The Assessment of Cardiac Status Before Prescribing Acetyl Cholinesterase Inhibitors for Dementia

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Disclaimer:

Healthcare professionals must make their own decisions about assessment and care on a case-by-case basis, after consultation with their patients, using their clinical judgement, knowledge and expertise. This guidance is not intended to take the place of physician judgment in assessing individual patients prior to treatment nor is it intended to be a prescriptive direction defining a single course of management. Variations, taking individual circumstances into account, will be appropriate. Ratification of this guidance for local use should follow the usual process within all affected organisation(s). Departure from local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

The authors of this guidance have made considerable efforts to ensure the information upon which they are based is accurate and up to date. However, the authors accept no responsibility for any inaccuracies or information perceived as misleading. In addition the authors assume no legal liability or responsibility for the accuracy, completeness or clinical efficacy of this guidance.
1 Executive summary

The aim of this guidance is to support consistent, evidence-based practice in the cardiac pre-assessment, monitoring and safe prescribing of acetylcholinesterase inhibitors (AChEIs) for people with dementia. It is intended for clinicians responsible for initiating and monitoring the use of AChEIs and will be useful for commissioners to help inform the development of the dementia care pathway and contracting arrangements with provider services.

Acetylcholinesterase inhibitors (AChEIs) are recommended as first-line treatment for Alzheimer’s Disease. These drugs can slow heart rate which could potentially result in an increased risk of falls. Given that the majority of people with Alzheimer’s Disease are older people and the possible consequences of a fall are more likely to be severe, it is of particular importance that appropriate assessment of a person’s cardiac function is carried out routinely before starting AChEIs. This will enable potential contraindications to be identified and alternative treatment options to be explored if needed.

There is however no definitive national guidance on the required assessment to identify cardiac abnormalities before initiating AChEIs and as a result there is considerable variation in current practice.

The ECG Reference Group (ERG) reviewed the evidence base for cardiac monitoring, including use of routine ECG compared with routine pulse monitoring, prior to AChEI initiation. The ERG found that there was no compelling evidence that undertaking a routine ECG in all patients prior to initiation of AChEIs was either justifiable or effective.

The group recommends that service providers and commissioners should consider adopting the pathway (see Appendix II) proposed by Rowland et al (Rowland, 2007) which incorporates taking a detailed cardiac history, careful pulse checking and subsequent monitoring. In addition to this pathway, the ERG recommends use of ECG as standard monitoring in certain ‘higher risk’ groups of patients (see Section 6.3) as an additional safety check.

However the responsibility for prescribing these medications rests with the clinician initiating treatment and these clinicians must always make the final decision based on the specific clinical circumstances of each individual patient with their best interests in mind.

The ERG recommends that:

- service commissioners review commissioned dementia pathways against the recommendations of this guidance and the algorithm shown in Appendix II
- provider services review current practice against this guidance
- additional work is carried out to review current ECG training for psychiatrists and that recommendations are developed for Yorkshire & Humber
2 Why has this guidance been developed and who is it for?

The aim of this guidance is to support consistent, evidence-based practice in the cardiac pre-assessment and safe prescribing of acetylcholinesterase inhibitors in people with dementia.

Acetylcholinesterase inhibitors (AChEIs) are recommended as first-line treatment for Alzheimer’s Disease. AChEIs currently used in the treatment of dementia are donepezil, rivastigmine and galantamine. Although memantine, is another drug used to treat dementia it is not an AChEI and has a different mode of action.

Acetylcholinesterase inhibitors (AChEIs) have some peripheral effects, including increasing parasympathetic activation by the vagal nerve. Studies have shown that these drugs can slow heart rate which could potentially result in an increased risk of falls.

It is therefore important that appropriate routine assessment of a person’s cardiac function is carried out before starting AChEIs so that potential contra-indications are identified and alternative treatment options can be explored if needed. This may include modifying their existing drug regimen e.g. switching a beta-blocker and/or other rate modifying drug to an alternative.

Despite this, there is no definitive national guidance which specifies what cardiac assessment should be undertaken routinely prior to initiating AChEIs. There is also no agreed national standard for the monitoring the potential cardiac side effects of AChEIs once these have been started.

A local audit undertaken in September 2014 (Crowther G, 2014) and a Yorkshire & Humber-wide online survey in November 2015 (link to survey report) show considerable variation in the type of cardiac assessment undertaken by Memory Services before starting AChEIs. For example, 45% of respondents from provider services within Yorkshire and Humber routinely organise a baseline ECG for all patients before starting AChEIs whereas the other 55% do not.

As a result, the Yorkshire & Humber Older People’s Psychiatrist’s Group and CCG GP Dementia Leads Forum both identified the need for specific guidance in this area as a priority for the Dementia Clinical Network.

This guidance is intended for clinicians with responsibility for initiating and monitoring AChEIs. It will also be useful for commissioners to inform dementia pathway developments and contracting arrangements with provider services. A glossary of terms is included in Section 11.

3 Who has developed this guidance?

Yorkshire & Humber Clinical Networks (CNs) work to bring about improvements in the quality, equity of care and health outcomes for people living within Yorkshire &
Humber. CNs bring together those who use, provide and commission services to make improvements in patient pathways using an integrated, whole system approach.

CNs help to:
- reduce unwarranted variation in health and wellbeing services
- encourage innovation in how services are provided now and in the future
- provide clinical advice and leadership to support decision making and strategic planning

This guidance was developed by the ECG Reference Group (ERG), supported by the Dementia Clinical Network. ERG members included representatives from cardiology, psychiatry, geriatric medicine, primary care and pharmacy (see Appendix I for full list of members).

4 Scope and limitations

This guidance applies to prescribing AChEIs and is therefore only relevant to people for whom AChEIs are being considered as treatment. This will be primarily people with Alzheimer’s Disease but is also applicable to people with other types of dementia who may be treated with AChEIs such as those with Lewy Body dementia and Parkinson’s-associated dementia. It does not apply to those with other forms of dementia, including vascular dementia, as AChEIs are not indicated for use for these groups. The only exception to this is where an individual with one of these dementias also has Alzheimer’s Disease (often known as ‘Mixed Dementia’) and may therefore be treated with ACHEIs.

This guidance does not apply to Memantine, another drug used to treat dementia, as its mode of action is different to AChEIs. Memantine protects brain cells by blocking the effects of excess glutamate and it therefore does not have the same peripheral effects as AChEIs.

The ECG Reference Group (ERG) has reviewed the evidence base for cardiac monitoring, including undertaking a routine ECG compared with routine pulse monitoring, prior to AChEI initiation.

ERG member discussions were informed by the findings of an earlier systematic literature review (Crowther G, 2014) and a rapid evidence review and public health appraisal of clinical and cost-effectiveness (Fell, 2015) which was specifically commissioned from the Public Health team at Bradford Metropolitan District Council to support this work.

This guidance is intended to present a pragmatic summary of the evidence base and the recommendations of the ERG (see Appendix I for group membership). The ERG worked on the basis of the ‘do no harm’ principle and this guidance has been written accordingly.
5 Why is this guidance important for people who have dementia?

People with certain types of dementia, most commonly Alzheimer's Disease, have depleted levels in the brain of the neurotransmitter acetylcholine and a reduced number of acetylcholine-producing neurones. Both these phenomena are linked to worsening symptoms of dementia.

Acetylcholinesterase is an enzyme which breaks down the neurotransmitter, acetylcholine. AChEIs act by inhibiting the action of this enzyme increasing the levels of acetylcholine available for neurotransmission and the duration of action of the neurotransmitter (Colovic M. B., 2013). This helps to increase communication between nerve cells which can temporarily alleviate or stabilise some symptoms of Alzheimer's disease.

The AChEIs are donepezil, rivastigmine and galantamine. NICE recommends these drugs for use for people who have mild to moderate Alzheimer's Disease (NICE, 2011). NICE guidelines also recommend that an AChEI is offered to a person who has dementia with Lewy bodies or Parkinson's disease dementia if they also have distressing symptoms (e.g. hallucinations) or challenging behaviours (e.g. agitation, aggression). Rivastigmine is licensed for use in Parkinson's disease dementia.

Increasing age is the main risk factor for Alzheimer's Disease and AChEIs are mainly (although not exclusively) prescribed for older people. Older people have a higher prevalence of cardiac co-morbidity (compared to the general population) and are therefore more likely to be taking rate-limiting cardiac medication e.g. beta-blockers. Older people are also more likely to experience a fall, even in the absence of a cardiac arrhythmia. Furthermore studies have shown that AChEIs can slow heart rate in those with an existing cardiac abnormality and as a result, further increase the risk of falls. The possible consequences of a fall (e.g. fracture, admission to hospital) are more likely to be severe in older people, particularly for those with dementia (Alzheimer's Society, 2009).

As a result of these risks and in the absence of clear national guidelines about appropriate cardiac monitoring prior to initiating AChEIs, many clinicians obtain a routine ECG before starting treatment with these drugs.

According to an on-line survey conducted in November 2015 (link to results) access to an ECG varies considerably across Yorkshire & Humber. Some services are able to obtain an ECG within 24 hours for the majority of patients but one service reported that some patients had waits of up to a month for an ECG. Furthermore, three services reported that 75% of their patients had to travel more than 5 miles to obtain an ECG.

This survey indicates that in some areas undertaking an ECG routinely before initiating AChEIs can potentially lead to a delay in treatment and an additional inconvenience to patients and carers if they need to travel to have an ECG.
6 Discussion

6.1 What type and frequency of cardiac side effects are caused by acetylcholinesterase inhibitors?

This section summarises the findings of two literature reviews carried out by Crowther et al in September 2014 (Crowther G, 2014). The aim of these reviews was to quantify the cardiac side effects of prescribing acetylcholinesterase inhibitors. The search methodology used and full details of findings are included in the authors’ unpublished paper. Details of the individual studies reviewed are available in the original paper and therefore are not replicated here. Owing to a large number of trials excluding participants with pre-existing cardiac conditions, the authors acknowledged that much of the data did not reflect a realistic clinical cohort, where pre-existing cardiac conditions are common.

All AChEIs have some peripheral effects which can include increased parasympathetic activation by the vagal nerve caused by acetylcholine-stimulating GABAergic and glycinegic inhibitory receptors (Wang J.). Such vagal activity, via muscarinic receptors, acts to slow heart rate. Theoretically therefore, AChEIs can induce sinus bradycardia, sino-atrial block, and aggravate pre-existing sinus node disease and atrioventricular block. However in trials that have included patients with pre-existing cardiac conditions, there do not appear to have been a greater incidence of adverse cardiac events.

The paper summarises the findings of the literature reviews as follows:

- The evidence suggests that AChEIs have a small, but significant risk of causing bradycardia. The aetiology of the bradycardia appears to be multifactorial, however the most commonly cited cause appears to be atrioventricular dysregulation causing PR prolongation. Other causes of clinically significant bradycardia include the concomitant prescription of other rate limiting drugs, or a pre-existing bradycardia.
- There is more convincing evidence that AChEIs carry a small to medium risk of dizziness. The aetiology of this was not explored in any of the published papers, therefore a cardiac cause for dizziness cannot be ruled out.
- Other cardiac risks were less commonly reported and include extrasystole, tachycardia and myocardial infarction.
- QT prolongation appears to be a rare side effect, and was documented infrequently in case reports only. There is potential however for fatal arrhythmias in those with a significant QT prolongation, particularly those with a co-morbid hypo/hyperkalaemia.

The paper concludes that there is no convincing evidence that persons with pre-existing cardiac abnormalities are at a greater risk of experiencing cardiac conduction abnormalities with AChEI treatment.

However, if a person’s baseline ECG parameters lie closer to the limits of normality, they may be less able to tolerate bradycardia induced by AChEIs. The same theory
applies to those on concomitant rate limiting drugs (such as beta blockers), and those with pre-existing heart block.

6.2 What routine cardiac monitoring should be conducted prior to starting AChEIs?

One of the key considerations for the ECG Reference Group was the evidence base to support an assumption that routine ECG is required prior to starting AChEIs. This is standard practice in 45% of Yorkshire and Humber Memory Service providers according to an online survey carried out in November 2015. However the BNF does not explicitly state that an ECG should be carried out routinely prior to prescribing AChEIs.

The case for undertaking an ECG is made on the basis of precaution ie. the possibility of identifying cardiac conduction abnormalities and therefore potentially reducing the risk of bradycardia or syncope. (The documented cardiovascular risks and their sequelae are described in section 6.1 above).

However, Rowland et al (Rowland, 2007) found that abnormal ECGs are not predictive of cardiovascular adverse events and that these events also occur in those with a normal pre-treatment ECG. The evidence is therefore unclear.

In some memory services (55% of respondents to the online survey), an ECG is not being routinely undertaken. In these services an ECG is only requested when there are specific clinical indications that it is required.

The findings of the systematic literature review (Crowther G, 2014) and rapid evidence review (Fell, 2015), were presented to the ERG. Based on these reviews, the ERG found that there was not compelling evidence that undertaking a routine ECG in all patients prior to initiating AChEIs was either justifiable or effective.

The group recommends that service providers and commissioners should consider adopting the pathway (see Appendix II) proposed by Rowland et al (Rowland, 2007) which incorporates taking a detailed cardiac history, careful pulse checking and monitoring. However, ERG members emphasize that the responsibility for prescribing these medications rests with the clinician initiating treatment and these clinicians must always make the final decision based on the specific clinical circumstances of each individual patient with their best interests in mind.

The ERG recommends that pulse checking is undertaken shortly before AChEIs are to be initiated and ideally rechecked. The pulse should be checked manually (not by an automated machine), timed for a full minute and an allowance made for the fact that attendance at a memory clinic may cause anxiety and an associated tachycardia. Pulse checking could be undertaken within primary care prior to or at the point of referral.

Patients who are fitted with a cardiac pacemaker do not need to have their pulse checked as the pacemaker safeguards them from developing a bradycardia (slow pulse rate).
6.3 What cardiac assessment should be undertaken in higher risk groups prior to initiating AChEIs?

Although pulse check is sufficient to pick up significant bradycardia, the evidence base is limited in this area and the ERG therefore recommends that an ECG in the following groups of patients is advisable. An ECG may facilitate the detection of other cardiac conduction system abnormalities in patients for whom one would be more cautious regarding use of AChEIs and the absence of ECG abnormalities may reassure the clinician that cautious use of AChEIs, with monitoring, is appropriate.

The ERG has identified specific groups of patients (estimated to be around 35% of the total cohort) in whom a baseline ECG is recommended as standard practice prior to initiating treatment with AChEIs:

- Unexplained syncope
- Bradycardia
- Patients taking concomitant cardiac rate-limiting medication e.g. beta-blockers, amiodarone

The following ECG changes may warrant further discussion with primary care, specialist primary care colleagues (where available) or your local cardiology service if they are felt to be clinically significant in the context of the patient's overall clinical picture:

- Newly identified atrial fibrillation
- Left bundle branch block
- QT prolongation (men >450ms; women >470ms)
- Second or third-degree Atrio Ventricular block ('Heart Block')
- Sinus bradycardia <50bpm

6.4 What pre-existing cardiac abnormalities should change prescribing of anti-dementia drugs and how?

The British National Formulary (Ref) states that these drugs should be used with caution in patients with sick sinus syndrome and other supraventricular conduction abnormalities. For galantamine, the BNF also recommends caution in patients with cardiac disease (including unstable angina and congestive cardiac failure).

Given the advice in the BNF, this section aims to give additional pragmatic advice to clinicians. The following cardiac abnormalities should result in a change in prescribing of AChEIs, as follows:

Absolute contraindication:

- Second or third-degree heart block in an unpaced patient– DO NOT prescribe AChEIs
• QT prolongation – Avoid prescribing AChEIs and seek advice
• Bradycardia of < 50 bpm - DO NOT prescribe AChEIs

Use with caution

AChEIs are potentially contraindicated in the following groups. Seek specialist advice and prescribe cautiously, if used, with ongoing monitoring:

• Left Bundle Branch block
• Patients on concomitant rate limiting drugs such as beta-blockers, amiodarone, digoxin, non-dihydropyradine calcium-channel blockers (e.g. diltiazem, verapamil) - prescribe cautiously if pulse is between 50-60 bpm and asymptomatic. If rate limiting calcium channel blockers or beta-blockers are being used to treat hypertension, alternative anti-hypertensive agents might be considered to facilitate the introduction of AChEIs.

6.5 What cardiac monitoring should be conducted in people established on AChEIs?

For ongoing monitoring, for the majority of patients, the algorithm proposed by Rowland et al (Rowland, 2007) for pulse monitoring is sufficient. However in this guidance we have raised the pulse rate threshold to 60 bpm, in line with the currently accepted practice for the prescribing of AChEIs in many local memory services.

Once an AChEI has been initiated the pulse rate and patient’s symptoms should be rechecked at 1 month. If the dose of the AChEI is to be titrated up at this stage, the pulse rate and symptoms should be reassessed after a further month. If there is an abnormal pulse rate or the patient has symptoms, the “Rowland algorithm” (see Appendix II) should be followed. However if the pulse rate is above 60 bpm and the patient is asymptomatic they can be rechecked at 6 months. If the pulse is satisfactory and the patient remains well, monitoring can be undertaken on an annual basis thereafter e.g. as part of the General Practice dementia Quality Outcomes Framework (QOF) check. If the patient becomes unwell or develops symptoms they would need a full assessment including a check of their pulse and blood pressure.

If a patient taking an AChEI presents with syncope or seizures, an underlying cardiovascular cause should be strongly suspected (Thompson S, 2004). The drug should be stopped and the patient referred to a physician for further investigation. If examination reveals no causal relationship with the drug, or if a pacemaker is fitted, the drug may be restarted.

6.6 Interpretation of ECGs

A local audit carried out in September 2014 demonstrated that in the geographical area studied, the interpretation of the results of cardiac monitoring inconsistently influenced prescribing practice within memory clinics.
The Yorkshire & Humber-wide online survey demonstrates variation in the support available to clinicians to interpret ECG findings. In some areas, there is a clear reliance on the results of automated ECG reports. Published papers indicate that automated ECG reports can over-report cardiac problems (Estes, 2013). Therefore over-reliance on automated reports without additional skills in ECG interpretation may lead to unnecessary changes in AchEI prescribing with patients unnecessarily being denied access to the most effective treatment options.

Several studies indicate that basic training in interpreting ECGs should be integrated as part of periodic training for both psychiatrists and GPs (Abdelmawla AJ, 2006).

7 Conclusions

Having reviewed the available evidence, the ERG found that although there is a theoretical risk of increased cardiac conduction abnormalities with these drugs, the evidence base is lacking for the need to carry out a routine ECG as standard baseline pre-prescribing practice.

The ERG has concluded that for the majority of patients, monitoring the pulse rate, in accordance with the algorithm proposed by Rowland et al (Rowland, 2007) will be sufficient prior to the initiation of AChEIs.

However, there are some patients for whom baseline ECG monitoring is advised and the criteria for these patient groups are set out in section 6.3.

The ERG emphasized the responsibility for prescribing these medications rests with the clinician initiating treatment and these clinicians must always make the final decision based on the specific clinical circumstances of each individual patient with their best interests in mind.

8 Recommendations and Pathway

1. The ERG recommends that providers review current practice against the findings of the group.

2. The ERG recommends that service commissioners review commissioned dementia pathways against the recommendations of this guidance and the algorithm shown in Appendix II.

3. Additional work is carried out to review current ECG training for psychiatrists and GPs and make recommendations for Yorkshire & Humber

9 Cost Implications

Looking at ECGs and their use prior to initiation of anticholinesterase medication, fits well with in the Quality, Innovation, Productivity and Prevention (QIPP) agenda.
There would be a considerable saving to the NHS if ECGs were not routinely undertaken on all patients referred to memory services with an opportunity for the savings accrued to be used in a different way to benefit these patients. Using national cost reference data as a guideline price, (https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015), for every ECG not carried out a saving of £52 would be made. If the use of ECG was reduced by 65% in those services where a routine baseline ECG is standard practice, there would be a saving of £3380 (£52 x 65) for every 100 new patients seen. For those services undertaking approximately 500 routine ECGs a year, implementing this guidance could save around £16,900 (£52 x 325) per year which could be reinvested to support other service developments.

10 References


11. Glossary of terms (click here to access online document)

12 Appendices
## Appendix I

### ECG Expert Reference Group Membership

<table>
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<tr>
<th>Name</th>
<th>Title and Role</th>
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Fig.1 Suggested guidelines for managing cardiovascular risk prior to and during treatment with acetylcholinesterase inhibitors in Alzheimer’s disease. bpm, heartbeats per minute; the ‘drug’ means the chosen AChE inhibitor.

**Pulse Check**

- **Under 50 bpm**
  - Asymptomatic
  - Continue drug
  - Pulse check 1 week after any increase in drug dose

- **50 – 60 bpm**
  - Symptomatic (e.g. syncope, ‘funny turns’)
  - Withhold/stop drug and seek GP or specialist review for underlying cause
  - If cause is found to be unrelated to the drug, or a pacemaker is fitted, consider retrial of drug
  - Start/continue drug
  - Review pulse and symptoms after 1 week

- **Over 60 bpm**
  - Asymptomatic
  - Start/continue drug
  - Carry out routine pulse checks

*Routine pulse checks should be carried out at baseline, at monthly intervals during titration and at 6 monthly intervals thereafter*