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REVIEW

Comparative risk of cardiac arrhythmias associated with acetylcholinesterase inhibitors used in treatment of dementias – A narrative review

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Abstract

Donepezil, galantamine, and rivastigmine are the three acetylcholinesterase inhibitors (AChEIs), out of a total of only four medications prescribed in the treatment of Alzheimer's Disease (AD) and related dementias. These medications are known to be associated with bradycardia given their mechanism of action of increasing acetylcholine (ACh). However, in March 2015, donepezil was added to the CredibleMeds "known-risk" category, a list where medications have a documented risk for acquired long-QT syndrome (ALQTS) and torsades de pointes (TdP) – a malignant ventricular arrhythmia that is a different adverse event than bradycardia (and is not necessarily associated with ACh action). The purpose of this article is to review the three AChEIs, especially with regards to mechanistic differences that may explain why only donepezil poses this risk; several pharmacological mechanisms may explain why. However, from an empirical point-of-view, aside from some case-reports, only a limited number of studies have generated relevant information regarding AChEIs' and electrocardiogram findings; none have specifically compared donepezil against galantamine or rivastigmine for malignant arrhythmias such as TdP. Currently, the choice of one of the three AChEIs for treatment of AD symptoms is primarily dependent upon clinician and patient preference. However, clinicians should be aware of the potential increased risk associated with donepezil. There is a need to examine the comparative risk of malignant arrhythmias among AChEIs users in real-world practice; this may have important implications with regards to changes in AChEI prescribing patterns.

KEYWORDS

Acetylcholinesterase inhibitor, adverse drug event, Alzheimer's Disease, cardiac arrhythmia, pharmacoepidemiology

Abbreviations: ACh, Acetylcholine; AChEI, Acetylcholinesterase inhibitor; AD, Alzheimer's Disease; aHR, Adjusted hazard ratio; ALQTS, Acquired long-QT syndrome; ECG, Electrocardiogram; LQTS, Long-QT syndrome; QT_C, Corrected QT interval; TdP, Torsades de pointes.

1 | INTRODUCTION

1.1 | Alzheimer's Disease and related dementias

Dementia is defined as the "acquired progressive cognitive impairment sufficient to impact [the] activities of daily living;" Alzheimer's Disease (AD) accounts for the vast majority of dementia cases.[1] Other types of dementia include Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment.[1] Clinical features of dementias include loss of episodic memory, difficulties multitasking, and loss of confidence, with later disease stages of disease presenting through behavioural changes, impaired mobility, and possibly hallucinations and seizures.[1] With regards to AD specifically, main features of AD pathology are neurofibrillary tangles and amyloid plaques; the amyloid hypothesis (which is the primary theory with regards to how AD occurs) suggests that the accumulation of pathological forms of amyloid-beta is the primary pathological process in AD.[1]

Current approved treatments for AD are limited: in the United States and Canada, three AChEIs are approved for the treatment of AD symptoms (generic names: donepezil, galantamine, rivastigmine) and one NMDA receptor (a type of ionotropic glutamate receptor) antagonist (generic name: memantine) is approved.[2,3] None of the medications are disease-modifying (ie reducing amyloid-beta deposition); disease-modifying treatments are not yet available[1] (although new AD drugs are in the development pipeline).[4] The mechanism of action for AChEIs is the compensation for the loss of central cholinergic neurons in AD (and thus loss of the neurotransmitter acetylcholine (ACh))[5] through decreased breakdown of ACh. Tacrine, an older AChEI, has largely been abandoned from use[6] although it is still available in countries such as the United States.

1.2 | Efficacy and safety differences between the three acetylcholinesterase inhibitors

Overall, it is considered that there are no profound differences between AChEIs with regards to efficacy or safety, and the selection of a specific agent to prescribe a patient is mainly based upon ease of use, patient tolerability, cost, and clinician/patient preference.[7] A 2008 systematic review of randomized controlled trials showed that evidence is unclear with regards to saying if one of the three AChEIs are more efficacious.[8] Active treatment of any of the three AChEIs found that cognition, functional, global assessment of change, and behavioural improvement is similar amongst patients treated.[8]

Regarding safety, rivastigmine appeared to have the highest incidence of common adverse events (such as vomiting, nausea, dizziness, diarrhea, weight loss) and donepezil appeared to have the lowest incidence.[8] Likewise, the frequency of withdrawals (in general) and withdrawals due to adverse events is highest in rivastigmine trials and lowest in donepezil trials.[8] However, a more recent (2017) review reported that the odds of adverse events was higher in galantamine trials, although donepezil still had the lowest odds of adverse events.[9] Still, all three AChEIs are considered to provide significant improvements compared to placebo, without any indication as to which AChEI is better safety- or efficacy-wise.[9]

Contrasting the common adverse events of AChEIs, there are some potential differences in uncommon/rare adverse effects. Fleet et al in 2019, for example, found that "donepezil was associated with a higher risk of hospital admission [for] rhabdomyolysis compared [to] rivastigmine or galantamine," with the rationale of the study being based upon a Health Canada alert for donepezil.[10] Post-marketing surveillance may indicate there are important differences within AChEIs with regards to safety. Among other emerging adverse effects that have arisen in recent years is the potentially fatal arrhythmia that can result from donepezil.

1.3 | QT_C-prolongation and malignant arrhythmia associated with general medication use

Medications are a common cause of the acquired form of long-QT syndrome (ALQTS),[11] whereby the QT interval on the electrocardiogram (ECG) – representing ventricular depolarization and the entirety of ventricular repolarization[12] – is abnormally prolonged. A Bazett heart rate-corrected QT (or QT_C) interval of ≥450 milliseconds (ms) in males and ≥460 ms in females[13] is generally deemed as abnormal.

Prolongation signals an abnormally long delay in ventricular repolarization[14]; this may cause torsades de pointes (TdP) ventricular tachycardia (a type of "malignant ventricular arrhythmia"[15]), one of the most devastating ventricular tachycardias – 15%-20% of TdP cases worsen to ventricular fibrillation,[16] causing cardiac arrest.[12,17,18] Although TdP-ventricular tachycardia is specifically a type of malignant arrhythmia, it must be noted that the term "malignant arrhythmia" also encompasses other ventricular tachycardias and ventricular fibrillation.[15]

At the cellular level, QT_C prolongation associated with medications is usually attributed towards the blockage of the "rapid" potassium current (I_{Kr}) – a major outwards potassium current in the repolarization of cardiomyocytes.[11] I_{Kr} goes through the hERG protein channel,[19] also known as $K_V11.1$.[20] Throughout the article, I_{Kr} is used when referring to the current, and $K_V11.1$ is used when referring specifically to the protein of which I_{Kr} flows through. Other cardiomyocyte currents and mechanisms are also implicated in QT_C interval prolongation[18,19,21–24] although current guidelines (ICH S7B and E14, introduced 2005) for pre-clinical cardiac safety assessments primarily focus on I_{Kr}.[19]

In an effort to reduce the occurrence of malignant arrhythmias such as TdP, the CredibleMeds.org online resource was created to categorize medications which have a risk of ALQTS and/or TdP.[18] Using a comprehensive search strategy,[25] this website categories medications into "known-risk," "possible-risk," and "conditional-risk," with medications on the known-risk list having been established to prolong the QT_C interval as well as being associated with TdP during routine use.[25] Validity of the known-risk list specifically has been

ascertained through multiple studies,[26–29] as well as through a systematic review.[30] Amongst many validated risk factors for acquired QT_C prolongation and TdP, and in addition to use of known-risk list medications, key patient-related risk factors include hypokalemia and loop diuretic use,[17,30] female sex,[17,30] advanced age (≥ 65 years[30] or ≥68 years[17]), and bradycardia.[31,32] Importantly, all AChEIs used in the treatment of AD are associated with bradycardia.[9,33,34]

1.4 | CredibleMeds and other regulatory agency updates regarding acetylcholinesterase inhibitors

In spite of review articles finding minimal safety differences between AChEIs, one key and perhaps concerning addition to the CredibleMeds known-risk (of ALQTS/TdP) list was donepezil – which was added to the known-risk list in March 2015.[35] On the other hand, galantamine is only on the conditional-risk list of CredibleMeds[36] whereas rivastigmine is not listed on CredibleMeds.

All three AChEIs were originally approved for use prior to the introduction of pre-clinical cardiac safety assessments in 2005. Donepezil was originally marketed in Canada in 1997 (initial approval in the United States in 1996), and rivastigmine and galantamine were initially marketed in Canada (and approved in the United States) in 2000 and 2001 respectively. In July 2015, coinciding with the CredibleMeds addition for donepezil, the FDA submitted a letter to Eisai Inc (the manufacturer of Aricept – brand name for donepezil) accepting a revision to the Aricept medication label – with the addition of QT_C prolongation and TdP to the postmarketing experience section.[37] Notably, Health Canada did not create any alerts regarding Aricept and its potential association with QT_C prolongation or TdP. However, alerts were issued in January 2015 regarding the risk of rhabdomyolysis and neuroleptic malignant syndrome.[38]

Neither the labels for Aricept, Razadyne (brand name of galantamine manufactured by Janssen Pharmaceuticals Inc), nor Exelon (brand name of rivastigmine manufactured by Novartis Pharmaceuticals Corp.) list QT_C prolongation under contraindications, warnings and precautions, nor adverse reactions (other than in postmarketing subsection for Aricept); there are also no relevant studies regarding cardiac function described under non-clinical toxicology either.[39–41] However, the label for Exelon does list tachycardia under postmarketing experience for cardiac disorders,[41] of which TdP is a type of tachycardia as previously described. The label for Razadyne also lists complete atrioventricular block under postmarketing experience,[40] which is a disorder which may result in QT_C prolongation or TdP.[42] It additionally lists one postmarketing report of QT_C prolongation and TdP, although it was attributed to a massive overdose.[40]

Donepezil is the most prescribed of the three AChEIs; thus, addition of donepezil to the known-risk list of CredibleMeds is of concern. Studies conducted in two Canadian provinces found that about two-thirds of new users of AChEIs were prescribed donepezil (66% in British Columbia[43] and 69% in Ontario[10]). CredibleMeds utilizes case reports in risk assessment,[25] but the Bradford Hill causality analysis is used to determine possible causality between usage of a certain medication and potential of QT_C prolongation and/or TdP.[25] As such, although there may be more case reports for donepezil given increased donepezil use, the additional utilization of pharmacological literature for causality analysis[25] may support that there is in fact an elevated risk with donepezil – and increased case reports are not simply due to increased use.

1.5 | Mechanistic differences between the three acetylcholinesterase inhibitors that may lead to donepezil being a higher-risk medication

Patients whom are prescribed donepezil usually have other risk factors for TdP/ALQTS, including female sex and advanced age,[17,30] as dementias such as AD are more prevalent in individuals of advanced age and in females.[44] To illustrate, amongst the British Columbia cohort of new AChEI users, 95% were over age 65 and 60% of the cohort were female.[43] Nonetheless, these characteristics are expected to be common among all AChEI users. In spite of similar efficacy and safety profiles between the three AChEIs, there are still some pharmacological differences (summarized in Table 1 alongside regulatory agency information) between the three AChEIs – differences which may theoretically provide an explanation as to why only donepezil has been identified as a medication with "known risk" to prolong the QT_C interval and be associated with TdP – which in turn gives credence to the CredibleMeds classification.

1.6 | Two important similarities that may be associated with risk of arrhythmia – but do not result in differences in risk between acetylcholinesterase inhibitors

Prior to listing pharmacological differences between the three AChEIs, it is important to note two similarities that are associated with risk – although these similarities should not result in *differing* risk between AChEIs. As mentioned, all AChEIs are associated with bradycardia; one mechanism is through the blockage of cholinesterase (associated with the vagal nerve) causing atrioventricular,[45,46] or sinoatrial block.[39] Blockage of cholinesterase associated with the vagal nerve can also cause prolonged QT[45]; atrioventricular block is known to be associated with increased risk of QT_C prolongation and TdP in certain patients.[42]

Notably, as previously stated, bradycardia is also known to increase the risk of medication-associated ALQTS[31] and bradycardia is a risk factor for TdP in patients with prolonged QT[32]; certain mutations occurring in congenital LQTS are also associated with bradycardia.[47] Contrasting this, other studies have not found bradycardia to be a risk factor for QT_C prolongation,[17,30] although this may be due to study methodology.[30]

Between AChEIs, it has been shown that bradycardia occurs at a similar frequency.[9] As such, although bradycardia may contribute

TABLE 1 Summary of mechanisms of QT_C prolongation and TdP malignant arrhythmia by AChEI medications, as well as summary of regulatory agency information

	Donepezil	Galantamine	Rivastigmine
CredibleMeds classification	Known-risk (prolongs QT_C interval and associated with TdP even when used as directed on medication label)[25]	Conditional-risk (associated with TdP but only under certain conditions, such as overdose, electrolyte abnormalities, or drug interactions)[25]	Not listed on CredibleMeds
Regulatory agency information, postmarketing	QT_C prolongation and TdP added to postmarketing section of FDA medication label for Aricept in 2015. However, no alert for Health Canada.	Mention of occurrence of QT_C prolongation and TdP in singular postmarketing report for Razadyne, but QT_C prolongation and TdP not specifically listed under postmarketing section of FDA medication label. Complete atrioventricular block listed under postmarketing.	Only tachycardia listed under postmarketing section of FDA medication label.
Common mechanisms of QT_C prolongation and TdP malignant arrhythmia	Increased intracellular calcium as a result of cardiac ACh receptor action Bradycardia-associated QT_C prolongation Drug-drug interaction due to metabolism by CYP3A4 and 2D6 (donepezil and galantamine only) Increases spatial dispersion of repolarization (donepezil and galantamine only)		
Unique mechanisms of QT_C prolongation and TdP malignant arrhythmia	Potent inhibitor of I_{Kr} (tail current inhibited at IC_{50} of 1.3 μM with metabolites inhibiting at similar IC_{50}); concentration of donepezil during regular and prolonged use may reach IC_{50} Inhibits the $K_V11.1$ channel protein expression and channel protein trafficking to the plasma membrane σ_1 receptor agonist at therapeutic doses	Weak inhibitor of I_{Kr} (IC_{50} of 760.2 μM) No studies found regarding other effects, such as $K_V11.1$ channel protein expression and trafficking	No relevant drug-drug interactions No studies found regarding inhibition of I_{Kr} or other effects on $K_V11.1$ channel protein Does not increase spatial dispersion of repolarization

Abbreviations: FDA, Food and Drug Administration; QT_C, corrected QT interval; TdP, torsades de pointes.

to an increased risk of QT_C prolongation and TdP in general, when the similar frequency of bradycardia is considered concurrently with the mechanism through which bradycardia (or atrioventricular block) may occur, increased risk of QT_C prolongation and TdP for an individual AChEI (ie, donepezil) cannot be attributed to bradycardia.

It has also been found that activation of cardiac ACh receptors will open voltage-gated calcium channels; this in turn leads to the conclusion that intracellular calcium levels increase, prolonging the cardiac action potential cycle, and hence increasing risk of ventricular arrhythmias.[48] However, it is unlikely that differences in risk of arrhythmia would occur on the basis of ACh activation of cardiac ACh receptors – as all AChEIs increase ACh levels. As well, there is no evidence that one AChEI results in drastically different levels of ACh in comparison to other AChEIs; otherwise, significant efficacy or safety differences should be seen.

1.7 | Mechanistic differences that may not be associated with differences in risk

There are some pharmacological differences between the three AChEIs that are likely *not* associated with QT_C interval prolongation and TdP – including the positive allosteric modulator activity of galantamine on the nicotinic ACh receptor, and the inhibition of butyrylcholinesterase by rivastigmine.[49] Donepezil and rivastigmine are reported to not have allosteric modulator activity on the nicotinic ACh receptor,[50] although one study on rat brains found that donepezil desensitizes the nicotinic ACh receptor on substantia nigra dopaminergic neurons by being a non-competitive *antagonist*.[51]

Nicotinic ACh receptor allosteric effects by galantamine, towards QT_C prolongation or TdP, are not known – and it may be that there are no relevant effects towards cardiac arrhythmias. This may be due to several reasons: there is a massive diversity and wide distribution of nicotinic ACh receptors,[52] all AChEIs increase ACh – which act on nicotinic ACh receptors regardless, and maximum levels of receptor activation remain unchanged in the presence of positive allosteric modulators.[53] However, one study found that galantamine increases dopamine output in the prefrontal cortex of rat brains, suggesting that this effect is due to the allosteric potentiation of nicotinic ACh receptors.[54] Dopamine is known to induce ventricular arrhythmias in animals and it may be associated with sinus tachycardia in humans as well.[55] On the other hand, it is not known if the particular increased release of dopamine *specifically* in the brain (caused by the potentiation of nicotinic ACh receptors by galantamine) would affect the heart.

Butyrylcholinesterase is dominant enzyme in the periphery and metabolises many different exogenous compounds.[49] For example, suxamethonium (an analogue of ACh) may cause arrhythmia when there is low butyrylcholinesterase activity.[56] A study also found that administration of butyrylcholinsterase with a lethal dose of sarin

vapour in minipigs increased survivability and also prevented cardiac abnormalities.[57] However, no definitive conclusions regarding overall cardiac function in humans and the inhibition of butyrylcholinsterase by rivastigmine can be drawn.

1.8 | Drug-drug interactions and acetylcholinesterase inhibitors

When considering differences between AChEIs that may affect risk of QT_C prolongation or TdP, donepezil and galantamine may have significant pharmacokinetic drug interactions[58]; this is explained by donepezil and galantamine being metabolized by the cytochrome enzymes CYP3A4 and CYP2D6.[9] These are two hepatic cytochrome enzymes associated with clinically significant drug-drug interactions,[12,59] or in other words, these cytochrome metabolic pathways are often shared by concomitantly prescribed medications.[9] Meanwhile, rivastigmine bypasses the hepatic metabolism pathways and relevant drug-drug interactions are not expected.[60]

However, hepatic metabolism (or lack thereof) by cytochrome enzymes would *only* explain a greater risk of QT_C-interval prolongation due to pharmacokinetic drug-drug interactions; donepezil is on the known-risk list of CredibleMeds, which is not necessarily "conditional" upon drug-drug interactions.[25] In contrast, though, these drug-drug interactions by galantamine *would* explain why galantamine is on the *conditional-risk* list.[36]

1.9 | Mechanistic differences that are associated with differences in risk

It can be speculated that the significant blockage of I_{Kr}[61] is a potential explanation as to why donepezil is on the known-risk list of CredibleMeds – and is associated with both QT_C prolongation and TdP during routine use. Other mechanisms that can also contribute to this increase in risk are: the effect of donepezil on $K_V11.1$ trafficking,[24] donepezil increasing spatial dispersion of repolarization[62] and, potentially to a lesser degree, the σ_1 receptor agonist activity of donepezil.[63]

1.10 | Potency of I_{Kr} inhibition by donepezil

A crucial difference in risk may lie in the potency of I_{Kr} inhibition; pharmacological research studies pertaining to I_{Kr} inhibition by donepezil and galantamine are found in the literature. Regarding rivastigmine, no literature is available regarding I_{Kr} inhibition; only a study on rivastigmine block of two hippocampal neuronal potassium channels was reported.[64]

Although the ability of a medication to block I_{Kr} cannot fully explain TdP risk,[18] it can explain the relative difference in risk. A study by Chae et al found that donepezil inhibits the tail current of I_{Kr} with an IC_{50} of 1.3 μM, with the metabolites of donepezil inhibiting the tail current at a similar concentration.[61] On the other hand, a study by Vigneault et al found that galantamine inhibits I_{Kr} with an IC_{50} of 760.2 μM.[65] In comparison, a study by Kamiya et al looked at terfenadine and cisapride (two medications withdrawn from market over proarrhythmic concerns about 20 years ago)[19] and found that IC_{50} of I_{Kr} block by terfenadine and cisapride was 0.35 μM and 0.63 μM respectively.[66]

Because the external potassium concentrations used by Chae et al and Vigneault et al is not entirely identical (5 mM versus 4 mM respectively,[61,65]), methodology differences could explain some variance but would not result in major differences (700 fold) in the IC_{50} values estimated. Still, the two studies were not head-to-head comparisons, and head-to-head studies would provide much stronger evidence with regards to the potency of inhibition of I_{Kr}. IC_{50} is defined as the concentration of an inhibitor in which a response is lowered by half, and it is considered as a measure of potency of an antagonist.[67] In lieu of a head-to-head comparison, using the two studies by Chae et al and Vigneault et al, donepezil is a far more potent inhibitor of I_{Kr} than galantamine (and an relatively potent I_{Kr} blocker overall when compared to cisapride) – the concentration of donepezil required to inhibit the I_{Kr} current (by half) is considerably lower than the concentration of galantamine required.

It must be noted that the IC_{50} experimentally determined (1.3 μM) is much higher than the therapeutic plasma concentration of donepezil used in the treatment of AD (Cmax of 60.5 μg/L or 0.16 μM for the 10 mg dose in healthy patients).[68] However, donepezil has been shown to accumulate in humans after multiple doses (in which the accumulated concentration is enough to block I_{Kr} according to Chae et al).[61] Indeed, donepezil has an elimination half-life of over 100 hours in the elderly – where reduced clearance is expected,[69] so repeated dosing will very likely cause clinically significant medication accumulation. As well, donepezil has a large volume of distribution which signifies a large proportion of the medication is distributed into the tissue; the heart-to-plasma partition coefficient of donepezil is 6.32 ± 0.79 in rat heart tissue.[70] With the 10 mg dose of donepezil having a Cmax of 60.5 μg/L (0.16 μM)[68]; when multiplied by the heart-to-plasma partition coefficient, the concentration in the heart would be approximately 1.01 μM, which is not much lower than the IC_{50} of I_{Kr} block by donepezil (1.3 μM). Importantly, although the aforementioned partition coefficient pharmacokinetic data is interesting to note, it is unknown if the 1.01 μM heart concentration calculated through the rat heart tissue plasma partition coefficient would accurately represent the concentration in human heart tissue during routine clinical use.

1.11 | Other relevant mechanisms which may contribute to the increased risk seen in donepezil

There are other differences between AChEIs – including donepezil inhibiting $K_V11.1$ channel protein expression and channel protein trafficking to the plasma membrane.[24] This characteristic is similar to inhibition of $K_V11.1$ protein channel trafficking by escitalopram[61]

– an antidepressant also on the known-risk list of CredibleMeds.[36] Donepezil, escitalopram and citalopram (the racemic mixture of escitalopram and of known-risk as well)[36] all inhibit $K_V11.1$ channel trafficking.[24] Similarly, arsenic trioxide (yet another medication on the CredibleMeds known-risk list[36]) is known to prolong the QT_C interval by inhibition of $K_V11.1$ trafficking, and not via direct I_{Kr} block.[71] Importantly, lowered $K_V11.1$ density (such as during hypokalemia) contributes to loss of function of $K_V11.1$.[72,73] No studies reported any interactions with galantamine or rivastigmine and $K_V11.1$ channel trafficking.

Another finding that may support the increased risk for donepezil and QT_C prolongation or TdP is a recently published (2020) study by Ellermann et al. Female rabbit hearts were treated with one of the three AChEIs in rising concentrations – donepezil was found to prolong the QT interval and action potential duration, induce early afterdepolarizations and TdP, and augment spatial dispersion of repolarization; galantamine induced early afterdepolarizations and TdP, and augmented spatial dispersion of repolarization, but *decreased* QT interval and action potential duration; rivastigmine prolonged the QT interval and action potential duration, but did not augment spatial dispersion of repolarization and TdP was not observed.[62] In other words, of the three AChEIs, *only* donepezil prolonged QT interval and action potential duration, triggered early afterdepolarizations and TdP, *and* augmented spatial dispersion of repolarization.

Regarding the last observation, some heterogeneity during the refractory period of cardiomyocyte conduction is considered normal.[74] However, an inhomogeneous (or more heterogenous) spatial dispersion of cardiac repolarization is what induces the early afterdepolarizations (a premature inwards depolarization current during the abnormally prolonged repolarization phase)[11] which then leads to TdP.[62,75] Importantly, a stable dispersion of cardiac repolarization, even in the presence of a substantially prolonged QT interval, actually prevents arrhythmia.[75]

Lastly, a mechanism that may be involved in the risk of QT_C prolongation/TdP by donepezil is the σ_1 receptor agonist activity of donepezil. σ_1 receptor activity of galantamine or rivastigmine is less researched and have conflicting results.[76–78] Donepezil binds to σ_1 receptors in the human brain at therapeutic doses, possibly contributing to the mechanism of pharmacological action of donepezil, as σ_1 receptors play a role in the pathophysiology of several neuropsychiatric diseases.[77]

Although σ_1 receptors are known to have high importance in the nervous system, σ_1 receptors are widely found.[79] Limited studies have shown that nanomolar concentrations of σ_1 receptor ligands increase contractility, contraction frequency, and cause irregular contractions in newborn rat cardiomyocytes; as well, various σ receptor ligands have been found to inhibit potassium currents in the central nervous system, which may also translate to inhibition of cardiac potassium channels – thus increasing QT_C duration and causing TdP.[63] Indeed, it has also been found that σ_1 receptor antagonists have antiarrhythmic effects against epinephrine-induced arrhythmias in rats, and σ_1 agonists had proarrhythmic effects; it was hypothesized that these particular results are dependent upon cardiac and not central nervous system σ receptors[80] and it is known that σ_1 receptors are found in the membranes of adult rat ventricular cardiomyocytes.[81] However, a recently published (2020) systematic review puts doubt upon the negative effects of σ_1 activation; it was found that activation of σ_1 receptors have a role in cardioprotection against hypertrophy, cellular toxicity/apoptosis, and maladaptive endoplasmic reticulum stress responses; as well, σ_1 receptors promote $K_V11.1$ expression (although results are conflicting on this matter).[81]

1.12 | Clinical and epidemiological literature regarding potential increased risk associated with donepezil

Studies have examined the association between AChEIs and bradycardia, likely due to the peripheral parasympathomimetic effects of AChEIs resulting in increased risk of bradycardia as already described. As previously mentioned, bradycardia has been determined to occur at similar frequency between AChEIs.[9] However, it is important to review studies of AChEI use and bradycardia – despite bradycardia being associated with risk for QT_C prolongation and TdP,[31,32] assessment of all adverse cardiac events at once may be difficult to do.

To illustrate, two relevant studies are cohort studies conducted using administrative databases by Gill et al and Hernandez et al, both published in 2009. Gill et al looked at Ontario data between 2002 and 2004; it was found that AChEI use in comparison to non-use was associated with increased frequency of hospital visits for syncope (adjusted hazard ratio (aHR) 1.76, 95% CI 1.57-1.98), bradycardia (aHR 1.69, 95% CI 1.32-2.15), permanent pacemaker insertion (aHR 1.49, 95% CI 1.12-2.00), and hip fracture (aHR 1.18, 95% CI 1.04-1.34).[33,82] However, using the comparison group of "non-use" may be confounded by indication and heathy user bias.[83] Nevertheless, both AChEI use and non-use cohorts were defined from patients with diagnoses of dementia.[33] Notably, though, a different study also conducted using Ontario administrative data found that AChEI use *reduced* risk of pacemaker insertion (unadjusted HR 0.58, 95% CI 0.55-0.61) with adjustment for covariates not notably changing results.[84]

Hernandez et al looked at a different population (New England Veterans Affairs Healthcare System between 1999 and 2007) and found a similar result to Gill et al; a greater risk for bradycardia in the patients taking AChEIs (in comparison to non-use, aHR 1.4, 95% CI 1.1-1.6) was seen.[34,82] It was also found that patients with bradycardia are more likely to experience falls, syncope, or have a pacemaker implantation.[34]

With regards to the studies by Gill et al and Hernandez et al, it must be noted that bradycardia can lead to syncope, and this can lead to falls and likewise fall-related injuries (such as hip fracture).[33] Notably, syncope (as a symptom by itself) is associated with malignant tachycardic arrhythmias such as TdP.[12] Neither the methodology of the Gill et al nor the Hernandez et al study allowed for the investigation of tachycardias; the methodology used only included

administrative data coding specifically for bradycardia or low heart rate.[33,34] As such, on a population scale, it was not determined how exactly AChEIs may be associated with QT_C prolongation or tachycardias such as TdP, despite AChEIs being strongly associated with bradycardia. Proxy measures such as syncope would not be valid, and a separate methodology is required.

Two studies that specifically analyzed donepezil treatment on a variety of ECG parameters are a study by Igeta et al, published in 2014, and a study by Wang et al, published in 2018.[45,85] The study by Igeta et al was retrospective in design with the analysis of medical records, whereas the study by Wang et al was prospective in design with the recruitment of patients. Both studies found that administration of donepezil reduced heart rate, supporting the findings by Gill et al and Hernandez et al where an increased risk of bradycardia was observed. Importantly, neither study found that QT_C was prolonged subsequently to the administration of donepezil.[45,85] However, both studies do note case reports involving donepezil, prolonged QT interval, and TdP. Limitations of both studies include small sample size (Igeta et al, n = 18; Wang et al, n = 60) and a lack of comparisons against the other AChEIs; furthermore, the study by Wang et al involved stringent inclusion and exclusion criteria, limiting generalizability. Importantly though, both studies were conducted in elderly patients.

Another study that assessed only donepezil was a population-based case-control study that analyzed co-prescribing of donepezil with antibiotics and associated bradycardia/syncope; it noted no significant differences with regards to risks and co-prescription of donepezil with different antibiotics.[86]

1.13 | A review of case reports

Despite AChEI use being associated with increased risk of bradycardia, changes in ECG or cardiovascular function reported in empirical data have been inconsistent, as demonstrated between studies showing no change in QT_C contrasting case reports demonstrating QT_C prolongation and TdP[9,45,85] Furthermore, only minimal studies even report on QT_C. A recent 2019 abstract for a systematic review pertaining to all AChEI effects on cardiac conduction (including QT_C intervals and occurrence of TdP) found only four randomized-controlled trials and five cohort studies which reported on QT_C interval – of which only one randomized-controlled trial and one cohort study reported clinically significant results.[87] Additionally, no population-based studies examined the *comparative* impact of the different AChEIs on malignant arrhythmias such as TdP. Given this, it would be prudent to review case reports that are published in the literature.

We identified and reviewed six individual case reports (summarized in Table 2). Four of them involved patients taking donepezil, while one case involved galantamine and one involved rivastigmine. Five identified cases occurred in very old individuals (one case age 78, other cases aged >80); most cases had prolonged QT_C intervals (some extremely prolonged;> 600 ms), with QT_C interval normalizing after discontinuation of the AChEI. Three cases occurred in males and three in females. Four of six identified cases also had occurrences of arrhythmia. However, not all patients were on multiple medications, nor did all patients have comorbidities.[69,88–92] Of the four donepezil cases, two cases had minimal comorbidity or polypharmacy relative to other cases,[69,88] perhaps making donepezil more likely to be causally associated with the QT_C prolongation and arrhythmia (relative to the other cases). For the Vogel et al case,[92] donepezil was also considered the likely cause of the observed QT_C prolongation, in spite of the existing comorbidities and polypharmacy. Importantly, the Vogel et al case was the only one we found occurring in a young individual.[92] Findings also worth highlighting include one case having observations of complete atrioventricular block, bradycardia, and ventricular tachyarrhythmia,[69] as well as a case with findings of low heart rate concurrently with premature ventricular contractions[89] (premature ventricular contractions are concerning when in combination with bradycardia[32]).

Four of the six case reports we reviewed also provided summaries of other case reports in literature. Gurbuz et al [88] noted that they found five reported cases of QT_C prolongation associated with donepezil use, with three cases experiencing TdP. Vogel et al reported two additional case reports (not previously described by us or by Gurbuz et al) of QT_C prolongation associated with donepezil use.[92] Most other cases had significant comorbidities and/or polypharmacy; all cases occurred in individuals aged 80 and over.[92] Another case report primarily summarized cases of bradycardia and atrioventricular block with donepezil use,[69] while the fourth case report[91] provided a summary of reports to the Australian Adverse Drug Reaction Advisory Committee prior to June 2007, and found that galantamine had the highest rate of reporting for arrhythmia.

Malik et al published a series of seven cases involving donepezil use, QT_C prolongation, and TdP. We reviewed this case series in detail as it was a more in-depth description of cases (relative to aforementioned case reports which only provided short summaries of other cases), it was more recent (published in December 2019), and only one case was previously reviewed by us (Takaya et al).[48] This case series focused on donepezil and did not examine galantamine or rivastigmine.[48,93] Two additional cases from this series (not previously described by us, by Gurbuz et al, or by Vogel et al) occurred in female patients over the age of 80 who were on multiple medications and had hypertension.[48] One of these cases is of exceptional significance as the patient developed asymptomatic TdP multiple times without a finding of prolonged QT_C.[48,94] Findings of TdP in the absence of prolonged QT_C have also occurred in other patients; for example, a 72 year old female patient on sotalol and dofetilide.[95]

In the seven cases reviewed by Malik et al,[48] six cases occurred in females and one occurred in a male; all cases occurred in patients over age 80. Of six cases that had findings of prolonged QT_C, three developed TdP (including the Takaya et al case we described). Donepezil was withdrawn in five of the six cases with prolonged QT_C (and also withdrawn for the case without prolonged QT_C); findings of normalized QT_C were seen in four of the five cases. The Takaya et al case did not result in a normalization of QT_C (as described in Table 2) although withdrawal of donepezil did reduce QT_C from 645 ms to 485 ms For

TABLE 2 Summary of selected case reports regarding acetylcholinesterase inhibitors and QT_C prolongation/malignant arrhythmia, chronologically ordered

Case report	Culpable medication	Patient age/sex	Relevant details
Walsh et al 2002[90]	Rivastigmine	78M	Polypharmacy (also receiving diltiazem, citalopram, furosemide, aspirin, ranitidine) Low-normal serum potassium (3.4 mM) Prior to initiation of rivastigmine, normal QT_C (397 ms) Seven days after initiation of rivastigmine, QT_C measured to be prolonged (477 ms) One-week post-discontinuation, QT_C measured to be normal at 399 ms; QT_C remained normal two-months post-discontinuation
Suleyman et al 2006[69]	Donepezil	82M	Patient admitted to ED for dizziness and syncope Patient used 10 mg/day donepezil for past month; no history of other drug use No history of cardiac disease ECG revealed complete AV block and ventricular tachyarrhythmia; heart rate at admission was extremely low at 35 beats per minute Patient treated via stoppage of donepezil and temporary pacemaker; discharged after six days
Fisher et al 2008[91]	Galantamine	85M	Patient treated with extended release galantamine 8 mg/day for 1.5 years History of CAD, hypertension, and other comorbidities; prior occurrence of syncope and bradycardia At time of admission, patient had syncope, prolonged QT_C, serious cardiac arrhythmias (including premature ventricular contractions), vomiting, and diarrhea At time of admission, use of multiple medications (irbesartan; clopidogrel; simvastatin; pantoprazole, ergocalciferol; calcium carbonate; acetaminophen) After admission, galantamine and irbesartan was ceased (the second cessation of galantamine for the patient) and QT_C normalized from 503 ms to 443 ms after four days
Takaya et al 2009[89]	Donepezil	83F	History of MI and multiple other comorbidities Admitted for diarrhea, vomiting, syncope; no previous history of syncope Lower than normal heart rate at admission at 54 beats per minute Use of 5 mg/day of donepezil for at least two years and bisoprolol Lab work showed low plasma potassium and ECG showed QT_C of 645 ms Ventricular premature contractions frequently recorded on ECG monitoring Confirmed TdP on continuous ECG monitoring Donepezil washed out; QT_C still prolonged (485 ms) on 14th day after admission, but patient discharged in stable condition
Gurbuz et al 2016[88]	Donepezil	84F	Patient admitted to ED due to recurrent syncope Concomitant drugs include donepezil 10 mg (used for one year at time of admission), ramipril, and ASA No history of antiarrhythmic drug use nor family history of LQTS or sudden cardiac death; prior occurrence of syncope (three years prior to current admission) Lab work showed normal electrolytes QT_C interval extremely prolonged (624 ms) at admission; TdP episode occurred during follow-up in coronary care unit Donepezil removed from drug regimen and QT_C interval normalized within 10 days (to 430 ms) One-year follow-up resulted in no further complaints of palpitations and syncope
Vogel et al 2019[92]	Donepezil	26F	Patient admitted to impatient psychiatric hospital for suicide attempt not from overdose Medical history of major depression, traumatic brain injury, seizures, hemiplegia, gastroesophageal reflux disease, tachycardia At time of admission, patient was taking quetiapine, divalproex sodium, metoprolol, montelukast, polyethylene glycol-3350, calcium with vitamin D, pantoprazole, and cephalexin Donepezil initiated several weeks after admission, starting at 5 mg/once daily, titrated up to 20 mg after three weeks (10 mg/twice daily) ECG after last dose change shows QT_C of 463 ms and follow-up ECG showed QT_C of 528 ms At last dose change, patient was also taking pantoprazole and quetiapine Laboratory results were normal during hospital stay; discontinuation of donepezil normalized QT_C

Abbreviations: ASA, acetylsalicylic acid; AV, atrioventricular; CAD, coronary artery disease; ECG, electrocardiogram; ED, emergency department; LQTS, long-QT syndrome; MI, myocardial infarction; QT_C, corrected QT interval.

the case where donepezil was not withdrawn, benidipine was switched to amlodipine which resulted in normalized QT_C.

Two other cases specifically worth noting from the case series are the cases published by Tanaka et al in 2009 – both cases (90-year-old male, 87-year old female) had bradycardia, atrioventricular block, and QT_C prolongation, with the 87-year-old female also developing TdP followed by ventricular fibrillation.[48]

2 | CONCLUSION

Donepezil is the only agent – among all AChEIs used to treat dementias such as AD – that is deemed to be associated with a known-risk of QTc prolongation and TdP malignant arrhythmia.[36] This narrative review found that the evidence for QT_C prolongation and associated TdP regarding donepezil consists only of case reports,[48,69,88,89,92,94] and pharmacological studies with potential explanations for increased risk.[24,61,62] Table 1 shows several mechanisms may explain the QT_C prolongation and TdP by donepezil and contrasts it against galantamine and rivastigmine. Still, the current knowledge on this topic is limited – no population-based epidemiological studies have examined the comparative risk of malignant arrhythmias associated with use of the three different AChEIs.[82]

A comparative study between AChEIs is needed, as case reports or pharmacological literature is not conclusive evidence of increased risk for donepezil. It is expected that observational epidemiological studies, such as a population-based retrospective cohort (in the same vein as studies regarding AChEIs and bradycardia,[33,34]) be conducted to confirm if the increased risk with donepezil use is in fact appearing in the real-life practice. If results show that there are differences in risk of malignant arrhythmias such as TdP between the AChEIs, then changes in prescribing patterns should be made.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

YH and WA conceived the concept of this article. YH performed the research and wrote the first draft of the article. YH and WA reviewed and approved the manuscript.

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