# Dementia Medicines AMBER0

DONEPEZIL, GALANTAMINE, RIVASTIGMINE and MEMANTINE

**Prescribing Information Sheet**

To be read in conjunction with the SPC , NICE TA 217 [1] and NICE CG42 [2]

## Dementia Medicines: General Prescribing Considerations

- The three acetylcholinesterase inhibitors(AChEI), donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease under the following conditions [1,2] :

  - Prescribers should only start treatment with donepezil, galantamine, rivastigmine or memantine on the advice of a clinician who has the necessary knowledge and skills and in line with local primary and secondary care protocols where they exist. This could include:[2]
    - 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 only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.

  - If prescribing an AChEI (donepezil, galantamine or rivastigmine), treatment should normally be started with the 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 AChEI could 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.

- 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 AChEI e.g. if there are cardiac conduction problems or bradycardia or severe Alzheimer's disease
  - **Generic donepezil** tablets have the lowest acquisition cost and should be considered as the 1st line AChEI. However, an alternative AChEI or formulation could be used if appropriate when taking into account adverse event profile, adherence, comorbidities and interactions.[1,2]
  - Check local formulary status and consider costs when changing formulations or choice of medication
  - **Galantamine** may be better than other AChEIs for insomnia.[3]
  - **Rivastigmine** is licensed for dementia in Parkinson's disease and may be helpful if hallucinations are a prominent presenting feature of the dementia.[3]
  - **Memantine** may be preferred if AChEIs are contraindicated or not tolerated
  - **For patients with swallowing difficulties** consider switching to orodispersible donepezil tablets in preference to using patches/ liquid formulations of other medications (if appropriate).

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**Table 1. Dementia Medications: Summary of Dosing and Licensing Information [4]**

All AChEIs are licensed for mild to moderate dementia but can be continued into severe dementia if they are deemed helpful.

| **Medication** (Licensed Indications) | **Dosing Information.** See SPC for more details. Slower titrations may be used on specialist advice/to minimise side effects | **Additional Information** (See table 3 and 4 for Side Effects and Interactions) |
|---|---|---|
| **Donepezil 1st Line** (Mild-Moderate Alzheimer's Dementia) | **Initial dose:** 5mg each evening, at bedtime.<br>**Increased to:** 10mg after 4 weeks | **Generic Donepezil** tablets have the lowest acquisition cost and should be considered as the 1st line AChEI.<br><br>**Nb Orodispersible tablets should be reserved for use in those with swallowing difficulties only. (Dispersible tablets are more cost effective compared to liquid preparations).** |
| **Rivastigmine 2nd Line** (Mild-Moderate Alzheimer's Dementia And Mild-Moderate dementia in Parkinson's disease) | **Capsules & liquid** (Should be taken with food)<br>Initial dose: 1.5mg twice daily for 2 weeks<br>Increased to: 3mg twice daily for 2 weeks, then 4.5mg twice daily. Maximum daily dose = 6mg twice daily.<br><br>**Transdermal preparations**<br>Initial dose: 4.6mg/24hours, for at least 4 weeks<br>Increased to: 9.5mg/24hours<br>If well tolerated after a minimum of 6 months treatment at 9.5 mg/24 hours, can be increased to 13.3 mg/24 hours in patients who have demonstrated a meaningful cognitive deterioration/functional decline (based on clinical judgement). | At least two weeks should lapse between oral dose increases, slower dose titration may help minimise GI and CNS side effects. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose.<br><br>Rivastigmine patches should be reserved for those patients who are unable to tolerate or swallow an oral AChEI. They are less likely to cause GI disturbance and may be helpful if nausea persists despite dose reduction/slower titration of oral rivastigmine preparations. |
| **Galantamine Alternative 2nd Line** (Mild-Moderate Alzheimer's Dementia). | **MR capsules**<br>Initial dose: 8mg once daily for 4 weeks<br>Increased to: 16mg once daily for at least 4 weeks<br>Usual maintenance Dose:16-24mg daily<br><br>**Normal release tablets and liquid**<br>Initial dose 4mg twice daily for 4 weeks<br>Increased to: 8mg twice daily for at least 4 weeks<br>Usual maintenance dose: 8-12mg twice daily<br>Preferably taken with morning and evening meals | Use modified release galantamine in preference to other formulations (may aid patient compliance).<br>Branded modified release generic preparations eg Gatalin XL, Gazylan XL also have a lower acquisition cost.<br><br>NB Liquid galantamine and normal release tablets are not approved for use in some CCGs please check local formularies.<br><br>Dose adjustment is required in moderate hepatic impairment. Use is contraindicated in severe hepatic impairment and if eGFR is less than 9ml/min<br><br>Treatment with cholinesterase inhibitors, including galantamine, has been associated with weight loss in these patients. During therapy, patient's weight should be monitored.<br><br>As with other cholinomimetics galantamine should be given with caution in the following conditions: cardiac disorders; gastrointestinal disorders; nervous system disorders; respiratory, thoracic and mediastinal disorders; renal and urinary disorders – please see SPC for full details<br><br>**Skin Reactions: Patients and carers should be told to watch out for signs of serious skin reactions and be told to stop treatment and seek medical help immediately if these develop [4,5]** |
| **Memantine 3rd Line** (Moderate Alzheimer's disease in patients who are intolerant to or have a contra-indication to AChEIs).<br>**Can be considered- 1ST line in** Severe Alzheimers Disease | **Tablets and Liquid**<br>**Initial dose:** 5mg once daily<br>**If tolerated increase:** by 5mg weekly to a maximum of 20mg daily<br>**If CrCl = 30 - 49 ml/min** the daily dose should be 10 mg per day. If tolerated after at least 7 days of treatment, the dose can be increased up to 20 mg/day. **If CrCl = 5 – 29 ml/min** max daily dose is10mg. | Check renal function before prescribing<br><br>Central nervous system side effects, such as dizziness and headaches are dose dependant. Slower dose titration and more frequent monitoring during initiation may help manage these.<br><br>**Nb Liquid should be reserved for use in those with swallowing difficulties only and in preference to orodispersible tablets (as more cost effective)** |

## Table 2. Monitoring and Review Requirements. [1,2,3]

In the early years of use, Acetylcholinesterase Inhibitors (AChEIs) were stopped when the Mini Mental State Examination reached 10/30 but evidence has emerged that supports continued usage in severe dementia and these strict historical protocols have relaxed as experience has grown and prices have fallen. NICE TA217 states that treatment should only be continued where there is a worthwhile effect on cognitive, global, functional or behavioural symptoms, however this can be difficult to assess in practice. Further guidance is provided by the NHS England document 'Dementia Revealed – What Primary Care Needs to Know' which also makes a number of recommendations regarding the primary care follow up and review of patients with dementia.

1. Follow-up should be initiated by secondary care and patients who do not attend, contacted and offered follow-up at home (if this is can be accommodated).

2. When a treatment has been initiated, the first follow-up should where possible be at ~ 3 weeks (and before the 2nd prescription has been issued). The aim of this review is to establish if there are any significant side effects, it should therefore include a pulse check (See table 3 for details of side effects).

3. AChEIs should be stopped if they are causing clinically significant bradycardia. GI side effects may respond to a dose reduction/slower titration. Anxiety or agitation might prompt a trial without AChEIs as they are stimulant drugs, the result might be more apathy but less agitation.

4. At about three months, a follow-up is needed where the patient should be assessed (by secondary care) for response to treatment. A cognition test may be done but especially in more advanced dementia, an assessment of well-being and functioning is more important. It is helpful to offer information about support organisations at every contact as people's receptiveness may be different at different times. If there is no subjective or objective improvement at the three month review, treatment can be continued if there are no side-effects, and the patient reassessed in a further six months, in which case secondary care would continue to issue prescriptions during this time period.

5. **After the secondary care ~3-month review, when response to therapy and tolerance has been confirmed, primary care may take over prescribing responsibilities and routine follow up. If routine primary care consultations give rise to concerns about side effects, tolerability or the appropriateness of ongoing treatment then referral for secondary care review should be considered.**

6. Further follow-up may include periodic assessment of cognition, as in a memory clinic, but should be omitted if it upsets or intimidates the patient. Overall functioning, medication issues and carer views will constitute most of the review.

7. It is anticipated that, providing the patient is tolerating the treatment and there are no contraindications the treatment will be maintained until such a time as it becomes inappropriate, such as in extreme frailty.

8. When dementia gets worse: AChEIs and Memantine have proved to be very safe drugs. The effectiveness of an AChEI becomes more difficult to assess the longer a patient is on it because the baseline will have changed. The only way to know if it is still helping is to stop the drug and be prepared to re-start it if there is a sudden significant deterioration, but this could be unnecessarily disruptive, and current guidance is to continue indefinitely unless there are problems.

9. There is no difference in effectiveness between AChEIs and the only reason for swapping is to see if a different drug is better tolerated.

**If routine primary care consultations give rise to concerns about side effects, tolerability or the appropriateness of ongoing treatment then consider referral to secondary care for review.**

**Table 3. Summary of Dementia Medication Side Effects[4]** Please refer to the individual medications SPC for more details

| **ACETYLCHOLINESTERASE INHIBITORS:** Donepezil, Galantamine, Rivastigmine | **NMDA RECEPTOR ANTAGONISTS:** Memantine |
|---|---|
| **Note: Serious skin reactions have been reported in people taking galantamine. These include Stevens Johnson Syndrome (SJS). [5]**<br><br>**Patients and carers should be told to watch out for signs of serious skin reactions and be told to stop galantamine treatment and seek medical help immediately if these develop. [5]**<br><br>**Very Common** (Incidence > 10%)<br>Diarrhoea, Fatigue, Nausea, Vomiting, Insomnia, Anorexia (rivastigmine), Headache (donepezil)<br><br>**Common** (Incidence 1- 10%)<br>Headache, Pain, Common Cold, Dizziness, Anorexia, Syncope, Muscle Cramps Rash, Pruritis, Urinary incontinence, Fatigue, Abnormal dreams and nightmares.<br><br>**Uncommon** (Incidence 0.1 – 1%)<br>Seizures, bradycardia, gastrointestinal haemorrhage, gastric and Duodenal ulcers.<br><br>**Rare** (Incidence 0.01- 0.1%)<br>Sinoatrial and atrioventricular block, Extrapyramidal symptoms and Liver Dysfunction including hepatitis<br><br>There have also been reports of psychiatric disturbances, including hallucinations, agitation and aggressive behaviour, which resolved on dose reduction or discontinuation of treatment.<br><br>No notable abnormalities in laboratory values were observed, except for minor increases in serum concentrations of creatinine kinase. | **Common** (Incidence 1- 10%)<br>Somnolence, dizziness, hypertension, dyspnoea, constipation, headache, drug hypersensitivity, balance disorders and elevated LFTs<br><br>**Uncommon** (Incidence 0.1 – 1%)<br>Confusion, hallucinations, abnormal gait, cardiac failure, venous thrombosis/thromboembolism, vomiting, fatigue, fungal infections<br><br>**Very Rare** (Incidence <0.01%)<br>Seizures<br><br>Isolated cases of psychotic symptoms and pancreatitis reported in post-marketing experience.<br><br>Alzheimer's disease has been associated with depression, suicidal ideation and suicide. In post-marketing experience these events have been reported in patients treated with memantine. |

**Table 4. Interactions[4]** Please refer to the individual medications SPC for more details

| **ACETYLCHOLINESTERASE INHIBITORS:** Donepezil, Galantamine, Rivastigmine | **NMDA RECEPTOR ANTAGONISTS:** Memantine |
|---|---|
| • Should not be prescribed with other acetylcholinesterase inhibitors, anticholinergics or cholinergic agonists<br><br>• NSAID's- Monitor for symptoms of ulcerative disease.<br><br>• Inhibitors of Cytochrome P450 3A4 and 2D6 may increase plasma levels. Examples include Erythromycin, Ketoconazole, Itraconazole, Fluoxetine, Quinidine.<br><br>• Enzyme inducers may decrease plasma levels. Examples include Rifampicin, Phenytoin, Carbamazepine and alcohol<br><br>• Potential to interfere with drugs having anticholinergic activity<br><br>• Potential for additive effects with Beta- Blockers<br><br>• Additive effects with Succinylcholine and other neuromuscular blockers | • Effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with memantine.<br><br>• The effects of barbiturates and neuroleptics may be reduced.<br><br>• Dose adjustment of dantrolene or baclofen may be necessary when co administered with memantine.<br><br>• 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. There is one published case report on a possible risk also for the combination of memantine and phenytoin.<br><br>• Cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine use the same renal cationic transport system as amantadine, and may also interact with memantine leading to a potential risk of increased plasma levels.<br><br>• Possibility of reduced serum level of hydrochlorothiazide (HCT) when co-administered with memantine.<br><br>• Close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants. |

**References.**


1. NICE TA 217. Donepezil, galantamine, rivastigmine and memantine for treatment of Alzheimer's disease. March 2011. (Updated May 2016) https://www.nice.org.uk/guidance/ta217
2. NICE CG 42 Dementia: supporting people with dementia and their carers in health and social care . November 2006 (Updated September 2016) https://www.nice.org.uk/guidance/cg42/chapter/1-Guidance
3. NHS England and Hardwick CCG. Dementia Revealed. What Primary Care Needs to Know. July 2014. http://wrivasww.england.nhs.uk/wp-content/uploads/2014/09/dementia-revealed-toolkit.pdf
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**Please access this guidance via the LMMG website to ensure that the correct version is in use.**

## Version Control

| Version Number | Date | Amendments Made |
|---|---|---|
| Version 1.1 | June 2015 | Approved |
| Version 1.2 | July 2015 | Donepezil cost updated |
| Version 1.3 | October 2015 | Table 2 monitoring requirements updated with point 5. |
| Version 1.4 | February 2016 | Information about severe skin reactions with galantamine added. Specific product costing information removed. |
| Version 1.5 | January 2018 | 1ST and 2nd line treatment options highlighted alongside lowest acquisition cost of Galantamine MR branded generics. Side effects and cautions updated |




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