concurrent medication: Medication should be reviewed at each visit in order to identify potential drug interactions.	✓	✓
Cardiovascular health: Acetylcholinesterase inhibitors may have vagotonic effects so baseline cardiovascular function must be monitored before starting treatment and repeated when indicated, for example, when additional drugs with vagotonic effects are added or in the event of emerging cardiovascular problems.	✓	When clinically indicated
Renal and hepatic function: Baseline creatinine and LFTs should be measured; Patients with renal or hepatic impairment should have doses titrated slowly and be monitored closely for adverse effects.	✓	When clinically indicated
Other Required Monitoring		
As it is not possible on an individual basis to determine whether somebody is deriving benefit from a cholinesterase inhibitor, decisions regarding continuation therapy are made primarily on the basis of tolerability and patient preference. These medications are effective in maintaining cognitive and general functioning even in moderate to severe illness, and may delay placement into long-term care.		

¹ This list is not exhaustive; please refer to current BNF and SPC.

² Refer to current version of BNF/Stockley for detailed information.

Withdrawal

Discontinuation of therapy must be discussed with the carers, family, and with the patient wherever possible. Discontinuation should be considered in the event of:

- Adverse reaction to the medication
- Emergent tolerability issues e.g. secondary to frailty or medical co-morbidities
- Lack of compliance with the medication - if swallowing solid dose preparations has become a problem an assessment should be made as to whether switching to a skin patch, orodispersible tablet or an unlicensed liquid preparation would be in the best interest of the patient.
- The patient is on the end of life care pathway
- An irreversible deterioration in the patients global clinical presentation since last review e.g. a CVA

When to seek Specialist advice / review

In the majority of cases treatment will be initiated by a specialist in the care of people with dementia in line with NICE guidance. Following dose titration the specialist will recommend continuation treatment on the basis of tolerability issues & patient preference.

Tolerability may change over time consequent upon the ageing process and the emergence of medical co-morbidities and frailty. In this situation it may appropriate to reduce the dose or discontinue treatment &/or consider an alternative drug, for example Memantine.

It may be appropriate to make such decisions in consultation with the specialist who initiated treatment.

Dementia Specialists, usually a Consultant Psychiatrist or Speciality Doctors are available to provide advice on such matters without the need for a formal re-referral. You may wish to seek advice in the following circumstances:

- Emergent concerns regarding tolerability
- To consider whether to discontinue treatment with a Cholinesterase Inhibitor at an advanced stage of the illness as outlined above.

Contact Numbers

The specialist dementia teams can be contacted via the Initial Response Team – South of Tyne and Wearside
Tel: 0303 123 1145

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