Cardiac monitoring in Acetylcholinesterase prescribing
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Acetylcholinesterase Inhibitors:
Levels of the neurotransmitter acetylcholine, and numbers of acetylcholine producing neurones are depleted in Alzheimer's and Lewy body dementia.

Acetylcholinesterase inhibitors are a class of drugs that inhibit the enzyme cholinesterase from breaking down the neurotransmitter acetylcholine, increasing the neurotransmitter levels and duration of action at the synaptic cleft (Colovic et al., 2013).

Donepezil, Rivastigmine and Galantamine are reversible acetylcholinesterase inhibitors, and are recommended in mild and moderate Alzheimer's dementia (NICE, 2011). Treatment should be initiated by specialists in the care of patients with dementia, and treatment should only continue while it is deemed to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. The choice of acetylcholinesterase inhibitor should normally be determined by lowest acquisition cost, though choice may be influenced by the side effect profile of the drug (NICE, 2011). Memantine is a glutamate receptor antagonist that is recommended in moderated to severe dementia when acetylcholinesterase inhibitors are ineffective or contraindicated (NICE 2011).

Donepezil, galantamine and rivastigmine have significant CNS selectivity, however some peripheral actions include increased parasympathetic activation by the vagal nerve caused by acetylcholine stimulating GABAergic and glycnergic inhibitory receptors (Wang et al., 2003). This vagal activity, via muscarinic receptors, acts to slow heart rate. Theoretically therefore, acetylcholinesterase inhibitors can induce sinus bradycardia, sino-atrial block, and aggravate pre-existing sinus node disease and atrioventricular block (Savci et al., 1998).

Acetylcholinesterase inhibitors are almost exclusively prescribed to older people, a group who have a high prevalence of cardiac co-morbidity and high likelihood to be prescribed medications that limit cardiac rate, (such as beta-blockers). This group is more likely to experience a fall, even in the absence of a cardiac arrhythmia. The consequences of a fall, for instance a fracture or a long lie, are more likely to be severe in older people. It stands to reason therefore that one might exercise caution when prescribing pro arrhythmic medication, to this already ‘at risk’ group.

Current national guidelines on whether or how clinicians should prescribe acetylcholinesterase inhibitors to patients with preexisting cardiac conditions are lacking both in their number and detail:

The National Institute for Health and Care Excellence (NICE) recommends ‘an alternative acetylcholinesterase inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical co-morbidity, possibility of drug interactions and dosing profiles’ (NICE 2011).
The British National Formulary lists the following cautions when prescribing acetylcholinesterase inhibitors (BNF 2015):

Donepezil - ‘sick sinus syndrome or other supraventricular conduction abnormalities’.

Galantamine - ‘Cardiac disease (including sick sinus syndrome, or other supraventricular conduction abnormalities, unstable angina, congestive heart failure)’.

Rivastigmine - ‘Sick sinus syndrome, conduction abnormalities’.

Neither of these resources give detail on specific parameters that need to be met to safely prescribe acetylcholinesterase inhibitors to people with pre-existing cardiac disease. Such ambiguity has the potential to give rise to inconsistent prescribing practice.

No local guidelines on whether or how clinicians should prescribe acetylcholinesterase inhibitors to patients with preexisting cardiac conditions exist.

In Leeds and York Partnership NHS Foundation (LYPFT) Trust acetylcholinesterase inhibitors are commenced by Doctors, (usually old age psychiatrists), working in the Leeds Memory Service (LMS). They will generally be commenced for people with mild or moderate Alzheimer’s, mixed or Lewy Body dementia, unless there are no contraindications to doing so. Memantine may be prescribed in moderate or severe dementia, where acetylcholinesterase inhibitors are contraindicated or ineffective in line with the NICE guidance set out above.

An audit carried out by this team has demonstrated that in Leeds the cardiac monitoring carried out before prescribing acetylcholinesterase inhibitors, and the interpretation of the results of cardiac monitoring inconsistently advise prescribing practice. A recommendation of this audit is that an evidence based prescribing guideline should be produced so that clinicians in the trust practice uniform, evidence based and safe prescribing. The following questions were generated from the audit, the answers of which will go on to inform any prescribing guideline.

**Questions generated:**

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

What preexisting cardiac abnormalities (if any) should contraindicate the use of acetylcholinesterase inhibitors?

What cardiac monitoring should be conducted prior to commencing acetylcholinesterase inhibitors?

What cardiac monitoring should be conducted in patients established on acetylcholinesterase inhibitors?

**Aim:**

...
To conduct a literature review to quantify the cardiac risks of prescribing acetylcholinesterase inhibitors, in order to inform a prescribing guideline.

**Method:**

The aim of the search was to look for studies that described and quantified the cardiac side effects of prescribing acetylcholinesterase inhibitors. We initially chose to look at trial data to ascertain, how what types of cardiac side effects were reported and how frequently they occurred.

This search was carried out in September 2014.

Papers for this review were obtained using OVID with the following electronic databases: PsychINFO, PsychArticles, EMBASE, MEDLINE.

**Search terms:** Search terms: acetylcholinesterase inhibitors, anti-cholinesterase, donepezil, galantamine and rivastigmine. These search terms were combined using the Boolean term or.

The search criteria were then filtered to only include randomised control trials and open label studies. The search was limited to English language articles and duplicates were removed.

A total of 2601 titles were reviewed by hand for relevance (randomised control trials and open label studies using donepezil, galantamine or rivastigmine on human subjects).

The titles and where necessary abstracts of these 2601 articles were hand reviewed with the following inclusion and exclusion criteria:

**Table 1.0: Inclusion and exclusion criteria of articles for the literature review.**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Randomised Control Trial</td>
<td>Systematic reviews</td>
</tr>
<tr>
<td>Open Label Trial</td>
<td>Case studies/series</td>
</tr>
<tr>
<td>Trial used any acetylcholinesterase inhibitor as its primary variable.</td>
<td>Audit</td>
</tr>
<tr>
<td>The trial reported rates and type of adverse outcomes.</td>
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<td>English Language</td>
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In addition to this, in order to ensure that key studies were not missed the references of three key reviews into the safety of acetylcholinesterase inhibitors were reviewed:


The same inclusion and exclusion criteria were applied.

Twenty eight randomised control trials and 11 open label studies were identified. These 39 papers were sought with the assistance of the LYPFT library service. Three randomised control trials were unavailable, 4 open label studies were unavailable.

The remaining articles were divided amongst the team and reviewed using an adapted Oxford Critical Appraisal Skills Program (CASP) checklist (copy in appendix 1). Reviews were asked to document the following information:

• Study Type
• Number of Participants
• Relevant Exclusion Criteria
• The number and type of adverse cardiovascular outcomes of those with preexisting cardiovascular co-morbidity.
• The number and type of adverse cardiovascular outcomes of those without preexisting cardiovascular co-morbidity.

The review team met to discuss each appraisal and the merits of each study (using CASP criteria). The above information was then extracted from each study and documented on one central database for further analysis (see appendix 2 for a copy of the database tables).

Results of search 1:

Randomised Control Trials:

25 RCT's were reviewed; the total number of participants included was 9579. 15 of the trials used donepezil as the sole treatment agent, 5 used galantamine, 3 used rivastigmine, one used both donepezil and galantamine (separately) and one used both rivastigmine and galantamine (separately).

Of the 25 RCT's reviewed 12 excluded patients from participation with a history of cardiovascular disease. The cardiovascular exclusion criteria were unclear or ambiguous in 2 studies.

The most common side effect quoted was dizziness or syncope with 12 trials reporting clinically significant of dizziness 4 – 20% in patients treated with acetylcholinesterase inhibitors (Rogers and Friedhoff, 1996, Rogers et al., 1998, Burns et al., 1999, Tariot et al., 2001, Mohs et al., 2001, Greenberg et al., 2000, Seltzer et al., 2004, Winblad et al., 2001, Wilkinson and Murray,
Dizziness was reported as frequently for all three types of cholinesterase inhibitors. The effect was reported as dose dependant in 2 studies (Rosler et al., 1999, Wilkinson and Murray, 2001). In no trial was a cause for the dizziness or syncope given therefore dizziness of a cardiac origin cannot be ruled out.

Cardiac side effects were reported in 6 trials (Tariot et al., 2001, Mohs et al., 2001, Salloway et al., 2004, Winblad et al., 2001, Bullock et al., 2005, Rogers et al., 1998). The most frequently reported cardiac adverse outcome was bradycardia with treatment groups reporting a 2.4 to 5 beats per minute reduction in heart rate (Rogers et al., 1998, Tariot et al., 2001, Mohs et al., 2001, Winblad et al., 2001). Winblad et al (2001) reported bradycardia rates of 9.2% in those treated with donepezil compared with 6.3% in placebo.

Winbald et al. (2001) also reported myocardial infarction in 1.6% of the treatment arm, though no comment was made as to whether this was related to the treatment or not.

New onset atrial fibrillation was reported in one patient in one trial (Salloway et al., 2004).

19 (n= xx) trials did not report any adverse cardiac side effects.

Open label studies:

Nine open label trials were reviewed, one of which was later excluded by group consensus due to poor quality, the total number of participants were 1528. Three used donepezil as the sole treatment agent, two used galantamine as the sole treatment agent, one used rivastigmine only, one used rivastigmine and donepezil (separately) and one used donepezil, galantamine and rivastigmine (separately).

Of the open label trials three excluded patients with pre-existing cardiovascular history.

Dizziness, syncope or giddiness were reported in 4 of the studies, with a prevalence ranging from 1-11% (Rogers et al., 2000, Froelich et al., 2004, Kurz et al., 2003, Pirttila et al., 2004). Once again, no causes for dizziness, syncope or giddiness were given, so a cardiac aetiology cannot be ruled out.

Cardiovascular side effects were reported in 5 trials (Mehta et al., 2012, Wilkinson et al., 2002, Mossello et al., 2004, Pirttila et al., 2004, Kurz et al., 2003, Froelich et al., 2004). Bradycardia was the most commonly reported cardiac side effect with prevalence figures ranging from 1 – 5.5%. Bradycardia was reported both in trials that included and excluded participants with a prior cardiovascular risk history (Froelich et al., 2004, Wilkinson et al., 2002, Mehta et al., 2012, Kurz et al., 2003).

Other reported cardiac side effects included Extrasystole (prevalence 1.3% (Froelich et al., 2004)) and tachycardia ((prevalence 1.3% (Froelich et al., 2004)).
Myocardial infarction was reported in two studies; Kurtz et al. (2003) reported a prevalence of 1% (n=374) of participants treated with. Rogers et al (2000) reported two people in the study as having had a myocardial infarction, however it was not felt the events were related to donepezil.

**Summary of RCT and open label evidence.**

Evidence from the studies above demonstrate that acetylcholinesterase inhibitors have a small, but significant risk of causing bradycardia.

There is more convincing evidence that acetylcholinesterase inhibitors carry a small to medium risk of dizziness, and a cardiac aetiology for dizziness cannot be ruled out using the evidence presented.

Other cardiac risks were less commonly reported and include extrasystole, tachycardia and myocardial infarction.

Owing to a large number of trials excluding participants with pre-existing cardiac conditions, much of the data does not reflect a realistic clinical cohort, where pre-existing cardiac conditions are common. In trials that have not excluded patients with pre-existing cardiac conditions however, there do not appear to be a greater incidence of adverse cardiac events.

No specific ECG abnormalities are commented on in any of the trials so specific conduction abnormalities cannot be commented on.

**Conclusion:**

The evidence presented does not give sufficient detail to answer the study aims: ‘To conduct a literature review to quantify the cardiac risks of prescribing acetylcholinesterase inhibitors, in order to inform a prescribing guideline for acetylcholinesterase inhibitors.’

As a consequence of this, with the same aim, I performed a new literature review which is described below.

**Methods part 2:**

The aim of the search was to look for case reports, and case series that described and quantified the cardiac side effects of prescribing acetylcholinesterase inhibitors.

This search was carried out in June 2014.

Papers for this review were obtained using OVID with the following electronic databases: PsychINFO, PsychArticles, EMBASE, MEDLINE.

**Search 1 terms:** acetylcholinesterase inhibitors, anti-cholinesterase, donepezil, galantamine and rivastigmine. These search terms were combined using the Boolean term or.

**Search 2 terms:** Cardiac side effects, cardiac arrhythmia, cardiac arrhythmias, arrhythmia, arrhythmias, bradycardia.
The search criteria were then filtered to only include case series, case reports. The search was limited to English language articles and duplicates were removed.

A total of 277 titles were reviewed by hand for relevance (case reports and series describing cardiac changes in patients treated with donepezil, galantamine or rivastigmine on human subjects).

The titles and where necessary abstracts of these 277 articles were hand reviewed with the following inclusion and exclusion criteria:

**Table 2.0: Inclusion and exclusion criteria of articles for the literature review.**

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<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Case series</td>
<td>Systematic reviews</td>
</tr>
<tr>
<td>Case report</td>
<td>Randomised control trials</td>
</tr>
<tr>
<td>English Language</td>
<td>Open label studies.</td>
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<td>Audit</td>
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Thirteen studies were identified, 4 case series and 9 case reports. Collectively three main ECG changes were reported, PR interval changes causing second and third degree heart block, QT prolongation on occasion leading to arrhythmia and torsade du pointe and RR prolongation.

Two case series and three case reports document an increase in PR interval (Suleyman et al., 2006, Hundae et al., 2014, Igeta et al., 2014, Leentjens and Kragten, 2006, Knudtzen and Christophersen, 2013). These case reports include patients prescribed donepezil, rivastigmine or galantamine. In the majority of cases the PR interval returned to baseline on the discontinuation of the cholinesterase inhibitor indicating causality (Knudtzen and Christophersen, 2013, Suleyman et al., 2006, Hundae et al., 2014). PR interval prolongation can lead to bradyarrhythmias or second or third heart block.

QT prolongation was reported in one case report and one case series, it is of note however the case series, (Tanaka et al., 2009) included only 2 cases. QT prolongation causes an increased risk of arrhythmia and torsade du pointe, potentially fatal conditions. A separate case report (Hadano et al., 2013) documents a of torsade du pointe without any QT prolongation.

As with the RCT and open label trial data, a RR prolongation and resultant bradycardia is the most commonly reported cardiac side effect of cholinesterase inhibitors. In 12 of the 13 articles reviewed bradycardia was a reported outcome of acetylcholinesterase inhibitors. One series reported prevalence as high as 10% (Babai et al., 2010). The aetiology of the bradycardia was variable including atrioventricular dysfunction causing PR delay and heart block (Hundae et al., 2014, Tanaka et al., 2009, Igeta et al., 2014, Leentjens and Kragten, 2006).
Sick sinus syndrome was reported in once case (Shahani, 2014).

One reported case of extreme bradycardia was described when rivastigmine was prescribed to a patient who was already taking atenolol (Paulison and Leos, 2010).

**Discussion:**

Despite mixed trial evidence there is convincing theoretical, and reported evidence that all three types of acetylcholinesterase inhibitors can cause bradycardia and dizziness. It is unclear with what frequency the former causes the latter.

The aetiology of the bradycardia appears to be multifactorial, however the most commonly sited 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.

QT prolongation appears to be a rare side effect, and 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.

There is no convincing evidence that persons with pre-existing cardiac abnormalities are at a greater risk of experiencing cardiac conduction abnormalities with acetylcholinesterase treatment. If a persons baseline ECG parameters lie closer to the upper limits of normality however, they may have less capacity to be able to tolerate further conduction abnormalities before they experience clinically significant arrhythmias. For instance if someone is asymptotically bradycardic before treatment with an acetylcholinesterase inhibitor, they may experience a symptomatic bradycardia post prescription. The same theory applies to those on concomitant rate limiting drugs (such as beta blockers), and those with a pre-existing heart block.

**Next steps:**

Evidence base to be presented to guideline writing committee.

**References:**


