Medicines Adverse Reactions Committee

Meeting date	14/09/2023	Agenda item	3.2.3
Title	**Acetylcholinesterase inhibitors and the risk QT prolongation and Torsade de Pointes**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Donepezil	Donepezil (Rex) 5mg and 10mg tablets[a]	REX Medical Ltd
Galantamine	Reminyl 8mg, 16mg and 24mg modified release capsule	Janssen-Cilag (New Zealand) Ltd
Rivastigmine	Exelon 1.5mg, 3mg, 4.5mg and 6mg capsule	Novartis New Zealand Ltd
	Exelon 2mg/mL oral solution[b]	Novartis New Zealand Ltd
	Rivastigmine 4.6mg/24h, 9.5mg/24h and 13.3mg/24h transdermal patch	Arrotex Pharmaceuticals (NZ) Limited
	Rivastigmine BNM 4.6mg/24h and 9.5mg/24h transdermal patch[a]	Boucher & Muir (New Zealand) Limited t/a BNM Group

Notes:

a. PHARMAC funded.
b. Registration status 'not available' but data sheet published.

Previous MARC meetings	Not discussed
International action	Relating to all acetylcholinesterase inhibitors: • Health Canada (July 2022) Relating to donepezil: • European Medicines Agency (2 August 2021) • Therapeutics Goods Administration (28 February 2022) • Health Sciences Authority (Singapore) (30 August 2022) • National Pharmaceutical Regulatory Agency Ministry of Health Malaysia (March 2023) Relating to galantamine: • European Medicines Agency (December 2020)
Prescriber Update	Donepezil: Syncope, Heart Block and Beta-adrenergic Blockade (September 2013) Syncope and Dementia Treatment – Catching falls (June 2005)
Classification	Prescription medicine
Advice sought	**The Committee is asked to advise whether:** • There is evidence of an association between acetylcholinesterase inhibitors as a drug class (or an individual acetylcholinesterase inhibitor) and QT prolongation and Torsade de Pointes? ○ If yes, is regulatory action required? • Further communication is required other than in MARC's remarks?

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1 PURPOSE

Donepezil, rivastigmine and galantamine are acetylcholinesterase inhibitors (AChEIs) indicated for the treatment of Alzheimer's disease (AD).

In 2020, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA's PRAC) reviewed the risk of QT prolongation and Torsade de Pointes (TdP) with galantamine and considered there was a casual association. In 2021, the EMA's PRAC also considered there to be a causal relationship with donepezil. The European product information for these products were updated with information on QT prolongation and TdP.

In 2022, the New Zealand rivastigmine (Exelon) data sheet was updated with information on the risk of QT prolongation and TdP. The current donepezil and galantamine data sheets do not have this information. Therefore, the purpose of this review is to consider whether the risk of QT prolongation and TdP can be considered a class effect for AChEIs and if the data sheets for all remaining AChEI medicinal products should be updated.

2 BACKGROUND

2.1 Alzheimer's disease

AD, a neurodegenerative disorder, is the most common form of dementia. AD accounts for 60 to 80% of cases of dementia in New Zealand [1].

The most common initial symptom is memory impairment [2]. Other symptoms include difficult performing normal tasks, changes in personality, geographic disorientation, trouble forming sentences in conversation, and loss of interest in normal activities. The onset of symptoms is gradual and is associated with progressive functional decline [1].

There are various hypotheses that have been proposed to explain the pathophysiology of AD. These include the amyloid hypothesis, hyperphosphorylated tau protein hypothesis, and cholinergic hypothesis.

Cholinergic neurotransmitters play a very significant role in memory, learning, attention and behaviour [3]. The cholinergic hypothesis suggests that reduced brain acetylcholine levels due to the atrophy of cholinergic neurons, primarily in the nucleus basalis of Meynert are the cause of cognitive decline in AD [3].

2.2 Management of Alzheimer's disease

The management of AD is focused on symptomatic treatment using lifestyle, behavioural and pharmacological methods, where appropriate. The aim of treatment is to improve quality of life for both the person with AD and their family [4].

Current available management of cognitive symptoms in mild to moderate AD include AChEIs and memantine. AChEIs can have a beneficial effect on cognitive symptoms, patient function, behaviour and reduce the burden on caregivers, but do not cure AD [4]. Memantine is a glutamate receptor antagonist which may be considered in patients with moderate-to-severe symptoms, if other approaches are ineffective and AChEIs are contraindicated or not tolerated [5].

2.3 Acetylcholinesterase inhibitors

AChEIs inhibit the acetylcholinesterase enzyme from breaking down acetylcholine, thereby increasing both the level and duration of the neurotransmitter action [6]. They are recommended for the treatment of cognitive symptoms of mild-to-moderate dementia due to AD [5]. The dose should be started low and increased according to tolerability. There is no evidence that one AChEI is more effective than the others and therefore the choice is usually dependent on the cost, mode of delivery and risk of adverse effects [5].

The differences in indication, formulation, half-life and mode of action of the three AChEIs are outlined in Table 1.

Table 1: Differences between donepezil, galantamine and rivastigmine

AChEI	Indication	Formulations available in NZ	Half-life [6]	Action [6]
Donepezil	Treatment of mild, moderate and severe Alzheimer's disease. Treatment of vascular dementia (dementia associated with cerebrovascular disease).	Oral tablets	70 hours	Selective, reversible inhibitor of AChEI
Galantamine	Treatment of mild to moderately severe dementia of the Alzheimer type.	Modified release capsules	7 hours	Selective, competitive, reversible AChE inhibitor. Galantamine also modulates nicotine receptors, thereby enhancing acetylcholinergic activity at the synapse [7].
Rivastigmine	Treatment of patients with mild to moderately severe dementia of the Alzheimer type.	Capsule Transdermal patch	1 hour [8] 3.4 hours	Slow-reversible carbamate inhibitor that inhibits both butylcholinesterase and acetylcholinesterase.

2.4 Cardiac adverse effects of acetylcholinesterase inhibitors

The cardiac side effects listed in the data sheets of AChEI include bradycardia, heart block, and syncope. This is thought to be due to enhanced vagal tone [9] in the sinoatrial node, slowing the sinus rate and various conduction systems [10]. The enhanced vagal tone may be particularly important to patients with sick sinus syndrome or other supraventricular cardiac conduction disturbances or who concomitantly use medicines that significantly reduce heart rate (eg, beta-blockers and digoxin) [8].

2.5 Drug-induced QT prolongation and Torsade de Pointes

QT prolongation

The QT interval is the time between the start of the QRS complex and the end of the T wave in an electrocardiogram (ECG) (Figure 1). The interval represents the duration between the onset of depolarisation and the completion of repolarisation of the myocardium. It is mediated by the closure and/or opening of ion channels in the heart with the influx of positive ions (sodium, calcium) causing depolarisation, and the efflux of positive ions (potassium) causing repolarisation. Disturbance in these ion channels in a way that leads to an excess of positive ions intracellularly will lead to prolongation of the action potential, and therefore QT prolongation [11]. Cardiac events and fatal arrythmias may occur when the QT interval is prolonged [12].

Figure 1: Schematic diagram of normal sinus rhythm for a human heart as seen on ECG

The QT interval is affected by heart rate. A higher heart rate will measure a shorter QT interval on ECG and a lower heart rate will measure a longer QT interval. To account for the variability in heart rate, the QT interval is often corrected – this is known as 'QTc' [12]. In general, QTc is considered prolonged if it is greater than 440 milliseconds (ms) in men or greater than 460 ms in women [12].

The Bazett formula is the most common method for correcting the QT. This is calculated as the QT interval divided by the quare root of the RR interval (the time between two successive R-wave on ECG) [12]. The QTc values for normal and prolonged after correction with Bazett's formula is outlined in Table 2.

Table 2: QTc values by age and sex for normal and prolonged QT interval after correction with Bazett's formula* [13]

	1-15 years (ms)	Adult males (ms)	Adult females (ms)
Normal	<440	<430	<450
Borderline	440-460	430-450	450-470
Prolonged (top 1%)	>460	>450	>470

*Can be unreliable at HR<50 bpm (undercorrect) or > 90 bpm (overcorrect)

Torsade de Pointes

Excessive QT prolongation can predispose patients to develop TdP [13]. A QTc >500 ms is associated with increased risk of TdP [12]. TdP is a form of polymorphic ventricular tachycardia and typically has a rate between 160 and 250 beats per minutes. TdP is usually short-lived and typically terminates spontaneously. Episodes of TdP can recur in rapid succession, potentially degenerating to ventricular fibrillation and sudden cardiac death [14].

The risk factors for TdP with QT prolonging drugs include [15]:

- Female sex
- Advanced age
- Recent conversion from atrial fibrillation with QT prolonging drugs
- Concurrent use of more than one drug that can prolong QT interval

- Electrolyte disturbance (hypokalaemia, hypomagnesemia and hypocalcaemia).
- Use of diuretics
- Hepatic and renal dysfunction
- Bradycardia
- Occult congenital long QT syndrome (LQTS) or silent mutations in LQTS genes
- Ion-channel polymorphism
- Underlying heart disease such as heart failure, left ventricular hypertrophy and myocardial infarction
- Baseline QT prolongation
- Rapid rate of intravenous infusion with a QT prolonging drug
- High drug concentration (except quinidine)
- Digitalis therapy.

Drug-induced QT prolongation and TdP

Medicines are a common cause of acquired QT prolongation. Most are thought to inhibit the flow of potassium out of the muscle cells of the heart in the repolarisation of cardiomyocytes (this current is known as IKr) [9]. Blocking IKr leads to a reduced potassium efflux or an excess sodium influx. This excess of positively charged ions causes an extended repolarisation phase, resulting in a prolonged QT interval and causing arrhythmias such as TdP [16]. IKr goes through the hERG protein channel, also known as Kv11.1 [9].

Other drug-induced mechanisms of QT prolongation include a drug-drug interaction whereby the plasma levels of the medicine known to prolong the QT interval is increased [17], using additional QT-prolonging medicines, and using medicines that can cause electrolyte imbalance [18].

Specifically, for the AChEI class, activation of cardiac acetylcholine receptors results in opening of voltage-gated calcium channels. This will increase the level of intracellular calcium leading to prolongation of phase 2 of the cardiac action potential cycle, hence increasing risk of ventricular arrhythmias [9, 19].

Table 3 provides a summary of the potential mechanisms of QTc prolongation/TdP from AChEIs

Table 3: Summary of mechanisms of QT_c prolongation and TdP malignant by AChEI (adapted from Huang et al 2020 [9])

	Donepezil	Galantamine	Rivastigmine
Common mechanisms of QTc prolongation and TdP	Increased intracellular calcium as a result of cardiac ACh receptor action. Bradycardia-associated QTC prolongation. Drug-drug interaction due to metabolism by CYP3A4 and 2D6 (donepezil and galantamine only). Increases spatial dispersion of repolarisation (donepezil and galantamine only).		
Unique mechanisms of QTc prolongation and TdP	Potent inhibitor of IKr (tail current inhibited at IC50 of 1.3 µM with metabolites inhibiting at similar IC50); concentration of donepezil during regular and prolonged use may reach IC50. Inhibits the KV11.1 channel protein expression and channel protein trafficking to the plasma membrane. σ1 receptor agonist at therapeutic doses.	Weak inhibitor of IKr (IC50 of 760.2 µM). No studies found regarding other effects, such as KV11.1 channel protein expression and trafficking.	No relevant drug-drug interactions. No studies found regarding inhibition of IKr or other effects on KV11.1 channel protein. Does not increase spatial dispersion of repolarisation.

CredibleMeds – categorising a medicine's risk for TdP

CredibleMeds.org is an online resource that categorises medicines into three categories for risk of developing TdP. The risks are defined as follows [20]:

- 'Risk' of TdP: Substantial evidence supports the conclusion that these drugs prolong QT intervals and have a risk of TdP when used as directed in labelling.
- 'Possible' risk of TdP: Substantial evidence supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in labelling, have a risk of causing TdP.
- 'Conditional' risk of TdP: Substantial evidence supports the conclusion that these drugs prolong QT and have a risk of developing TdP but only under certain known conditions (eg, excessive dose or overdose, or being the index or interacting agent in a drug-drug interaction).

The required and supporting evidence that must be positive in order for a drug to be placed in one of the three risk categories are shown in Figure 2.

Figure 2: Required and supporting of evidence used classify a medicine as having a known, possible or conditional risk of TdP in the CredibleMeds database [20]

Donepezil is categorised as having a 'known' risk of TdP.

Galantamine is categorised as having a 'conditional' risk of TdP, with the following conditions: bradycardia, low serum potassium, excessive dose, use with concomitant QT/TdP medicine.

Rivastigmine has not been classified. CredibleMeds states that the evidence available at this time did not result in a decision for it to be placed in any of the TdP risk categories. This is not an indication that this drug is free of a risk of QT prolongation or TdP since it may not have been adequately tested for these risks in patients.

Comment:

Despite the three medicines falling under the same drug class, Credible Meds have classified each AChEIs with different risk categories. The differences reflect the level of available evidence.

It is not known when the risk categories for the above medicines were last reviewed, however the last revision of the database was on 26 June 2023.

2.6 Usage

Number of people dispensed a funded AChEI from 2017 to 2021 is outlined in Table 4. Note there is no usage data for galantamine or rivastigmine capsules and 13.3mg/4 hour patches as these products are not funded.

Table 4:

AChEI	2017	2018	2019	2020	2021
Donepezil	8,014	8,138	8,343	8,361	8,658
Rivastigmine	478	495	550	574	647

Source: Pharmaceutical Data web tool, Te Whatu Ora https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 24 July 2023)

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature review was conducted on the risk of QT prolongation and TdP with donepezil, rivastigmine and galantamine. A summary of the literature is provided under the following headings: 'acetylcholinesterase inhibitors' as a class, 'donepezil', 'rivastigmine' and 'galantamine'.

Studies are presented first, followed by case reports.

3.1.1 Acetylcholinesterase inhibitor as a class

3.1.1.1 Malone et al (2020), QT interval prolongation and Torsades de Pointes with donepezil, rivastigmine and galantamine [21]

Aim: To evaluate the evidence in the literature on case reports that link TdP and QTc interval with donepezil, rivastigmine and galantamine.

Methods: A literature review was conducted using PubMed on AChEIs and QT prolongation. Each paper was screened for relevance which yielded 13 case reports (in 12 articles) up to October 2019. The causality of the cases was evaluated using both the Naranjo scale and the World Health Organization (WHO) Uppsala Monitoring Centre (UMC) causality assessment.

QT interval prolongation in the identified case reports was also analysed using a QT nomogram where a plotted QT-RR (or heart rate) values above the nomogram line is considered to represent an abnormally long QT interval and at risk of TdP.

Results: Two case reports were identified for galantamine, one report for rivastigmine (Table 5) and ten for donepezil (Table 6).

Review of the cases showed patients were predominately female. All cases had at least two modifiable risk factors for TdP such as electrolyte disturbances, bradycardia or concomitant use of QT prolonging medicine. Non-modifiable risk factors included cases generally having advanced age and other co-morbidities. There was a case of QTc prolongation occurring with a young adult taking donepezil, indicating the risk can occur in younger patients.

Hypokalaemia was not a common feature of the cases, with borderline hypokalaemia in one rivastigmine case, and one case with donepezil.

Some cases involved a recent dose increase or sudden re-administration of AChEI following a break.

The Naranjo scale classified six cases as probable and four cases as possible. The WHO UMC criteria classified two cases as certain, four cases as probable/ likely and four cases as possible.

Table 5: Summary of case reports with galantamine and rivastigmine

[redacted]

Table 6: Summary of case reports with donepezil

[redacted]

Figure 3 shows a QT nomogram with plots from case reports. Because the correction formula for QTc was not specified in most reports, these were converted to the uncorrected QT interval using Bazett's formula (Panel A) and Fridericia's formula (Panel B). Irrespective of the formula used, five donepezil cases lay clearly above the

nomogram line, consistent with a QT-prolonging effect of the drug. Although the cases for rivastigmine and galantamine lay very close on the nomogram line, conclusions from the data cannot be drawn as there were very few cases.

Figure 3: QT interval nomogram using (A) Bazett's formula and (B) Fridericia's formula. The figure contains plots of uncorrected QT intervals against corresponding heart rate for donepezil, galantamine and rivastigmine. With this nomogram, points plotted above the line indicate QT interval prolongation.

Conclusions: Analysis of case reports showed a strong association between donepezil and QTc prolongation and risk of TdP. Attention to risk factors for QTc prolongation/TdP should be exercised when prescribing donepezil and modifiable risk factors corrected. Case reports from galantamine and rivastigmine are sparse, making it difficult to make definitive conclusions.

3.1.2 Donepezil

3.1.2.1 Kho et al (2021), Long term use of donepezil and QTc prolongation [22]

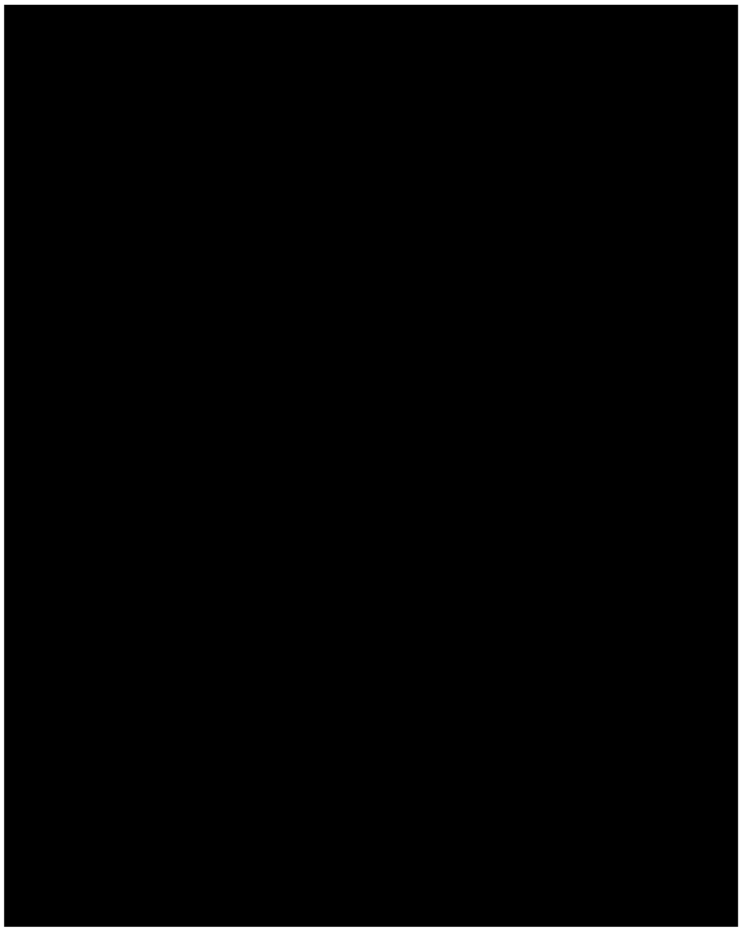
Background and aims: The neurocognitive benefits of donepezil are well recognised, but the potential side effects on cardiac conduction remains unclear. This study investigated whether long-term donepezil therapy is associated with ECG changes and in particular to assess its effect on the QT interval.

Methods: A retrospective analysis of all acute admissions of patients on donepezil treatment was conducted in a UK hospital between March 2019 to March 2020. An admission ECG was obtained and compared to the patient's ECG prior to commencement of donepezil therapy. Patients were excluded if they had recently started on donepezil (<6 months), had electrolyte disturbances, deranged thyroid function on admission, paced rhythm on ECG, or had no ECG record before commencement of donepezil. All data were collected from the local hospital electronic care record and memory-based clinic database.

Wilcoxon signed rank test was used to compare the mean ECG parameters while the Mann-Whitney U test was used to compare the changes in ECG parameters between gender and donepezil doses. Point-biserial correlations (r_{pb}) was performed to assess whether cardiac comorbidities and concurrent use of medicines alongside donepezil were associated with changes in ECG parameters. The Kruskal Wallis test was used to evaluate whether any changes in ECG parameters were associated with duration of donepezil treatment. Statistical significance was defined as a p-value <0.05.

Results: 59 patients were included in this study. The baseline demographics and characteristics are outlined in Table 7.

Table 7: Patient demographics and characteristics



Analysis of a resting ECG prior to commencing donepezil treatment was compared to the ECG obtained during the patient's most recent acute hospital admission. There was significant prolongation of the PR, QRS and QT intervals (Table 8). The QT corrected using Bazett, Fredericia, Framingham and Hodges formulae were also compared, which all confirmed significant QTc prolongation following donepezil therapy.

Table 8: Comparison of ECG parameters before donepezil treatment and on admission to hospital

Analysis using a QT nomogram revealed that 8 (13.6%) patients (3 male and 5 female) went from low arrhythmogenic risk to high while on donepezil therapy (Figure 4). No significant change in mean HR was observed.

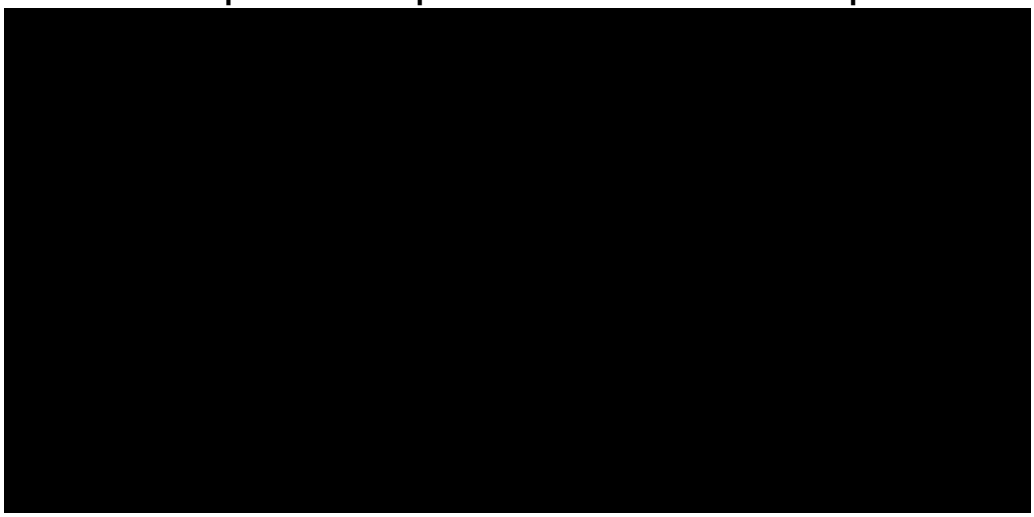
Figure 4: Comparison of QT nomogram plots before (A) and after (B) the initiation of donepezil

Analysis by gender showed that men experienced a significantly greater increase in their corrected QT intervals compared to women with donepezil treatment (Table 9).

Table 9: Comparison of ECG parameters by gender

There were no significant differences in all ECG parameters when comparing donepezil doses (Table 10). Although there was a significant difference in QT interval between the different treatment duration groups, no significant difference was found once QT intervals were corrected. Duration of donepezil therapy did not affect the HR, PR interval or QRS interval.

Table 10: Comparison of ECG parameters based on dose of donepezil



Point-biserial correlation found that concomitant use of rate-limiting calcium channel blockers was associated with significant PR prolongation (point biserial correlation, r_{pb} = 0.314, p=0.030), while beta-blockers in combination with donepezil were found to significantly reduce the HR (r_{pb} =0.256, p=0.050). All QTc intervals whilst on donepezil were significantly prolonged by the use of tricyclic antidepressants (QTcB: r_{pb} = 0.344, p=0.008, QTcFred: r_{pb} = 0.382, p=0.003, QTcFram: r_{pb} = 0.379, p=0.003, QTcH: r_{pb} = 0.352, p=0.006). There was no significant correlation between cardiac comorbidities and changes in ECG parameters.

Conclusions: Use of donepezil significantly prolonged the PR, QRS and QT intervals. Men had a significantly greater prolongation of their QTc interval compared to women, and concomitant use of tricyclic antidepressants significantly increased the risk of QT interval prolongation, while no dose or treatment duration related differences with donepezil were found. Caution should be exercised when prescribing donepezil, particularly in patients with pre-existing factors known to cause QT prolongation. ECG should be measured before and after initiation of donepezil therapy.

Previous studies have evaluated ECG changes in patients taking donepezil for up to four months with no associated change in the QT interval. The authors postulate that a longer duration may be necessary to demonstrate a significant QT interval prolongation such as in their study.

Discussion on limitations: ECGs were taken before and during donepezil treatment in one point in time and may not reflect their predominant rhythm. The ECGs were also taken when patients were admitted to hospital with conditions where their QT could be prolonged, such as an infection.

It is interesting to note that men had significantly greater QT prolongation compared to women whilst on donepezil treatment. Generally, women are more susceptible to QT prolongation however, this difference decreases with age due to men having a more pronounced age-related increase in their QT interval.

Comments:
This study was conducted in a single UK hospital with predominately Caucasian population which may limit the generalisability of the results to New Zealand.

3.1.2.2 Kuwahata S et al (2021), Effect of QT prolongation in patients taking cholinesterase inhibitors (donepezil) for Alzheimer's disease [23]

Aims: The aim of this cross-sectional study in Japan was to determine whether donepezil is associated with QTc prolongation and how many patients have QTc prolongation. In addition, the authors aimed to examine whether QTc prolongation could be predicted.

Methods: Fifty-seven consecutive outpatients over 65 years of age with AD and treated with donepezil, who had a regular screening at a Japanese hospital were selected as cases. Cases were age and sex matched with 57 outpatients who also visited the same hospital during the same period for internal therapy without donepezil. Both cases and controls had undergone ECG exams. Patients in the control group were not necessarily diagnosed with AD.

Exclusion criteria for both groups included the presence of atrial fibrillation, a history of cardiac surgery, and renal failure requiring haemodialysis. Patients taking antiarrhythmic medicines, antibiotics, and first-generation antihistamines that affect QT prolongation were also excluded in both groups. Patients with comorbidities such as chronic heart failure, previous myocardial infarction, hypertrophic cardiomyopathy, dilated cardiomyopathy, hypertensive heart disease, diabetes, and hypothyroidism were included in both groups.

The physical findings, laboratory data and ECG parameters were compared between cases and control. A univariate and multivariate linear regression analysis was used to determine if certain parameters (eg, age, sex, obesity, QT prolonging medicines, electrolyte disturbances and renal function) affected the QTc interval.

Results: Patient characteristics are outlined in Table 11. There were no statistically significant differences between donepezil group and controls expect for serum calcium, which was higher in the controls. The adjusted serum calcium was not significantly different. Overall, the patient characteristics appear to be balanced between the two groups.

Table 11: Patient characteristics of cases and controls

[redacted]

There were no significant differences between the two groups with respect to heart rate, PR or QRS interval, however the QTc duration was significantly prolonged in the donepezil group compared to controls (Table 12).

Table 12: ECG parameters in the donepezil and control groups

[redacted]

There was a significantly higher percentage of patients with QTc prolongation in the donepezil group compared to control (30%, n=17 vs. 9%, n=5; odds ratio 4.42, 95% CI 1.50–13.0, p<0.004).

Eighty-nine percent of patients in the donepezil group were on 5 mg per day, with a mean duration of treatment of 528±376 days. In 46 of the 57 patients in the donepezil group where ECG records were available before therapy, the QTc interval was significantly prolonged after therapy. The mean QTc before and after therapy was 433±34 ms and 442±33 ms respectively (p=0.014).

The results of univariate and multivariate linear regression analyses for QTc prolongation are given in Table 13. On univariate analysis, taking donepezil, haemoglobin levels, serum calcium levels and eGFR were significantly associated with QTc prolongation. On multivariate analysis, taking donepezil, serum potassium levels and eGFR were significantly associated with QTc.

Table 13: Regression analysis for QTc prolongation based certain parameters

[redacted]

Conclusions: The incidence of QTc prolongation was higher in patients taking donepezil compared to those who did not. In patients taking donepezil, the QTc interval was also significantly prolonged compared to baseline measurements. This suggest that patients taking donepezil should undergo periodic ECG examinations considering the possibility of adverse effects with donepezil. Risk factors for QTc prolongation were difficult to predict.

Comments:

There were several limitations to this study. The study population was small which may have resulted in insufficient statistical power to demonstrate a relationship between QTc and certain parameters. In addition, the retrospective nature of this study meant that not all laboratory and ECG records were available in the two groups. Finally, although the baseline characteristics in cases and control were generally balanced, the control group were not necessarily diagnosed with AD.

3.1.2.3 Jia et al (2020), Safety and efficacy of donepezil 10mg/day in patients with mild to moderate Alzheimer's disease [24]

Background and aim: As AD progresses, there is a decrease in the number of acetylcholinergic cells that leads to a weaker treatment response to AChEI therapy. It has been demonstrated that higher-dose donepezil could improve cognition in patients with diminished response to donepezil 5 mg/day treatment. This Chinese study aimed to conduct a single-arm, prospective, multi-centre clinical trial looking at the safety of donepezil 10 mg/day in patients with mild-to-moderate AD.

Methods: A 20-week, single-arm, prospective, multi-centre study was conducted at 16 sites in China. Patients were between 50 to 85 years of age with a diagnosis of AD. Patients were included if they were taking donepezil 5 mg daily for at least four weeks before screening. Patients were excluded if they had certain medical conditions, including severe cardiac insufficiency (congestive heart failure, myocardial infarction, sick sinus syndrome, II-III degree atrioventricular block or a heart rate less than 50 bpm).

All patients received donepezil 10mg per day, however the dose could be reduced for four weeks then increased back to 10mg per day. If this was still not tolerated, the patient would have deemed to have quit the study.

The primary endpoint for the present study was the incidence of adverse events evaluated by physical examinations such as vital signs, weight, clinical laboratory tests, and ECG during the 20 weeks. Patients were examined at baseline, week 4 and week 20.

Results: 241 patients were included in the study. The majority of patients were women (55.6%) and aged between 75 to 85 years (45.64%). 16.18% (n=39) had past cardiovascular diseases and 9.13% (n=22) were taking a cardiovascular medicine. At baseline, the mean QTc interval was 419±29.9 ms and a mean heart rate of 72.35±9.49 bpm.

There were small changes in the heart rate, QT and QTc interval during the 20-week study compared to baseline (Table 14). There was a statistically significant drop in the heart rate at week 4 and 20 compared to baseline ($p<0.01$). No significant QTc prolongation was found at the end of the study (–0.66±19.66 ms, $p=0.6561$), although it was significantly shortened at week 4 (–3.91±18.68 ms, $p<0.005$).

[redacted]

One and three cases of clinically significant QTc prolongation (QTc extended to more than 500 ms or >60 ms prolongation from baseline) occurred at weeks 4 and 20, respectively. Of these, 2 cases were from one patient whose QTc was 505 ms at baseline. A case of mild QTc prolongation was judged to be related to donepezil, however they had a complete right bundle branch block at baseline.

Conclusions: Although there was a statistically significant decrease in heart rate at week 4 and 2, the magnitude of this was small. Only one patient was deemed to have developed QT prolongation related to donepezil treatment but had a complete right bundle branch block at baseline. Overall, donepezil 10 mg/day can be tolerated in Chinese patients with mild-to moderate AD and therefore can be used to treat patients when their treatment response to lower dose donepezil diminishes.

Discussion on limitations: Only 93 out of the 241 patients completed the 20-week study. The reasons for the withdrawal were not given but the authors postulate that this could be due to the time and effort required to participate in the study. As this was a single-arm study, the authors could not compare the safety and tolerability of 5 mg vs 10 mg donepezil.

Comments:

Baseline in this study was at least 4 weeks of donepezil treatment at 5 mg per day. This study compared a lower and higher dose of donepezil and effects of ECG parameters, rather than before they started any donepezil therapy. In addition, this study was done in Chinese patients, so the applicability of the study results to the general New Zealand population is unclear.

3.1.2.4 Wang et al (2018), Electrocardiogram changes of donepezil administration in elderly patients with ischaemic heart disease [25]

Aim: To examine the effects of donepezil on ECG parameters including HR, QT interval, QTc, QT interval dispersion (QTd, defined as the difference between the minimum and maximum QT interval), and $T_{peak-end}$ interval, which are associated with the risk of bradycardia and TdP.

Methods: Patients in this Chinese study were included if they were 65 years and older with established coronary artery disease and mild cognitive impairment. Patients were excluded if they had been taking AChEIs in the past three months, have atrial fibrillation, acute myocardial infarction or acute coronary syndrome in the past three months or currently have bradycardia, pacemakers or using anti-arrhythmic medicines.

Patient's laboratory measurements (for plasma glucose, potassium, magnesium and calcium) and ECG were measured prior to commencing donepezil 5 mg per day continuously for at least four weeks. ECG was taken during the four week follow-up if a patient complained of syncope, palpitation, fatigue, or weakness.

Results: Sixty patients were enrolled. The mean age was 75.7±5.8 years. Baseline blood pressure and heart rate of all individuals were reported as normal. The mean follow-up period following initiation of donepezil was 35.1±4.6 days of which syncope, palpitation, fatigue or weakness was not reported.

Comparison of ECG parameters at baseline and four weeks after donepezil is outlined in Table 15. The mean heart rate significantly reduced, and PR interval significantly increased following four weeks of donepezil treatment ($p<0.05$). There were no statically significant differences in the QT, QTc, QTd, QRS intervals.

Table 15:ECG parameters comparison from baseline to four weeks of donepezil therapy

[redacted]

Conclusions: In elderly Chinese patients with ischaemic heart disease, donepezil caused mild decrease in heart rate and prolongation of the PR interval without affecting QRS and QT interval. This suggest that donepezil can be used safely in this population.

Discussion on limitations: This study involved a small study size, followed up for a relatively short period of time. Rarer cardiovascular events or longer-term effects on ECG cannot be concluded from this study. The selected subjects in this study were mainly patients with ischaemic heart disease and mild cognitive impairment.

Comments:
Participants were included if they had mild cognitive impairment rather than patients with a diagnosis of AD. The symptoms of mild cognitive impairment are not as severe as AD, however it is unclear whether this would impact the QTc interval.

3.1.2.5 Igeta et al (2014), Cardiovascular pharmacodynamics of donepezil hydrochloride on the PR and QT intervals in patients with dementia [26]

Aim: To determine the impact of donepezil on RR, PR and QT intervals.

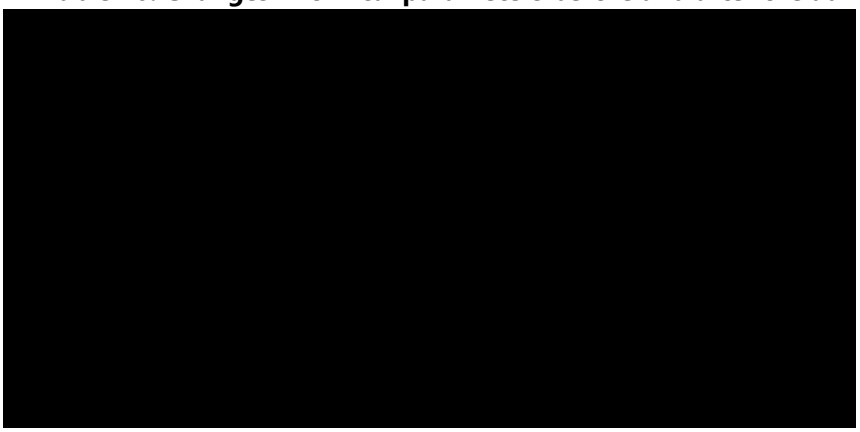
Methods: Eighteen patients in Japan were diagnosed with dementia, hospitalised and treated with donepezil. Every patient's age, body mass index, diagnosis, blood chemistry test, and ECG were retrieved from medical

records. The QT interval was corrected using the Bazett's formula. Paired t-tests were used to compare all parameters before and after the administration of donepezil.

Results: This study was carried out over a period averaging 16.6 weeks. At baseline, participants had a mean age of 74.1±7.8 years, 8 were female and 10 male, and 7 participants were diagnosed with AD, 5 with Lewis bodies and the rest with other types of dementia.

The mean laboratory and ECG tests before and after donepezil administration is outlined in Table 16. There were no statistically significant differences in the mean QTc interval before and after donepezil treatment (433.6 ±23.0 ms vs 433.2 ± 31.0 ms). There was a statistically significant increase in the mean PR and RR interval following donepezil administration.

Table 16: Changes in clinical parameters before and after the administration of donepezil



Conclusions: Donepezil did not affect the QT interval. However, care should be taken when administering donepezil to patients with atrioventricular block, or patients orally taking other drugs that can prolong the PR interval.

Comments:

This study was carried out looking at medical records retrospectively in a very small group of patients. Any missing data and how this was handled were not discussed. Other important comorbidities and concomitant medicines were not collected so it unclear whether this sample population had generally good cardiovascular health or represents the general characteristics of people with AD.

The methodology did not specify how these patients were selected.

3.1.2.6 Isik et al (2012), Cardiac safety of donepezil in elderly patients with Alzheimer Disease [27]

Background and aim: This study in elderly patients with AD examined the adverse effects of donepezil on the cardiac rhythm and postural blood pressure changes.

Methods: Seventy-one patients, newly diagnosed with AD were enrolled. Patients who were initially treated with cardio-stimulatory medicines or with pacemakers were excluded from the study.

Patients were treated with a flexible 4-weekly donepezil dosage titration regimen up to 10 mg per day. ECG parameters and blood pressure measurements were recorded at baseline and 4-weeks after each dose titration was given. The ECG parameters, including heart rate, PR, Q, QTc (using Bazett's method) and QRS duration were recorded.

Results: Of the 72 patients enrolled, 52 completed the study- 25 men and 27 women. The average age of participants was 74.9 ±6.4 years. 73% of participants had hypertension and 40.3% had coronary artery disease.

No statistically significant changes were observed in any of the ECG parameters from baseline and after treatment of donepezil at each dose (Table 17). Data for dropouts were not included in the results, however

the authors state that the mean values of all available data for the dropouts were similar to those who continued.

Table 17: ECG parameters at each donepezil dosage titration and comparisons)*

The arterial blood pressure remained unchanged at each dose compared to baseline.

Conclusions: This study demonstrated that at each dose of donepezil, no significant changes in ECG parameters and arterial blood pressure were observed in elderly patients with AD.

Discussion on limitations: The small sample size and short duration of 2 months may not be enough to detect any significant changes.

3.1.2.7 Jackson et al (2019), Lesson of the month 1: Prolonged QT syndrome due to donepezil: a reversible cause of falls? [28]

Case report

An 83-year old Caucasian female presented to the Emergency Department following a syncope episode. Her past medical history included early AD, hypertension and recurrent falls. She was taking bendroflumethiazide, simvastatin and donepezil 10 mg per day.

On admission, her ECG demonstrated normal sinus rhythm with a prolonged QTc of 638 ms. Her blood tests, including electrolytes were normal. Given her history of syncope without prodromal symptoms, it was suspected that the patient had fallen as a result of cardiogenic syncope relating to prolonged QT syndrome.

Donepezil was withdrawn as the potentially causative medicine. ECG measured by day 10 showed that the QTc interval returned to normal (436 ms).

Comments:
Patients living with AD have an increased risk of falls as this can be related to impaired gate, balance or orthostatic hypotension. It is not clear whether the fall was related to donepezil or AD. There is no information on baseline ECG measurement that could tell us whether donepezil caused QT prolongation. In addition, there is no case detail on how long the person had been on donepezil or how recent her dose increased to 10 mg per day. However, a positive dechallenge with donepezil may suggest that it was implicated in the reaction.

3.1.2.8 Yasuyuki et al (2013), Donepezil-induced torsades de pointes without QT prolongation [29]

Case report

An 86-year-old female who had been taking donepezil 5 mg per day for three years for AD was admitted to hospital because of syncope.

The patient had no history nor family history of cardiovascular disease or previous syncope episodes. She also had hypertension which was treated with amlodipine and her blood pressure was 124/60 mmHg on admission.

Initial 12-lead ECG showed atrial fibrillation and with a normal QTc interval (QT= 390 ms; QTc= 436 ms) (Figure 5, panel A). She had not undergone 12-lead ECG before donepezil treatment. Her potassium, magnesium, calcium, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen and creatinine were within normal limits.

Following admission, her blood pressure dropped to 98/58 mmHg and amlodipine was stopped. At midnight, her atrial fibrillation spontaneously recovered to normal sinus rhythm. Several hours later, in the daytime, TdP was detected for 10 seconds and terminated spontaneously without intervention. A repeat ECG showed normal sinus rhythm and normal QTc interval (QT 380 ms; QTc 433 ms) (Figure 5, panel B)

Lignocaine was given and donepezil was discontinued. Serum donepezil levels were not measured. After washout of donepezil, TdP was not observed again. QTc interval was normal throughout the remainder of her stay.

In the serial ECG follow up on day 16, QTc interval was normal with a normal sinus rhythm (Figure 5, panel C). She was discharged in a stable condition without administration of donepezil.

Figure 5: Changes in 12-lead ECG. (A) Admission, (B) just after the documentation of TdP on the second day, and (C) the day before discharge

Discussion of case: This patient had multiple risk factors for TdP: increasing age, female sex and paroxysmal atrial fibrillation. The patient's QTc interval was normal throughout hospitalisation. Although the patient's donepezil plasma level was not measured, no TdP was observed following donepezil washout. The authors concluded that TdP in her case may have been induced by donepezil without QTc prolongation. Although the risk of TdP increases with increasing length of the QTc interval, the relationship is not linear. This case report highlights that even if the QTc interval is normal in patients taking donepezil, ECG is recommended when experiencing symptoms associated with TdP.

3.1.2.9 Kitt et al (2015), A case of donepezil-related torsades de pointes [30]

Case report

An 80-year-old female was admitted to hospital with a 2-day history of anorexia and diarrhoea. The patient had a history of cerebrovascular disease with mixed vascular and Alzheimer dementia, atrial fibrillation with prior permanent pacemaker implantation for slow ventricular response, and hypertension.

Her donepezil increased from 5 to 10 mg two weeks prior to hospitalisation. No ECG was performed prior to the increased dose.

The patient's serum sodium, potassium, and adjusted calcium levels were normal.

Her blood pressure was 148/82 mmHg, and heart rate was 85 bpm. ECG showed QTc prolongation of 490 ms, with underlying paced rhythm.

The patient was treated with intravenous fluids and donepezil was reduced to 5 mg per day. 24-hours after admission, she became unresponsive, and an ECG demonstrated TdP. The patient was resuscitated successfully. Post-arrest, her serum electrolyte levels were within normal range but her QTc remained prolonged at 550 ms.

A diagnosis of TdP due to QTc prolongation, following an increase in the dose of donepezil, was made. The timing of this event occurring two weeks after an increase in the dose of donepezil suggests a potential role. Subsequent ECG prior showed normalisation of QTc interval to 431 ms.

3.1.2.10 Poumand et al (2017), Cholinergic symptoms and QTc prolongation following donepezil overdose [31]

Case report

An 84-year old male with a past medical history of AD, hypertension, stroke and benign prostatic hypertrophy inadvertently ingested 35 mg of donepezil. Six to seven hours later he arrived in hospital with gastrointestinal symptoms, fatigue and excessive sweating. His heart rate was 50 bpm and blood pressure 131/58 mmHg. His ECG showed sinus rhythm at 70 bpm with premature atrial contractions and QTc prolongation of 502 ms. The patient had no prior history of QTc prolongation nor was on medicines known to cause QT prolongation.

The patient’s received intravenous fluids and atropine, and his daily donepezil dose was withheld. During his time in hospital, the QTc interval decreased to normal range and bradycardia was corrected.

Comments:
This case did not state whether the patient’s serum potassium and calcium levels were taken. This is important to determine if there were other underlying factors for the QTc interval prolongation.

3.1.2.11 Gurbuz AS et al (2015), Acquired long QT syndrome and Torsades de Pointes related to donepezil use in patients with Alzheimer disease [32]

Case report

This case report describes a woman experiencing QT prolongation in association with donepezil on two separate occasions. In both cases, she was symptom free when donepezil was stopped.

Three years prior to her current hospital admission, she presented to hospital with chest pain and syncope. At the time, she had been taking donepezil for a year. An electrophysiology study was performed to determine whether the syncope was related to arrhythmia. The results confirmed prolonged QRS and QT interval and normal sinus and atrioventricular node functions. Three days after stopping donepezil her QT and QTc shortened to 440 and 450 ms respectively. Discharge on day seven showed normal QTc interval. She was cautioned not to use donepezil but was re-prescribed two years later after worsening of AD symptoms.

Her second admission to hospital was at the age of 84-years due to recurrent episodes of syncope for two days. Her blood pressure was 160/100 mmHg, heart rate was 65 bpm. Her ECG showed atrial fibrillation and the QTc interval was 624 ms (using Bazett’s formula). Renal function, cardiac biomarkers and electrolytes were normal.

This patient had no history of antiarrhythmic drug use or family history of long QT syndrome or sudden cardiac death. Her regular medicines included donepezil 10 mg for AD, ramipril 5 mg for hypertension and aspirin 100 mg for coronary artery disease.

During follow-up, a sudden TdP episode occurred. The rhythm spontaneously returned to her previous rhythm of atrial fibrillation. Donepezil was stopped and on day four and her average heart rate was 60 bpm and QTc interval 500 ms. On day ten her heart rate was 70 bpm and QTc 430 ms.

As the patient did not have bradycardia or further TdP following this, she was discharged without donepezil. At one year follow-up, she did not have complaints of palpitation and syncope and her QTc was within normal range.

The Naranjo probability scale confirmed that donepezil was the probable cause of QT prolongation, TdP and syncope in this patient. However congenital causes of QT prolongation could not be ruled out as genetic testing was not available.

3.1.2.12 Takaya et al (2009), Torsade de Pointes wit QT prolongation related to donepezil use [33]

Case report

An 83-year old woman with repeated diarrhoea and vomiting in the morning, later developed syncope and was admitted to hospital. Her heart rate was 54 bpm with regular heart rhythm. Her plasma potassium level was low (3.3 mEq/L). ECG demonstrated QTc prolongation of 645 ms.

The patient had a history of AD, treated with donepezil 5 mg per day for the past two years, hypertension treated with bisoprolol, diabetes, paroxysmal atrial fibrillation and a history of anterior myocardial infarction.

Following admission, all medicines were discontinued and hypovolaemia and electrolyte disturbances corrected. The authors reported that hypokalaemia was difficult to correct because of her frequent watery stools. TdP was detected five hours later for 35 seconds, and magnesium sulphate and lignocaine were given. A second TdP with transient convulsion and syncope was detected another five hours later.

After washout of donepezil, the patient's dementia did not worsen. Her QTc interval gradually decreased and on day 14, her QTc interval was 485 ms.

The authors state that the plasma half-life of donepezil is 70-100 hours, and therefore the TdP that occurred following withdrawal of donepezil could be due to the medicine still being in her system. Bradycardia or TdP were not detected after the washout period donepezil.

3.1.2.13 Tanaka et al (2009), Donepezil-induced adverse side effects of cardiac rhythm: 2 cases report of atrioventricular block and Torsade de Pointes [34]

Case series

Case 1: A 90-year-old male presented with bradycardia. His ECG showed advanced atrioventricular block and complete right-bundle block. QT and QTc prolongation were observed (514 ms and 538 ms respectively). The patient's blood pressure was 158/49 mmHg with a heart rate of 36 bpm. Laboratory tests were unremarkable. He had no previous cardiovascular disease or syncope.

The patient had been treated with donepezil 5 mg daily for many years. Three days prior to his bradycardia, his dose of donepezil was increased to 10mg daily.

The patient's donepezil was withdrawn and a medicine with beta stimulating effect (orciprenaline) was given for 5 days. The following day, his ECG showed sinus rhythm, but the first degree atrioventricular block (PQ 220 ms) and QT prolongation (QT 536 ms; QTc 538 ms) remained. ECG on the fifth day showed that the QT interval was shortened to QT 450 ms and QTc 456 ms. The patient did not have significant arrhythmia occurrence thereafter for 2 months.

Case 2: A 87-year-old woman, with a long-term history of hypertension, chronic atrial fibrillation and AD, was diagnosed to have bradycardia (heart rate 40 bpm). Her ECG showed atrial fibrillation and negative T-waves in leads V1-2 and bi-phasic T-waves in leads V3-6 with QT prolongation (QT of 570 ms and QTc of 461 ms).

She had a history of hypertension, chronic atrial fibrillation and AD. She was on regular amlodipine, spironolactone, warfarin and donepezil 5 mg daily.

A month following the event, she had a sudden fall due to transient syncope. Her blood pressure was 115/63 mmHg, heart rate 40 bpm and laboratory tests were unremarkable. Her ECG showed QT prolongation (QT of 720 ms and QTc of 594 ms) and she later developed TdP.

Donepezil was discontinued on day 5. Her heart rate then increased to 55 bpm and no adverse ventricular arrythmia was seen. On day 18, her QT shortened 490 ms (QTc 446ms).

Discussion of cases: In both cases, bradycardia an QT and QTc prolongation resolved following donepezil discontinuation. However, ECG was not measured at baseline prior to donepezil therapy.

The authors concluded that the observed changes were caused by donepezil. There is also the possibility that donepezil worsened potential conduction disturbances of the heart, because of the patients old ages.

3.1.2.14 Vogel et al (2019), Donepezil-induced QTc prolongation: A case report [35]

Case report

A 26-year old female was admitted to an inpatient psychiatric hospital after a suicide attempt. She had a complex medical history that included major depressive disorder, traumatic brain injury, seizures, and tachycardia.

She initially continued her previous outpatient medicines which included quetiapine, divalproex sodium, metoprolol and montelukast, polyethylene glycol, pantoprazole, cephalexin and vitamin D with calcium. Two baseline ECGs were taken showing a QTc of 425 ms and 438 ms respectively. She was noted to be in sinus tachycardia with a heart rate of 112 bpm.

Changes to her medicine therapy and ECG monitoring were made during 96 days in hospital. Of note on admission, she had normal QTc on ECG. The dose of quetiapine was significantly reduced during her time in hospital and donepezil was initiated for cognitive rehabilitation due to traumatic brain injury which was titrated to 10 mg twice daily. Her QTc interval increased following the titration and normalised following donepezil withdrawal.

Discussion of case: Donepezil, pantoprazole and quetiapine are known to potentially contribute to QTc prolongation. QTc prolongation with quetiapine is minimal when used within recommended therapeutic doses.

Following rapid titration of donepezil to a total daily dose of 20 mg (without documented gastrointestinal side effects), QTc prolongation was found on ECG. Her QTc improved following a dose reduction of donepezil to 10 mg daily, and her QTc eventually normalised following discontinuation of donepezil.

The patient's QTc remained within normal range while taking quetiapine and pantoprazole.

The Naranjo Adverse Drug Reactions Probability Scale provides a score of 5, indicating this event is a probable adverse event resulting from donepezil use.

Comments:
The dose of donepezil administered in this case was beyond the recommend dose in the New Zealand donepezil data sheet. The maximum dose is 10 mg per day for the treatment of AD and vascular dementia.

3.1.3 Rivastigmine

3.1.3.1 Isik et al (2014), Which rivastigmine formula is better for heart in elderly patients with Alzheimer's disease: oral or patch? [36]

Background and aim: The aim of this study was to compare the ECG and hypotensive effects of transdermal and oral formulations of rivastigmine in elderly patients with AD.

Methods: The medical records of 212 elderly patients were retrospectively reviewed to identify newly diagnosed patients with AD (who had records of a comprehensive geriatric assessment and ECG measurements during rivastigmine therapy). Patients who were treated with cardio-stimulatory medicines or had a pacemaker were excluded.

Patients with AD were treated with a flexible 4 weekly rivastigmine dosage titration regimen up to an oral dose of 12 mg/day, or a 10 cm^2/day patch. The ECG parameters and blood pressure measurements were recorded at baseline and at 4 weeks after the administration. The heart rate, PR, QT and QTc interval (using Bazett's formula) and QRS duration were calculated. QTc prolongation was defined as a QTc interval > 450 ms.

Results: Eighty-five patients were identified (45 men and 40 women). Of those, 23 patients were taking oral rivastigmine and 62 patients were using transdermal rivastigmine.

Table 18 (top table) shows the patient demographics. Patients on oral rivastigmine were older than those on transdermal patch (81.7±6.6 years vs 76.7±8.2 years, p=0.01). Cardiovascular co-morbidities were numerically imbalanced between the two groups, however there was no statistically significant differences.

Table 18 (bottom table) shows the ECG parameters at baseline versus four weeks after starting oral or transdermal rivastigmine. When compared with the baseline, there were no changes in any of the ECG parameters in all patients (p>0.05). In addition, when compared with the mean change from baseline in each treatment group, there were no changes in any of the ECG parameters (p>0.05) except heart rate (p=0.035) where the mean change in heart rate from baseline was significantly lower in the rivastigmine patch-treated patients compared to oral-treated patients. This was not considered clinically important as only one patient had a heart rate lower than 50 bpm and that patient was asymptomatic.

Table 18: Demographics and other patient characteristics (top table) and ECG parameters before and after therapy (bottom table)

Conclusions: Transdermal and oral formulations of rivastigmine were not associated with increased arrhythmogenic or hypotensive effects in elderly patients with AD and were not superior to each other.

Discussion of limitations: The authors highlight the short-follow up time and small number of patients included in this study. Other limitations include the differences in the mean age of both groups.

3.1.3.2 Morganroth et al (2002), Electrocardiographic effects of rivastigmine [37]

Background and aims: The safety and tolerability of rivastigmine for the treatment of AD was evaluated in four 26-week, double-blind, placebo-controlled, phase III clinical trials. The aim of this study was to pool together those trials to determine if rivastigmine had any adverse cardiac effects.

Methods:

ECG analysis results were pooled and evaluated from the four clinical trials. Each trial used a prospective, randomised, double-blind, placebo-controlled, parallel-group design, and all assessed the same safety parameters at the same time points. Each trial had the same schedule of evaluations and used the same safety and efficacy measures (refer to Table 19 for detail of the trials).

The participants studied were ≥50 years of age with mild to moderately severe AD. Patients with co-existing diseases were included unless the disease was severe and/or unstable. Patients were excluded at screening or baseline if they had a clinically significant abnormality identified by physical examination, ECG, laboratory tests, or vital signs for their age that would place them at special risk. All concomitant medicines for co-existing diseases were allowed, except anticholinergic medicines, putative memory enhancers, ACh precursor health food supplements, insulin, psychotropic drugs (short-acting benzodiazepines and low-dose haloperidol were permissible in studies that took place in Europe).

Table 19: Designs of the rivastigmine Phase III randomised placebo-controlled studies

[redacted]

Standard 12-lead ECGs were performed during all studies. Starting at screening and baseline, ECGs were repeated at weeks 2, 4, 8, 12, 16, 18, 22, and 26 or at early termination.

The pooled ECG data from the four phase III studies were analysed in two ways: (1) calculation of treatment differences as the mean change in values from baseline to endpoint and (2) the incidences of newly occurring or worsening abnormalities. For all analyses, the baseline value was defined as the latest ECG measurement prior to receiving treatment. Change from baseline values was calculated so that a positive change indicated an increase in the post-baseline interval assessment.

Mean±SD and median baseline ECG variables (heart rate, PQ or PR, QRS, and corrected and uncorrected QT intervals) by treatment group and mean±SD and median change from baseline to endpoint values for the ECG variables listed were calculated. Baseline ECG PR, QRS, and QTc (using Bazett formula as worst case) intervals were examined. For this analysis, a difference from baseline was calculated for each post-baseline ECG interval, and the percent change was calculated. If a patient only had negative changes (eg, all post-baseline PR intervals were less than the baseline value), then the value chosen was the smallest negative percent change.

The number of patients with a maximum increase of percent change in any post-baseline PR interval and QRS interval of <15%, ≥15% to <25%, and ≥25% was determined as well as the number of patients with a maximum increase of percent change in any postbaseline QTc interval of <10%, ≥10% to <15%, ≥15% to <25%, and ≥25%. Finally, a heart rate shift-table analysis of bradycardia (defined as <50 bpm) and tachycardia (defined as >110 bpm) by maximum prescribed dose was conducted.

Results:

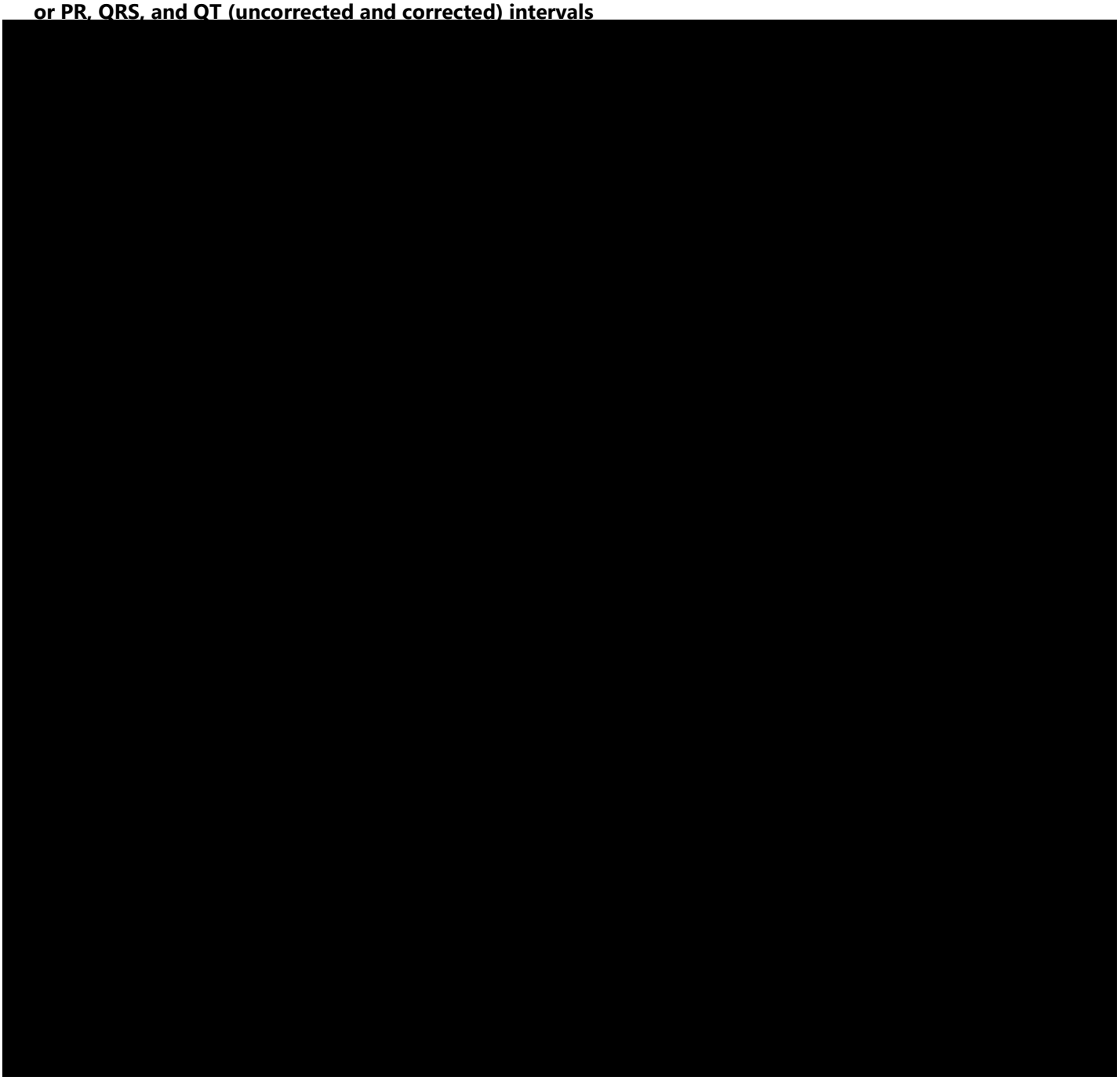
2,791 patents were pooled from the four rivastigmine studies. The mean age of patients were 73.0 years (range 41 to 95 years), majority female (59%) and Caucasian (95%). The mean duration of dementia at the beginning of the studies was 38.7 months (range: 2-240 months). No clinically meaningful differences were observed between the rivastigmine and placebo groups with regard to demographic characteristics. Table 20 shows patient baseline characteristics.

Table 20: Patient baseline characteristics from four pooled Phase III studies

Most patients enrolled in the study had concurrent illnesses and approximately 71% took medicines for conditions other than AD. The overall incidence of concurrent medical conditions and concomitant medicine use was slightly higher in the rivastigmine < 6 mg/day group than in the other two groups; however, the incidences of cardiovascular disorders and cardiovascular drug use were comparable across treatment groups.

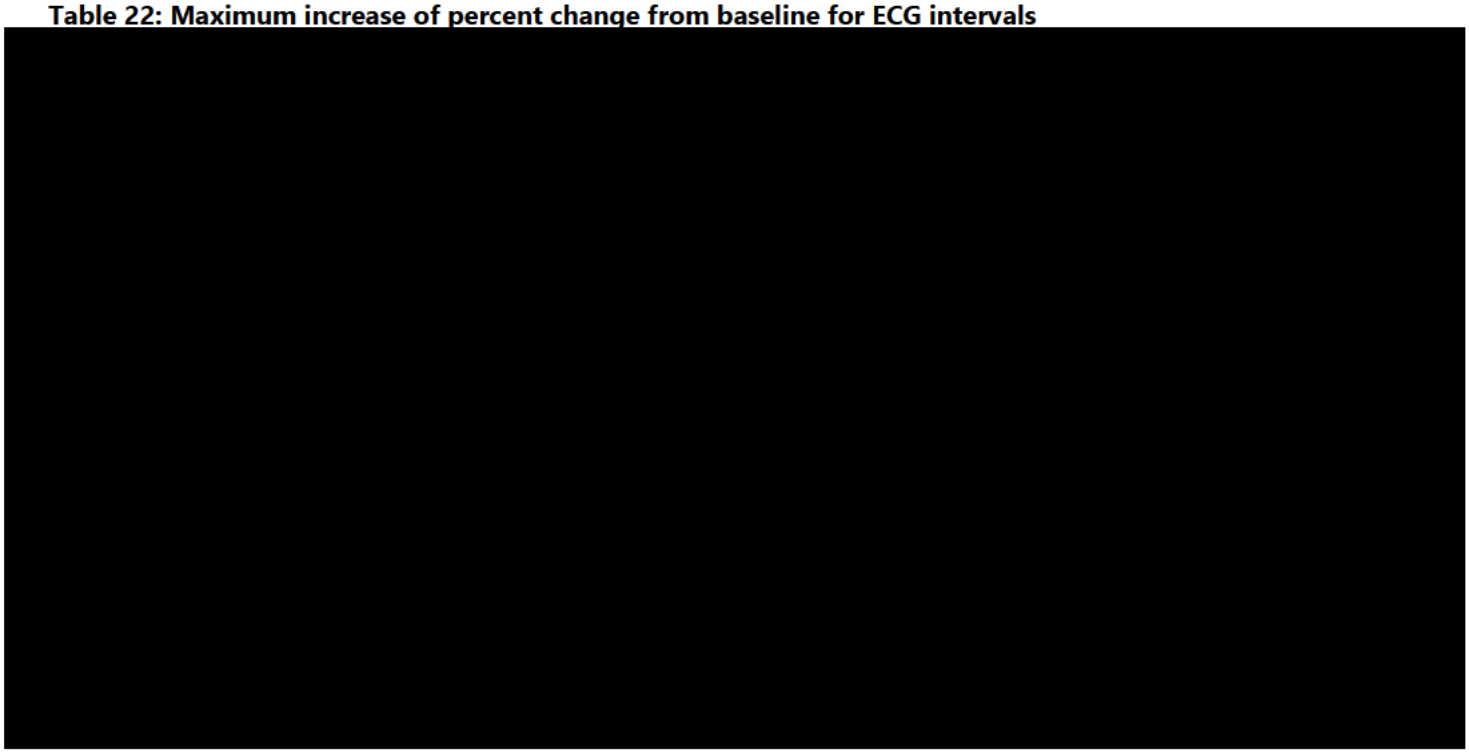
Mean±SD and median change from baseline to endpoint values for the ECG variables are presented in Table 21. No clinically meaningful differences were apparent between the rivastigmine and placebo-treated patients with regard to mean change from baseline to endpoint.

Table 21: Mean±SD, median baseline, and endpoint values and change from baseline for heart rate, PQ or PR, QRS, and QT (uncorrected and corrected) intervals



No clinically meaningful differences between treatment groups were apparent with regard to maximum increases in percent change from baseline for PR, QRS, and QTc intervals (Table 22). The majority of patients (≥82% in any treatment group) demonstrated <10% or 15% maximum percent change from baseline in these three ECG parameters.

Table 22: Maximum increase of percent change from baseline for ECG intervals



Authors' conclusions: the pooled ECG results from the four 26-week phase III controlled studies of rivastigmine, composed of more than 2,700 probable AD patients where the majority had concurrent illnesses and/or taking other medicines, demonstrated that rivastigmine did not appear to produce any adverse effects on cardiac electrophysiology. Therefore, rivastigmine can be safely administered to AD patients without the need for cardiac monitoring.

3.1.3.3 Riepe M (2014), High-dose cholinergic therapy with rivastigmine patch does not prolong QTc time in patients with Alzheimer's disease [38]

Letter to the Editor

Aim: To determine whether high-dose rivastigmine patch induced QTc prolongation in patients with AD.

Methods: This publication describes an analysis of further data from a study by Cummings et al 2012, a 48-week randomised, double-blind, parallel-group study looking at the efficacy and safety of a higher-dose rivastigmine patch. 1,584 patients were included in this open-label treatment phase if they were already using rivastigmine 9.5mg/24 hour patch.

Of patients, 22.1% were diagnosed with cardiac disease, among whom 5.4% had coronary artery disease, 5.1% had atrial fibrillation, 3.9% had myocardial infarction, 1.5% had bradycardia and 1.5% had arrythmia. Patients were only excluded if they had severe or unstable cardiovascular disease or bradycardia, sinus sick syndrome or heart block.

After 24-weeks of treatment, 567 patients entered the double-blind phase in which they continued treatment with the 9.5mg/24 hour patch or increased to the 13.3mg/24 hour patch.

Results: 287 patients received the 9.5mg/24 hours patch and 280 patients received the 13.3mg/24 hour patch. At baseline the RR, PR and QT interval were comparable between the two groups. QTc using Bazett's (QTcB) and Fridericia's (QTcF) methods were also similar between groups (Table 23).

After 48-weeks of treatment, the RR interval was slightly prolonged in the group receiving the 13.3mg/24 hour patch (lengthened by 6.0 ±134.77 ms from baseline, p=0.01603). There were no significant differences in QT and QTcF between the two patch strengths, however, the QTcB was shortening in the group treated with 13.3mg/24 hour patch (Table 23).

Table 23: ECG for the safety population in patients receiving rivastigmine patches from the OPTIMA study

[redacted]

Conclusions: This analysis does not provide evidence for QTc prolongation even with high-dose rivastigmine transdermal therapy. As nearly a quarter of patients were diagnosed with cardiac disease in this study, the data is relevant for routine clinical practice and demonstrates that rivastigmine patch is well tolerated and does not increase the risk of TdP.

3.1.3.4 Isik et al (2011), Cardiac effects of rivastigmine patch in elderly patients with Alzheimer disease [39]

Poster abstract

This study aimed to evaluate the effects on ECG with rivastigmine patch.

Thirty participants were enrolled with late-onset AD and 15 men and 11 women completed the study. The mean age was 78.2 years. ECG and blood pressure were measured at baseline and at each dose of rivastigmine patch therapy. The dose of rivastigmine was increased every 4-weeks.

Table 24 shows the ECG parameters at each rivastigmine dose titration and comparisons. There were no statistically significant differences in these parameters at each dose titration compared to baseline.

Table 24: ECG parameters at each rivastigmine dosage titration and comparisons

[redacted]

There were no statistically significant changes in blood pressure at each dose titration compared to baseline.

The authors conclude that the results suggests that the usual dosage of rivastigmine patch seems to be safe for elderly patients, however it is recommended that patients are closely monitored for ECG changes during therapy.

Comments:
Although not specified in the study, the patches 5 cm^2 and 10 cm^2 likely represents 4.6 mg/24 hour and 9.5mg/24 hour release rate respectively. A higher strength patch of 13.3mg/24 hour is also approved in New

Zealand.

3.1.3.5 Walsh et al (2002), Prolonged QT interval with rivastigmine [40]

Case report

A 78-year old man with dementia commenced treatment with rivastigmine. His other long-term medicines were diltiazem, citalopram, furosemide, aspirin and ranitidine.

Few weeks prior, the patient developed diarrhoea which was deemed responsible for his low potassium (3.4 mmol/L). Electrolyte testing in the past did not show he had problems with hypokalaemia. He received potassium supplements while his diarrhoea was ongoing and once the diarrhoea stopped the potassium was rechecked and the potassium supplements were discontinued. The patient had no diarrhoea at any stage during his treatment with rivastigmine that could have led to a further development of hypokalaemia.

A pre-treatment ECG showed evidence of an old inferior myocardial infarction (that occurred 6 years previously) and a QT interval of 383 ms and QTc interval 397 ms.

Seven days after commencement of rivastigmine, repeat ECG showed a QT interval of 476 ms and a QTc interval of 477 ms. Rivastigmine was the only recent medicine added at that time.

Rivastigmine was stopped and a week later, the ECG showed a normal QT interval of 402 md and QTc interval of 399 ms. An ECG two months later showed normal QT and QTc interval.

Comments Unclear from the case narrative is this was oral or transdermal rivastigmine. The patient had risk factors for QT prolongation as he was on medicines known to prolong the QT interval, had low potassium levels and underlying cardiac disease. Introducing rivastigmine may have potentially increased the patient's risk of QT prolongation.

3.1.4 Galantamine

3.1.4.1 Isik et al (2010), Evaluation of the effects of galantamine on cardiac function in elderly patients with Alzheimer's disease [41]

Background: To evaluate the effects of galantamine on electrophysiology and arterial blood pressure in elderly patients with AD.

Methods: For the period March 2008 to August 2009, patients 65 years and over were approached for enrolment in the study. The patients underwent a comprehensive geriatric assessment to determine study eligibility. Patients with newly diagnosed AD were treated with an escalating dose of extended release galantamine, using a 2 to 4 week schedule, starting at 8 mg once daily, increasing to a maximum of 24 mg once daily if tolerated.

Patients were excluded if they had cardiac arrythmias, acute myocardial infarction in the last 3 months, a prosthetic heart valve, pacemaker, congestive heart failure or were treated with cardio-stimulatory medicines.

Blood pressure and ECG parameters (heart rate, QRS complex and PR and QT interval) were measured at baseline and after 2 to 4 weeks on each dosage of galantamine. The QTc interval was calculated using Bazett's formula.

Results: Of the 814 patients who underwent the geriatric assessment, 64 were enrolled in the study. Fifty-one participants completed the study with a follow-up time of ~4 months. Only those who completed the study were included in the analysis.

There were 28 females and 23 males with an average age of 78.5 years. 37% of patients had hypertension.

The mean ECG parameters for patients at each galantamine dose is outlined in Table 25.

No significant changes in ECG parameters were observed relative to baseline. Similarly, no significant differences were observed with arterial blood pressure.

Table 25: Mean (standard deviation) ECG parameters for each galantamine dose. QTc using Bazett's formula

Conclusions: This study found that none of the investigated dosages of galantamine (8, 16, or 24 mg per day) had any significant effect (relative to baseline) on ECG parameters or arterial blood pressure in elderly patients with AD. Because of the short duration of the study and the strict exclusion criteria, ECG parameters should still be monitored

Discussion on limitations: Data from the dropouts were not considered. However, the mean values from the dropouts and those from patients who completed the study were identical and thus would not have affected the study results.

The short duration of this study may be a limitation because no long-term results of treatment with galantamine were obtained. Only 51 elderly patients with AD were studied, which is a small sample group. Due to the strict exclusion criteria, this was a highly selected sample that did not account for other comorbidities or concomitant medicines. The strict exclusion criteria also limited the generalisability of the study results.

Comments:

It is not clear from the methodology how patients were approached/selected for the study and whether this could impact the study outcome. The study did not state if all participants that completed the study (or how many) ended up escalating to the full 24 mg per day dose.

3.1.4.2 Bozoglu at al (2009), Galantamine is safe as well as metoprolol on cardiac electrophysiology of patients with Alzheimer's disease [42]

Poster abstract

The ECG records of 32 consecutive elderly patients with newly diagnosed late-onset AD treated with a flexible 4-weekly galantamine dose titration regimen up to 24 mg/day and 41 elderly patients with hypertension, treated with metoprolol (50 mg/day) as a control group were evaluated. ECG records were measured at baseline and at each dose of galantamine therapy (8mg, 16 mg, and 24 mg). In the metoprolol group, the ECG records were received at the baseline and one week after therapy.

Compared to the baseline values of galantamine treated patients, there were no statistically significant changes at each dose of galantamine in the ECG parameters including; heart rate, QRS duration, intervals of PR and corrected QT. In addition, the magnitude of these changes in the rivastigmine group were smaller than changes observed in metoprolol treated patients.

This study demonstrated that each dose of galantamine did not affect the ECG parameters compared with the baseline, significantly, and this effect was similar to metoprolol.

3.1.4.3 Fisher et al (2008), Prolonged QT interval, syncope, and delirium with galantamine [43]

Case report

An 85-year old male with dementia of mixed aetiology (AD and vascular) was treated with galantamine 8 mg extended release for 1.5 years. The patient has a history of cardiovascular disease including coronary artery disease, hypertension and hypercholesteremia. The patient's regular medicines were irbesartan, clopidogrel, simvastatin, pantoprazole, ergocalciferol, calcium carbonate and paracetamol.

He was admitted to hospital after losing consciousness and falling. Three weeks prior to hospitalisation, he re-started on galantamine after being off it for 2 weeks.

On admission to hospital the patient was confused, restless, agitated and had incontinence. His blood pressure was 84/46 mmHg and pulse of 79 bpm. His QT interval was also significantly prolonged regardless of the formula used (Table 26).

Table 26: ECG characteristics and corrected QT intervals calculated by different correction formulas

[redacted]

ECG 24 hour Holter recording on the third day of admission showed sinus rhythm with average heart rate of 60 bpm.

Galantamine and irbesartan were stopped, while the patient's other long-term medicines continued. His QTc interval shortened from 503 to 443 ms (using Bazett's formula) four days after stopping galantamine and remain normal thereafter. He has since been discharged with his normal medicines except galantamine and irbesartan which he remained asymptomatic for six months. The Naranjo probability scale indicated that galantamine was the probable cause of QT prolongation in this patient. TdP could not be ruled out for this patient given there was no ECG monitoring during the first days after admission.

The authors also reviewed Australian cases associated with the three available AChEIs reported to the Australian Adverse Drug Reaction Advisory Committee (ADRAC) database for cardiac, neurological and gastrointestinal adverse reaction terms up to 31 May 2007 (Table 27). Eight cases of syncope, 13 cases of bradycardia and 6 cases of other arrythmias or conduction abnormalities were reported for galantamine. There were no reports of TdP.

Table 27: Main cardiac, neurological and gastrointestinal adverse effects reported to the Australian Adverse Drug Reactions Advisory Committee database up to 31 May 2007 for three AchEI

[redacted]

The authors conclude that the syncope experienced by their patient may be related to QT interval prolongation with TdP. Increased vagal tone due to the increased amount of acetylcholine in the synapses is the most likely explanation for QTc prolongation and arrythmias with AChEIs.

Conclusions: This case, along with other previously identified cases illustrates that in addition to gastrointestinal symptoms, AChEIs may lead to delirium, syncope, and QTc prolongation, thereby increasing the risk of life-threatening arrythmias.

3.1.4.4 Nelson et al (2006), Galantamine-induced QTc prolongation [44]

Case report

A 47-year old male was treated with galantamine for schizophrenia. The patient's QTc interval ranged from 420 to 443 ms on his annual ECG in the 5 years prior to starting galantamine. An ECG three months prior to starting galantamine was 415 ms. Immediately before initiating galantamine 8 mg per day his QTc was 417 ms with a heart rate of 71 bpm.

After titration of galantamine to 12 mg twice daily over two months, his QTc interval increased to 518 ms with a heart rate of 70 bpm. Serum electrolytes were within normal limits and there were no changes to his regular medicines for four months prior to starting galantamine.

The galantamine was discontinued and his QTc shortened to 459 and 414 ms, 1 and 2 weeks, respectively, after stopping the medicine.

The patient had a history of diabetes, hypertension and hyperlipidaemia. His regular medicines were aripiprazole, quetiapine, lithium, benztropine, and trazodone when needed.

While the patient had existing risk factors for QT prolongation, the temporal relationship of this occurring when galantamine was initiated and subsequent de-challenge after discontinuation implicates the medicine's involvement.

3.2 Company position

[redacted]

[redacted]

3.2.1 Pfizer – for donepezil

[redacted]

3.2.2 Janssen-Cilag – for galantamine

[redacted]

[redacted]

3.3 Spontaneous reports

3.3.1 CARM data

Up to 31 July 2023, the Centre for Adverse Reactions Monitoring has received three reports of 'electrocardiogram QT prolonged' following galantamine use (Table 28). No reports of QT prolongation have been reported for donepezil or rivastigmine.

Table 28: Reports of QT prolongation following galantamine

CARM ID	Age in years	Sex	Reactions	Outcome/causality	Other information
74737	82	M	Medication error Electrocardiogram QT prolonged Accidental overdose	[redacted]	
89440	82	M	Medication error Electrocardiogram QT prolonged		
74868	82	M	QT prolonged Overdose (accidental)		

Comments: The three cases above are likely duplicates given the same age, sex and onset date.

There have not been reports of TdP following AChEIs use in New Zealand.

A broader query using the MedDRA high level group term (HLGT) 'cardiac arrythmias' retrieved 13 reports for donepezil, 1 report for galantamine and 6 reports for rivastigmine. Summary of the cases are outlined in Tables 29-31.

Table 29: Cases of MedDRA HLGT 'cardiac arrythmias' reported for donepezil

Report_id	ReportDate	Sex	Age	[redacted]	Reactions	[redacted]
46169	1/11/2000	Male	77		Sudden death	
53974	1/11/2002	Male	85		Ataxia; Headache; Heart block; Vomiting	
54325	1/01/2003	Male	85		Ataxia; Bradycardia; Dizziness; Drug interaction; Heart block	
55732	1/04/2003	Female	0		Concussion; Sudden death; Syncope	
55742	1/04/2003	Male	0		Sudden death	
55949	1/05/2003	Female	63		Bradycardia; Syncope	
57652	1/09/2003	Male	75		Bradycardia; Heart block; Myocardial infarction	
65326	1/05/2005	Female	84		Bradycardia; Syncope	
94732	1/03/2011	Female	82		Bradycardia; Drug interaction; Feeling of warmth; Palpitation; Syncope	
100540	1/03/2012	Female	85		Bradycardia	
101281	1/05/2012	Male	86		Bradycardia; Drug interaction; Syncope	
104216	1/10/2012	Female	72		Atrial fibrillation	
109538	1/01/2014	Female	79		Bradycardia; Coma	

Table 30: Cases of MedDRA HLGT 'cardiac arrythmias' reported for galantamine

Report_id	ReportDate	Sex	Age	[redacted]	Reactions	[redacted]
77777	1/02/2008	Male	84		Arrhythmia ventricular	

Report_id	ReportDate	Sex	Age	[redacted]	Reactions	[redacted]
57398	1/08/2003	Female	73		Arrhythmia; Syncope	
82596	1/01/2009	Female	87		Atrial fibrillation	
95597	1/05/2011	Male	11 mor		Bradycardia; Extrasystoles; Felt faint	
99326	1/01/2012	Male	70		Atrial fibrillation; Ocular haemorrhage	
109672	1/01/2014	Female	0		Bradycardia	
110952	1/04/2014	Male	75		Bradycardia	

Comments:

Events of sudden death, arrythmia, and syncope may be caused by QT prolongation/TdP. [redacted] Therefore, QT prolongation/TdP causing these events cannot be fully excluded.

3.3.2 World Health Organization Global Database

[redacted]

Comment:

A positive IC value indicates that a particular drug-reaction pair is reported more often than expected, based on all the reports in the database. Conversely, a negative IC value means that the drug-reaction pair is reported less frequently than expected. A positive IC value does not imply causality and can be influenced by reporting bias, among other factors.

The $IC_{0.25}$ is the lower limit of the 95% credibility interval for the IC. It provides information about the stability of a particular IC, with the narrower the interval, the higher the stability.

4 INTERNATIONAL REGULATOR REVIEW AND ACTION

4.1 European Medicines Agency

The EMA's PRAC reviewed the signal of QT prolongation and TdP for galantamine and donepezil in 2020 and 2021 respectively.

Galantamine: Review of the data on QTc prolongation /TdP from spontaneous case reports where the relationship between galantamine and the event was assessed as probable in one case and possible in seven cases, two case reports from the literature, knowledge from overdose of galantamine and the cholinergic mechanism (which increases the propensity for bradycardia), the PRAC concluded that the product information be updated with the following [45]:

Section 4.4

> *'There have been reports of QTc prolongation in patients using therapeutic doses of galantamine and of torsade de pointes in association with overdoses (see section 4.9). Galantamine should therefore be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.'*

Donepezil: the PRAC reviewed the available evidence in EudraVigilance and in the literature and considered that the causal relationship between donepezil and QT prolongation and TdP is at least a reasonable possibility and has agreed that donepezil product information should be updated with the following [46]:

Section 4.4

> *'Cardiovascular conditions*
>
> *There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required'*.

Section 4.5

> *'Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:*
>
> - *Class IA antiarrhythmics (e.g. quinidine)*
> - *Class III antiarrhythmics (e.g. amiodarone, sotalol)*
> - *Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)*
> - *Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)*
> - *Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin).'*

Section 4.8

'Frequency not known: Polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged.'

4.2 Health Canada [47]

In 2022, Health Canada's reviewed the risk of QT prolongation and TdP with AChEIs.

Health Canada reviewed information from searches of the Canada Vigilance database, international databases and the literature. Twenty articles in the literature showed limited evidence to support a link between the AChEIs and QT prolongation and TdP.

53 case reports were reviewed (1 Canadian and 52 international).

- Thirty-five reports were for donepezil. Two of these cases were found to be probably linked, 30 cases were possibly linked, 2 cases were unlikely to be linked and 1 case could not be assessed. Four deaths were reported (2 of which were determined to have a possible link and 2 unlikely to be linked).
- Ten reports were for galantamine. Three cases were found to be probably linked, 5 cases were possibly linked, 1 case was unlikely to be linked and 1 case (Canadian) could not be assessed. One death was reported and was unlikely to be linked.
- Seven reports were for rivastigmine. Seven cases were found to be possibly linked and 1 case was unlikely to be linked.

Health Canada concluded that their review supported a link between the use of all three AChEIs and the risk of QT prolongation and TdP. This risk is increased in patients with a history of certain heart conditions, a history or family history of QT interval prolongation, low levels of certain electrolytes, such as magnesium, potassium or calcium in the blood, or taking certain medicines that can affect heart rhythm at the same time as the cholinesterase inhibitors.

The product informations have been updated with this risk.

4.3 Therapeutic Goods Administration [48]

In 2022, the TGA published a Medicines Safety Update on donepezil and cardiac conduction disorders. This communication advised that the product information for donepezil will be updated to advise caution in patients with known QTc prolongation or a family history of this condition. Additionally, caution is advised in patients also receiving other drugs that affect the QTc interval, or who have certain types of cardiac disease or electrolyte disturbances. As these adverse effects can be severe and potentially life threatening, clinical monitoring may be required.

TGA's review of post-marketing reports to 5 January 2022 showed 18 cases of atrioventricular block, atrioventricular block complete, atrioventricular block second degree, bundle branch block, bifascicular block or TdP associated with donepezil.

5 REVIEW OF DATA SHEETS

The market innovator data sheets in Australia and United Kingdom for donepezil, galantamine and rivastigmine were reviewed for information on QT prolongation and TdP. Tables are provided below that compares the wording against the current New Zealand donepezil (Rex) data sheet (the available generic) and the galantamine and rivastigmine innovator data sheets.

- For donepezil, there is information on QT prolongation/TdP in sections 4.4, 4.5 and 4.8 of the Australian and UK Aricept data sheets, but no information in the Donepezil (Rex) New Zealand data sheet.
- For galantamine, there is information on QT prolongation/TdP at therapeutic doses in section 4.4 and 4.5 of the Australian and UK Reminyl data sheets, but no information in the New Zealand data sheet. All data sheets have information on QT prolongation/TdP in overdose (section 4.9).

- For rivastigmine, there is information on QT prolongation/TdP in section 4.4 and 4.5 for the Exelon data sheets in all 3 countries.

Table 32: Donepezil data sheet review

Section of the data sheet	New Zealand Donpezil (Rex) data sheet	Australian Aricept data sheet	UK Aricept data sheet
4.4	No information on QT prolongation or TdP, but has the following cardiovascular warnings: **Cardiovascular Conditions** Vagotonic effects on heart rate (e.g. bradycardia) may be induced by cholinesterase inhibitors such as donepezil. The potential risk for this action may be increased particularly in patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as atrioventricular or sinoatrial block.	**Cardiovascular conditions** There have been post-marketing reports of cardiac conduction conditions including atrioventricular block, QTc interval prolongation and Torsade de Pointes (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (undesirable effects)). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients being treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.	**Cardiovascular conditions** There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.
4.5	N/A	Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil (see Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects)). Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring may be required. Examples include: • Class IA antiarrhythmics (e.g. disopyramide) • Class III antiarrhythmics (e.g. amiodarone, sotalol) • Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline) • Other antipsychotics (e.g. phenothiazine derivatives, pimozide, ziprasidone) • Certain antibiotics (e.g. clarithromycin, erythromycin, moxifloxacin).	
4.8	No information on QT prolongation or TdP, but has the following cardiovascular ADRs: Syncope, atrioventricular block, bradycardia, and sinoatrial block, angina pectoris, hot flushes, hypertension, hypotension, vasodilation	Post-market experience: Electrocardiogram QT interval prolonged, polymorphic ventricular tachycardia including Torsade de Pointes.	Post-market experience: Electrocardiogram QT interval prolonged, polymorphic ventricular tachycardia including Torsade de Pointes With the ADR frequency 'not known'.

Table 33: Reminyl (galantamine) data sheet review

Section of the data sheet	New Zealand Reminyl data sheet	Australian Reminyl data sheet	UK Reminyl data sheet
4.4	No information on QT prolongation or TdP, but has the following cardiovascular warnings:	**Cardiovascular conditions:** There have been reports of QT prolongation in patients using therapeutic doses of galantamine and of torsade de pointes in association with overdose. Galantamine should therefore be used with caution in patients with prolongation of the QT	

	Cardiovascular conditions: Because of their pharmacological action, cholinomimetics may have vagotonic effects on heart rate, including bradycardia and all types of atrioventricular node block (see section 4.8). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or who concomitantly use medicines that significantly reduce heart rate (eg digoxin and beta blockers) (see section 4.5). Cholinomimetics should therefore be given with caution to patients in the immediate post-myocardial infarction period, who have new-onset atrial fibrillation, who have second-degree heart block or greater, who have unstable angina pectoris, uncorrected electrolyte disturbance (eg hyperkalaemia, hypokalaemia) or congestive cardiac failure, especially NYHA group III-IV. In clinical trials, use of REMINYL has been associated with syncope and rarely with severe bradycardia.	interval, in patients treated with drugs affecting the QT interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances
4.5	N/A	Caution should be taken with medicinal products that have potential to cause torsades de pointes. In such cases an ECG should be considered.
4.8	No information on QT prolongation or TdP, but has the following cardiovascular ADRs: Atrioventricular block complete, Atrioventricular block first degree, Palpitations, Sinus bradycardia, Supraventricular extrasystoles.	
4.9	**Overdose** There have been post-marketing reports of Torsade de Pointes, QT prolongation, bradycardia, ventricular tachycardia and brief loss of consciousness in association with inadvertent overdoses of galantamine.	

Table 34: Exelon (rivastigmine) data sheet review

Section of the data sheet	New Zealand Exelon data sheet	Australian Exelon data sheet	UK Exelon data sheet
4.4	**QT prolongation and torsade de pointes:** Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalaemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required (see section 4.5 Interaction with other medicines and other forms of interactions).		**Bradycardia**: Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

4.5	**Medicinal products known to prolong the QT interval** Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required (see section 4.4 Special Warnings and Precautions for Use).	**Medicinal products known to prolong the QT interval** Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin, chlorpromazine, levomepromazine, sulpiride, sultopride, amisulpride, tiapride, veralipride, haloperidol, droperidol, diphemanil, methadone, and pentamidine). Clinical monitoring may also be required (see section 4.4 Special warnings and precautions for use).	Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

Comment:
There are generic rivastigmine products available in New Zealand. The data sheets of these products do not have information on the risk of QT prolongation/TdP.

6 DISCUSSION AND CONCLUSIONS

Overview

The cardiac adverse effects of bradycardia, heart block and syncope are well described for AChEIs. However, there are limited studies looking at the relationship between QT prolongation/TdP and AChEIs as a class.

The study by Malone 2020 was based on case reports which found a strong association between donepezil and the risk of QT prolongation and TdP. Although the study did not find a strong association for galantamine and rivastigmine, this may be due limited published studies and case reports for these medicines compared to donepezil. This may be a reflection on how widely each of these medicines are used/prescribed.

A plausible mechanism for AChEIs to cause QT prolongation/TdP is the increased cholinergic receptor activation and subsequent increase of intracellular calcium. This may increase the risk of ventricular arrythmias. There are however unique mechanisms for each AChEI that may explain the differences in their risk of QT prolongation/TdP through their level of inhibition of potassium channels.

There have been reviews of AChEIs and the risk of QT prolongation/TdP by other regulators. Their review supported an association and the product information for all three AChEIs have been updated with information on the risk.

Donepezil

Kho 2021 was a retrospective study showing that the use of donepezil significantly prolonged the QT interval. The cross-sectional study by Kuwahata 2021 showed that the incidence of QT prolongation was higher and QT interval was significantly prolonged in patients on donepezil compared to patients who were not on donepezil. In other studies where the ECG was measured at baseline and after donepezil treatment did not show a significant QT prolongation. However, these studies were generally small with a short follow-up time.

There is no information on the risk of QT prolongation and TdP in the New Zealand donepezil data sheet.

Galantamine

Published literature on QT prolongation/TdP with galantamine was limited and dated. Isik 2010 measured participants' ECG at baseline and following each galantamine dose titration. The QT interval did not change significantly. There were several case reports in the literature of QT prolongation following galantamine use.

There is no information on QT prolongation and TdP in the New Zealand galantamine data sheet at therapeutic doses. However, section 4.9 states there have been post-marketing reports of QT prolongation and TdP. CARM has received cases of QT prolongation following galantamine, in the context of overdose.

Rivastigmine

There are limited published studies on QT prolongation/TdP. Studies that measured ECG from baseline following rivastigmine or following a dose titration did not find a significant increase in the QT interval. A pooled study from four Phase III trials did not appear to affect ECG parameters. Nonetheless, the data sheet for the market innovator (Exelon) has information on the risk of QT prolongation and TdP. The generic products have not yet updated their data sheets to reflect the innovator.

Overall conclusion

While most studies that monitored the patient's ECGs before and after AChEI therapy did not demonstrate a significant increase in the QT interval, patients were often excluded if they had unstable cardiovascular disease or taking cardio-stimulatory medicines. Whilst this may help separate out the potential effect of the AChEI on the QT interval/TdP, it does not reflect 'real life' use of these medicines. This is highlighted in case reports where AChEIs were often used in patients with modifiable and non-modifiable risk factors for QT prolongation (eg, cardiovascular disease, electrolyte disturbances, taking concomitant medicines that may prolong the QT interval). This may raise a need to further advise healthcare professionals that the risk of QT prolongation/TdP in patients taking AChEIs may be increased in certain patients with risk factors.

QT prolongation and subsequent TdP can be life-threatening. The Committee is asked to consider whether the risk can be considered a drug-class effect and therefore if regulatory action is required (eg, updates to the data sheet). The Committee may consider the wording in the current Exelon (rivastigmine) data sheet as an appropriate class wording that can be applied to all AChEIs (see Table 34).

7 ADVICE SOUGHT

The Committee is asked to advise whether:

- There is evidence of an association between acetylcholinesterase inhibitors as a drug class (or an individual acetylcholinesterase inhibitor) and QT prolongation and Torsade de Pointes?
    - If yes, is regulatory action required?
- Further communication is required other than in MARC's remarks?

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