Herefordshire and Worcestershire Medicines and Prescribing Committee

NHS Herefordshire and Worcestershire Clinical Commissioning Group

Guidelines for Primary Care Prescribing and Monitoring of Dementia Drugs in Alzheimer's Disease

Recommendations:

Following specialist recommendation in line with NICE Guidance [1,2] and the manufacturer's Summary of Product Characteristics (SmPC) [3] donepezil, galantamine, rivastigmine and memantine may be initiated and monitored in primary care. For people with an established diagnosis of Alzheimer's disease who are already taking an acetylcholinesterase inhibitor (AChEI), primary care prescribers may start treatment with memantine without taking advice from a specialist clinician.

Pharmacological Management of Alzheimer's Disease [1]

In line with NICE guidance:

1. The three acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease.
2. Memantine monotherapy 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 AChEIs **or**
    - severe Alzheimer's disease
3. For people with an established diagnosis of Alzheimer's disease who are already taking an AChEI in:
    - consider memantine in addition to an AChEI if they have moderate disease
    - offer memantine in addition to an AChEI if they have severe disease
4. Treatment should be under the following conditions:
    - For people who are not taking an AChEI 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 advanced nurse practitioners and Community Dementia Nurses), if they have specialist expertise in diagnosing and treating Alzheimer's disease.
    - Once a decision has been made to start an AChEI 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 AChEI, primary care prescribers may start treatment with memantine (see recommendation 3) without taking advice from a specialist clinician.
    - Do not stop AChEI in people with Alzheimer's disease because of disease severity alone.
5. If prescribing an AChEI (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost. 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.

Generic donepezil tablets have the lowest acquisition cost and should be considered as the 1st line AChEI. In Herefordshire and Worcestershire, in line with the netFormulary, all preparations should be prescribed **generically** except for galantamine MR capsules which should be prescribed as **Gatalin XL®** and rivastigmine patches when the preferred brand is **Alzest®**.

Initiation of therapy

For detailed prescribing information refer to product SmPC and the BNF

Tests prior to starting treatment:

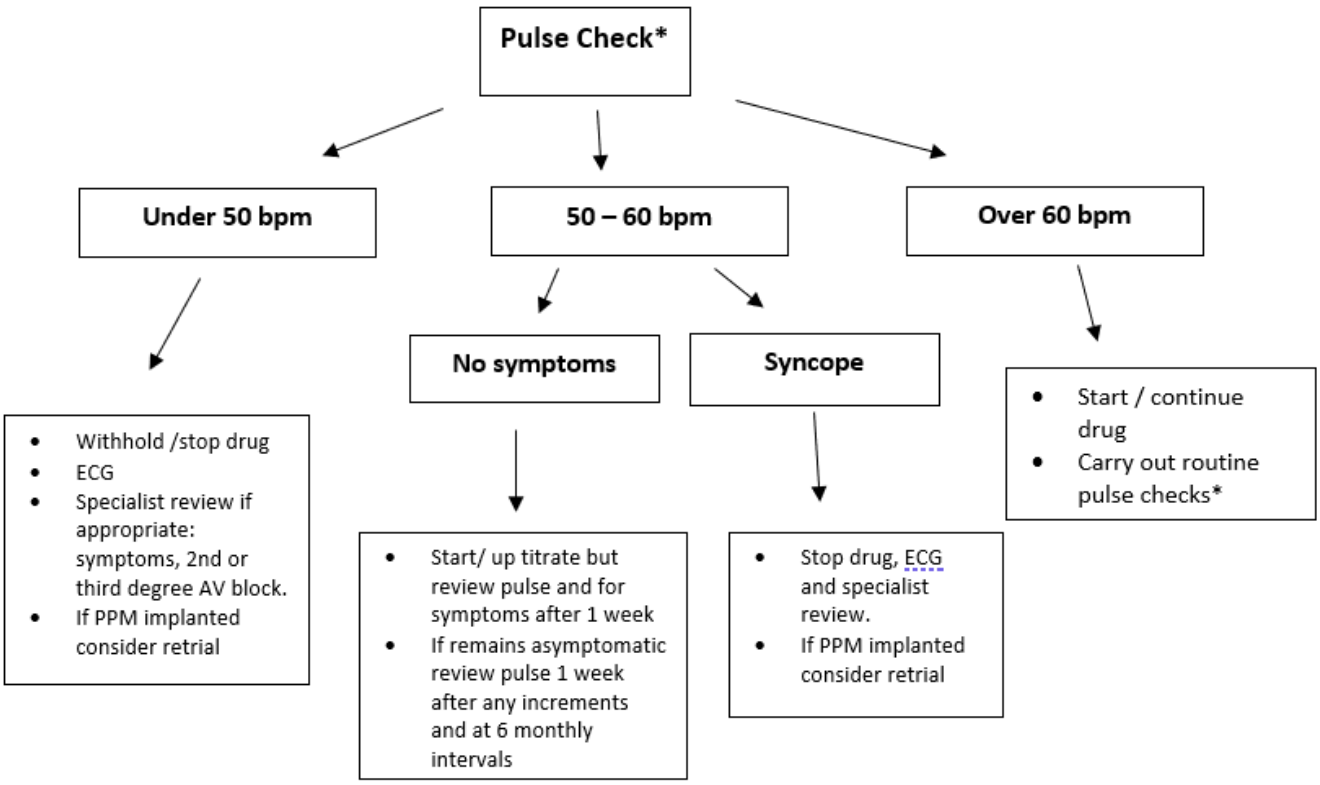
- Renal function. (Refer to SmPC if abnormal).
- Liver function. (Refer to SmPC if abnormal).
- Pulse

AChEIs tend to slow the heart rate and may cause syncope. Do not use if history of:

- Conduction disease (sinus node disease 2nd or 3rd degree AV block) without protection of a pacemaker.
- Unexplained syncope. [5]

Perform a routine pulse check at baseline, within one month of initiation / dose titration and at 6 monthly intervals. Action as in figure 1 below. [5]

Figure 1. Guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors



*Perform a routine pulse check at baseline, within 1 month of initiation / dose titration and at 6 monthly intervals
(bpm = heartbeats per minute
(PPM = Permanent Pacemaker)

Before prescribing AChEIs, it is important to look at the drugs the patient already takes. Consider stopping or reducing anticholinergic drugs, in particular.[4] Consider other drugs that can increase the risk of bradycardia such as beta-blockers and diltiazem (refer to the BNF).

All AChEIs are licensed for mild to moderate dementia but can be continued into severe dementia if they are deemed helpful. There is very little difference in effectiveness or side-effects between the various drugs and the cheapest is generally used first. Rivastigmine is licensed for dementia in Parkinson's disease, so may be preferred if hallucinations are a prominent presenting feature. If the first AChEI is not tolerated, try a second, but not a third. AChEIs and memantine may be trialed in severe dementia for improving Behavioural and Psychological Symptoms of Dementia (BPSD). (4)

Patients prescribed galantamine should be warned of the signs of serious skin reactions and advised to stop taking galantamine immediately and seek medical advice should such symptoms occur. (6)

Summary of indications, doses and common adverse effects (4)

Drug	Indication	Dose	Common adverse effects
Donepezil (first line choice)	Mild to moderately severe Alzheimer's dementia.	Start at 5mg daily at night. After one month can be increased to 10mg once daily.	Diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
Rivastigmine	Mild to moderately severe Alzheimer's dementia.	Start at 1.5mg twice daily with morning and evening meals. Increase dose by 1.5mg twice daily at a minimum of two weekly intervals, if tolerated, to maximum of 6mg twice a day. Effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose.	Gastrointestinal, including nausea and vomiting. Patches are also available but are significantly more expensive, refer to SmPC for dose. (Preferred brand for 4.6mg & 9.5mg patches is **Alzest**®) (7)
Galantamine XL (Preferred brand is **Gatalin XL**®) (7)	Mild to moderately severe Alzheimer's dementia.	Starting dose 8mg once daily in the morning with food, increased to 16mg after 4 weeks. May be increased to 24mg daily after 4 weeks if tolerated.	Nausea and vomiting. Serious skin reactions.
Memantine	Moderate to severe Alzheimer's disease.	5mg once daily for 7 days, then 10mg once daily for 7 days, then 15mg once daily for 7 days then to 20mg once daily.	Dizziness, headache, constipation somnolence and hypertension.

Key points (4)

- There is little to choose between AChEIs. Price and tolerability are the key deciders.
- The main side-effects of AChEIs are syncope and GI upset and they are contraindicated in heart block or significant cardiac conduction problems.
- Memantine is an alternative, if cardiac problems preclude an AChEI, and also has a licence for use in severe dementia but it is more expensive.

Monitoring Treatment (4)

About 60 per cent of patients with Alzheimer's disease have useful improvements in functioning with memory drugs; they may be brighter in mood, more interested in things, and capable of doing and enjoying things that they could not do before. Cognitive testing results may improve, but the most important thing is that the patient shows some improvement in functioning. **It should be noted, however, that that any improvement is symptomatic only and often modest, and that there is no effect on disease progression, and this should be discussed with patients and carers.**

When an AChEI has been initiated, the first follow-up contact with the patient and carers will be to establish whether there are any significant side effects. It is useful to do this before the second prescription is due, so an interval of around three weeks is about right.

The second follow-up should be about three months later when the patient should be assessed 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.

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. Follow-up is well within the remit of a practice nurse with knowledge of dementia and its problems, and who is trained in cognitive testing.

When to stop treatment [4]

When dementia gets worse:
AChEIs and memantine have proved to be very safe drugs. Stopping AChEIs when the MMSE reached 10/30 is no longer supported as evidence has emerged to support their continued usage in severe dementia. 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. Memantine may be tried in addition to donepezil in severe dementia.

When they might not be working:
AChEIs result in improvements in functioning in about 60 per cent of patients with Alzheimer's disease (they may be brighter in mood, more interested in things, and capable of doing and enjoying things that they could not do before). However, there will be some in whom they are not effective. If there is no subjective or objective improvement at the three-month review, they can be continued if there are no side-effects, and the patient reassessed in a further six months. 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 two AChEIs have been tried there is no point in trying another.

When they are not tolerated:
AChEIs should be stopped if they are thought to be causing problems – such as nausea, weight loss or bradycardia. Anxiety or agitation might prompt a trial without AChEIs as they are stimulant drugs. The result might be more apathy but less agitation.

Key points

- AChEIs and memantine work in most people and confer a valuable benefit.
- AChEIs can be continued when dementia enters the more severe stages.

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 97 Dementia: assessment, management and support for people living with dementia and their carers June 2018 https://www.nice.org.uk/guidance/ng97 (replacing NICE CG 42 and recommendation 1.3 in TA217)
3. EMC https://www.medicines.org.uk/emc
4. 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
5. Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol, JP Rowland et al, Advances in Psychiatric Treatment (2007), vol. 13, 178–184 https://doi.org/10.1192/apt.bp.106.002725
6. BNF https://bnf.nice.org.uk/drug/galantamine.html#drugAction accessed on 27.08.20
7. HWCCG net formulary http://www.worcsformulary.nhs.uk/default.asp accessed on 27.08.20

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