



Cholinesterase inhibitors in people with dementia with Lewy bodies and cardiac conduction abnormalities

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Lancet Neurol 2026; 25: 864–72

See [Comment](#) page 795

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Bradycardia due to cardiac conduction abnormalities is prevalent in patients with dementia with Lewy bodies possibly due to autonomic dysfunction and neurodegeneration. Cholinesterase inhibitors remain the most effective treatment for cognitive and neuropsychiatric symptoms in patients with dementia with Lewy bodies, but are often withheld due to concerns of potentially worsening cardiac risk. Randomised clinical trials and meta-analysis evidence support a favourable cardiac safety profile for cholinesterase inhibitors in dementia with Lewy bodies. Emerging evidence challenges the conventional avoidance of cholinesterase inhibitors in patients who have dementia with Lewy bodies and cardiac abnormalities, and suggests that these patients can also be treated with cholinesterase inhibitors without increasing the risk of major cardiovascular events. Integrating available evidence with a pragmatic, expert-informed approach, and cardiac screening and monitoring, can enable patients with dementia with Lewy bodies and cardiac abnormalities to benefit from cholinesterase inhibitors.

Introduction

Dementia with Lewy bodies is the second most common neurodegenerative cause of dementia, affecting approximately 1.4 million people in the USA alone.¹ The condition is characterised neuropathologically by accumulation of α -synuclein-containing Lewy bodies, and clinically defined by the presence of dementia, plus at least two of four core symptoms: recurrent visual hallucinations, parkinsonism, cognitive fluctuations, and rapid eye movement sleep behaviour disorder.² Additional multisystem symptoms include autonomic dysfunction, urinary symptoms, constipation, depression, and delusions. Dementia with Lewy bodies is closely related to Parkinson's disease dementia, which has overlapping symptoms. The two conditions are separated by a so-called 1-year rule: dementia with Lewy bodies is diagnosed when dementia occurs before or within 1 year of parkinsonism onset, whereas Parkinson's disease dementia is diagnosed when dementia occurs more than 1 year after onset of parkinsonism. Lewy body dementia, an umbrella term, is used to refer to both dementia subtypes.

Cholinesterase inhibitors are the core treatment option to improve cognition in people with dementia with Lewy bodies, and are usually prescribed as rivastigmine or donepezil.³ Although rivastigmine is only licensed for Parkinson's disease dementia in the USA and Europe, and donepezil for dementia with Lewy bodies in Japan, both drugs are recommended by the UK National Institute for Health and Care Excellence as first-line treatment for dementia with Lewy bodies⁴ and are widely used. Comparatively less evidence supports the use of galantamine in dementia with Lewy bodies.³

Cholinesterase inhibitors are usually effective in dementia with Lewy bodies, but a concern is their propensity to cause or worsen cardiac conduction abnormalities due to their cholinergic effects on the heart. Although also a potential risk in other dementias, such as Alzheimer's disease, greater clinical implications exist for patients with dementia with Lewy bodies, for whom cardiac abnormalities are more common.⁵ With the recent

creation of biological frameworks for diagnosis of Parkinson's disease and other synucleinopathies,^{6,7} and advances in diagnostic biomarkers,⁸ dementia with Lewy bodies is more readily diagnosed, making a reassessment of the role of cholinesterase inhibitors timely.

In this Personal View, we discuss the higher frequency of cardiac conduction abnormalities in dementia with Lewy bodies compared with other dementias, and review their potential pathophysiological mechanisms. We also synthesise evidence of the effects of cholinesterase inhibitors in dementia with Lewy bodies on cognition and of their cardiovascular safety in general, with a focus on their safety in Lewy body dementia. By integrating this evidence, and on the basis of our clinical experience, we propose a pragmatic, expert-informed framework for safely administering cholinesterase inhibitors in patients with dementia with Lewy bodies.

Frequency of cardiac conduction abnormalities

Patients with dementia with Lewy bodies are more likely to have cardiac conduction abnormalities than patients with other causes of dementia. In an observational study that did not differentiate between subtypes of Lewy body dementia, higher percentages of prolonged P-wave durations and increased P-wave terminal forces (ie, an electrocardiogram [ECG] marker of impaired atrial function, overload, and risk of atrial fibrillation) were seen in patients with Lewy body dementia (58%) than in those with Alzheimer's disease (12%); however, no differences in the prevalence of atrial enlargement were observed.⁵ A Swedish study of 73 619 individuals with dementia found that sick sinus syndrome requiring pacemaker implantation was more frequent in those with dementia with Lewy bodies (2.2%) than in Alzheimer's disease (1.5%).⁹ After adjustment for confounders, people with dementia with Lewy bodies had nearly 50% greater odds of pacemaker-treated sick sinus syndrome than those with Alzheimer's disease.⁹ Consistent with these findings, an autopsy-based study found a higher incidence of sudden cardiac death in individuals with autopsy-confirmed

α -synuclein pathologies (ie, Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy) compared with healthy controls (51% vs 23%), with a greater number of patients with sick sinus syndrome who also had α -synuclein pathologies compared with controls (5.2% vs 1.9%).¹⁰ However, medication exposure was not reported in the study, which could be an important potential confound, as patients with synucleinopathies are often treated with cholinesterase inhibitors, which themselves could cause cardiac side-effects. In a Swedish memory clinic study of 30 patients with dementia with Lewy bodies, designed to explore undetected bradyarrhythmias, 13 patients (46%) had bradycardia at rest and three patients were diagnosed with sick sinus syndrome.¹¹ During follow-up, two patients with sick sinus syndrome required pacemaker insertion.¹¹

A greater incidence of atrial fibrillation is also seen in people with dementia with Lewy bodies. In a mixed cohort of people with Alzheimer's disease and dementia with Lewy bodies (n=461), the incidence of atrial fibrillation was double in those with dementia with Lewy bodies (22%) compared with Alzheimer's disease (11%), after adjusting for vascular risk factors.¹² Differences in heart rate variability were also found in patients with autopsy-confirmed dementia with Lewy bodies, compared with autopsy-confirmed Alzheimer's disease.¹³ Over a period of 10 years, heart rate variability decreased and corrected QT intervals increased in those with dementia with Lewy bodies, but not in people with Alzheimer's disease. The higher frequency of cardiac conduction abnormalities in people with dementia with Lewy bodies compared with other dementias means that clinicians might avoid prescribing cholinesterase inhibitors due to concerns around cardiac risk.

Potential pathophysiological mechanisms

At least three potential mechanisms exist for the increased prevalence of cardiac conduction abnormalities in dementia with Lewy bodies (figure 1). The first involves cardiac conduction deficits, which can arise due to direct effects of α -synuclein on cardiac tissue. α -Synuclein inclusions are found beyond the brain, including in the sinoatrial and atrioventricular nodes—crucial components of the cardiac conduction system.⁹ Post-mortem data show α -synuclein deposition in epicardial nerves in about 94% of individuals with Lewy body dementia, compared with 6% of those with multiple system atrophy and none in controls.¹⁰ A post-mortem study revealed greater densities of α -synuclein in the myocardium of people with dementia with Lewy bodies than in controls, with cardiac α -synuclein density correlating with α -synuclein density in the brain.¹⁴

A second mechanism for the increased prevalence might be cardiac sympathetic denervation, which can be detected using cardiac [¹²³I]metaiodobenzylguanidine scanning. In a study examining ¹⁸F-dopamine PET images in multiple body organs of people with Parkinson's disease and pure autonomic failure, with post-mortem

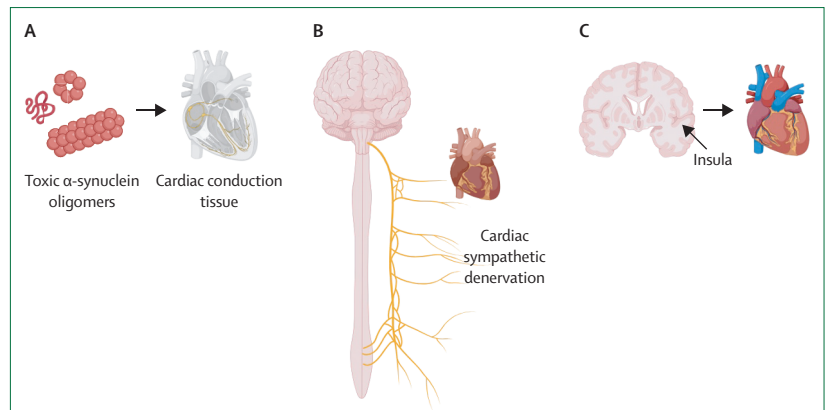


Figure 1: Potential pathophysiological mechanisms for cardiac conduction abnormalities in dementia with Lewy bodies

(A) α -Synuclein has a direct effect on cardiac tissue, with post-mortem data showing α -synuclein inclusions in epicardial nerves and in the sinoatrial and atrioventricular nodes. (B) Cardiac sympathetic denervation, detected using cardiac [¹²³I]metaiodobenzylguanidine scanning, is a second potential mechanism contributing to cardiac conduction abnormalities in dementia with Lewy bodies. (C) Effects from the insula on the heart are a third potential mechanism. The insula regulates autonomic activity via autonomic central tracts and has been implicated in dementia with Lewy bodies in studies with [¹⁸F]fluorodeoxyglucose-PET and grey matter atrophy studies.

neurochemical norepinephrine quantification, ¹⁸F-dopamine depletion was cardiac-specific, with decreased norepinephrine in the myocardium, but not in other systemic organs.¹⁵

A third mechanism for increased cardiac conduction deficits in people with dementia with Lewy bodies could be associated with the remote effects from the insula on the heart. The insula has a central role in regulating autonomic activity, with studies showing it can affect cardiac conduction. For example, in a study of patients with epilepsy undergoing intraoperative insular stimulation, cardiovascular changes could be elicited by stimulating the insular cortex.¹⁶ In post-stroke patients, those with strokes involving the insular cortex had higher concentrations of plasma norepinephrine and associated increases in heart rate, compared with patients whose strokes did not involve the insular cortex.¹⁷ In a large study of 43 994 healthy individuals, reduced integrity of central autonomic networks, especially connections with the insula, was linked with an increased hazard ratio [HR] for major cardiovascular events.¹⁸ The insula is strongly implicated in dementia with Lewy bodies. At post-mortem, increased α -synuclein is found in the insular cortex,¹⁹ and reduced insula synaptic density²⁰ is seen in patients with dementia with Lewy bodies compared with controls. Insula involvement in dementia with Lewy bodies is also shown in imaging studies using [¹⁸F]fluorodeoxyglucose-PET²¹ and grey matter atrophy.²² However, there is no direct evidence showing that insula changes cause cardiac conduction abnormalities in people with dementia with Lewy bodies. The insula is also affected in other dementias; early insula involvement is seen in people with frontotemporal dementia,²³ in whom autonomic dysfunction is also recognised.²⁴ These mechanisms likely act cumulatively to produce the increased prevalence of

cardiac conduction abnormalities seen in people with dementia with Lewy bodies.

Effects of cholinesterase inhibitors on cognition

The main treatment for cognitive decline in dementia with Lewy bodies is acetylcholine augmentation using cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine. There is strong evidence for dysfunction in cholinergic pathways for people with the condition: the nucleus basalis of Meynert, the main source of cholinergic transmission in the brain, shows early atrophy in dementia with Lewy bodies²⁵ and in mild cognitive impairment due to Lewy bodies,²⁶ and a loss of structural connectivity.²⁷ A study using [¹⁸F]fluoroethoxybenzovesamicol PET to examine cholinergic terminals revealed severe cholinergic terminal loss in dementia with Lewy bodies,²⁸ as well as more pronounced cholinergic deficits than in people with Alzheimer's disease.²⁹

Benefits of donepezil^{30,31} and, to a lesser extent, rivastigmine,³² in treating cognitive deficits in dementia with Lewy bodies have been shown in randomised, placebo-controlled trials and observational studies in real-world settings. Although a Cochrane review³³ supported the use of cholinesterase inhibitors in Parkinson's disease dementia, evidence for their use in dementia with Lewy bodies was less clear. Of the six trials included in this review, only one focused on dementia with Lewy bodies³² and showed no improvement in Mini-Mental State Examination (MMSE) scores for oral rivastigmine over placebo. Furthermore, in the Cochrane review, the number of drop-outs was higher in patients on oral rivastigmine compared with placebo, a circumstance that was not found for donepezil. A systematic review of randomised controlled trials in Parkinson's disease dementia and dementia with Lewy bodies³⁴ also showed overall benefits of cholinesterase inhibitors on cognition, global clinical impression, and behaviour, with benefits of donepezil—but not rivastigmine—found in dementia with Lewy bodies. However, of the 15 included trials, only two focused on oral rivastigmine in dementia with Lewy bodies,^{32,35} of which only one assessed its benefits on MMSE scores³² (ie, the same trial included in the Cochrane review), with a high number of drop-outs due to side-effects.

A meta-analysis has also shown superiority of cholinesterase inhibitors over placebo,³¹ and a network meta-analysis of eight randomised controlled trials of cholinesterase inhibitors in dementia with Lewy bodies showed that both donepezil and rivastigmine had significant effects on cognition, with donepezil showing the greatest improvement; no improvement for either memantine (a low-affinity antagonist of NMDA receptors) or quetiapine (a serotonin and dopamine receptor antagonist) was found.³⁶ However, many of these trials were short, lasting only 12 weeks.

In a retrospective study of 204 patients with dementia with Lewy bodies in memory clinics, those treated with

cholinesterase inhibitors had higher MMSE and Montreal Cognitive Assessment scores than untreated patients after an 18-month follow-up.³⁷ In a large observational study of 1095 patients with dementia with Lewy bodies, use of cholinesterase inhibitors was associated with less cognitive decline compared with either memantine alone, or no treatment.³⁸ A meta-analysis of more than 80 trials using cholinesterase inhibitors in different forms of dementia revealed that the only moderator of treatment effect was the subtype of dementia, with larger treatment effects for Parkinson's disease dementia and dementia with Lewy bodies (2.11 MMSE points compared with 0.91 points in Alzheimer's disease or vascular dementia) at 6 months.³⁹ Overall, observational studies show that cholinesterase inhibitors generally offer improvements in cognition and daily functioning for people with dementia with Lewy bodies, while also reducing neuropsychiatric symptoms (including hallucinations). However, caution is required when interpreting treatment effects from observational studies, as they have a high risk of bias, including confounding by indication bias.

Cardiovascular safety of cholinesterase inhibitors

The cholinergic deficit in dementia with Lewy bodies originates from the CNS, arising from basal forebrain degeneration and loss of cortical cholinergic projections. By contrast, the dominant cardiac autonomic signal in synucleinopathies is noradrenergic (sympathetic) denervation, with α -synuclein-positive epicardial nerves and reduced concentrations of myocardial tyrosine hydroxylase and norepinephrine.^{10,14,15} Direct human evidence for parasympathetic cholinergic loss in the heart is scarce. Reported changes are mostly functional. For example, reduced vagal modulation on heart-rate variability or baroreflex measures and progressive corrected QT interval or heart rate variability differences are more frequent in people with dementia with Lewy bodies than in those with Alzheimer's disease.¹³

Randomised controlled trials provide the most reliable evidence for cardiac safety in Lewy body dementia; however, this evidence should be taken in the context that cardiac outcomes were not the primary endpoints and, in some trials, patients with known conduction abnormalities or bradyarrhythmias were excluded. In patients with dementia with Lewy bodies, two 12-week, randomised, placebo-controlled trials of donepezil reported efficacy, with no excess cardiac side-effects in the treatment groups,^{30,31} and a 20-week randomised controlled trial of rivastigmine showed no excess cardiac side-effects in the treatment group.³⁰⁻³² Although the two donepezil trials excluded patients with bradycardia, sick sinus syndrome, and atypical corrected QT intervals,^{30,31} there were no exclusions based on cardiac features in the rivastigmine trial.³² In a large randomised controlled trial of 410 patients with Parkinson's disease dementia, with no specific cardiac exclusion, no excess bradycardia, syncope, or cardiac deaths were found in the treatment group.⁴⁰

Evidence for the cardiac safety of cholinesterase inhibitors is supported by meta-analyses. In a review of safety data for rivastigmine in patients with dementia with Lewy bodies and Parkinson's disease dementia, modest mean heart-rate reductions were found (1.5–2 beats per min [BPM]), but there were no clinically meaningful differences in bradycardia or ECG abnormalities in patients on rivastigmine.⁴¹ A Cochrane review³³ found reduced mortality in patients treated with cholinesterase inhibitors, but these patients also reported more falls.³³ Taken together, evidence from randomised controlled trials and meta-analyses support a favourable cardiac safety profile for cholinesterase inhibitors for people with dementia with Lewy bodies. Whether this evidence extends to patients with existing cardiac disease was not examined in these studies.

Cholinesterase inhibitors and cardiovascular risk in patients at high risk for cardiac disease

Although most randomised controlled trials excluded patients with evidence of cardiac conduction deficits or known cardiac disease, several cholinesterase inhibitor studies have included patients with cardiac comorbidities. A retrospective study examined the effects of transdermal rivastigmine on cardiovascular safety in patients attending a geriatric outpatient clinic.⁴² Of 722 patients with dementia, 98 had dementia with Lewy bodies, of whom 57 were treated with transdermal rivastigmine (mean age 81 years).⁴² Patients had substantial baseline cardiovascular comorbidity. Of the eight patients who developed bradycardia (defined as heart rate <60 BPM), one stopped treatment due to symptomatic bradycardia. Blood pressure and ECG did not differ by group after starting treatment.⁴²

Data on the safety of cholinesterase inhibitors in patients with other dementia diagnoses and high cardiac risk are also available. In a randomised controlled trial of donepezil for Alzheimer's disease in 208 nursing-home residents (mean age 86 years), donepezil was associated with a small reduction in mean heart rate (2.4 BPM), the frequency of bradycardia was similar to placebo (6% vs 5%), and no excess clinically relevant ECG abnormalities on serial monitoring were observed.⁴³

A pooled analysis examined ECG data from four randomised controlled trials of rivastigmine in Alzheimer's disease (n=2791) that included patients with cardiovascular disorders and rhythm disturbances at baseline. No differences in treatment-emergent ECG abnormalities or bradycardia were seen between groups with or without treatment.⁴⁴ A retrospective Swedish registry study using propensity-matched cohorts with Alzheimer's disease, with and without established heart failure (n=455 per group), found that use of cholinesterase inhibitors in those with heart failure was associated with fewer hospital admissions for heart failure and reduced mortality, without any difference in admissions for bradycardia or atrioventricular block, or requirement for pacemaker insertion.⁴⁵ Similarly, a retrospective real-world

discontinuation study of rivastigmine and galantamine (n=3358, including patients on cardiac medications) showed no excess of patients hospitalised for syncope or atrioventricular block during exposure.⁴⁶

However, some observational studies indicate an increased risk of bradycardia in patients receiving cholinesterase inhibitors, with associated poor outcomes. In a large observational study of 11328 veterans with dementia, those receiving cholinesterase inhibitors had an increased risk of bradycardia (HR 1.4, 95% CI 1.1–1.6), with higher risk for doses 15 mg or above.⁴⁷ Patients with bradycardia were more likely to experience falls or syncope, or require a pacemaker.⁴⁷ A population-based, observational, case-controlled study compared patients initiated on cholinesterase inhibitors who had been admitted to hospital for bradycardia with matched patients who had not been admitted.⁴⁸ Of 1009 patients on cholinesterase inhibitors hospitalised for bradycardia, 11% required a pacemaker and 4% died. Initiation of cholinesterase inhibitors was associated with a two-fold increase in risk of

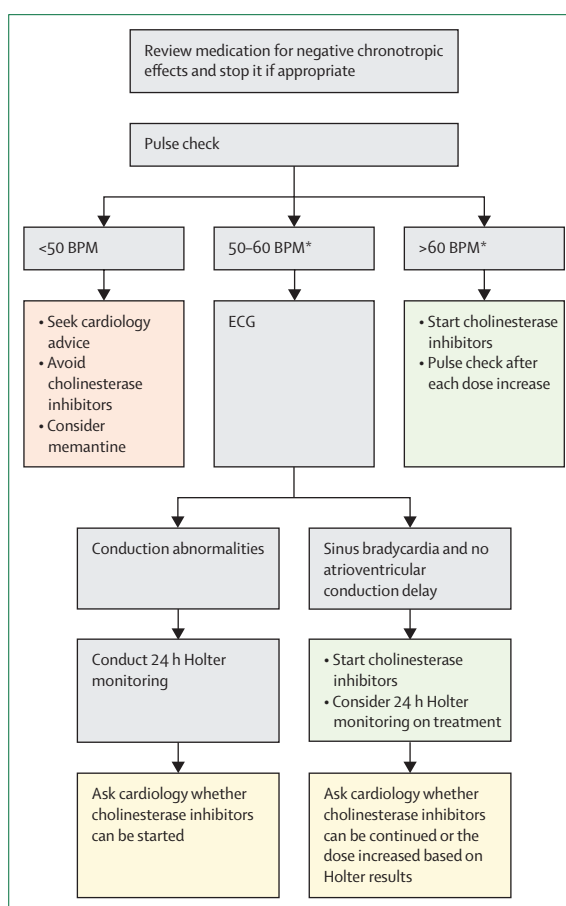


Figure 2: Practical guidance on initiating cholinesterase inhibitors in patients with dementia with Lewy bodies and bradycardia or arrhythmia
Adapted from Rowland et al.,³⁷ by permission of Cambridge University Press. BPM=beats per min. *If there are symptoms suggestive of bradycardia or arrhythmia (eg, unexplained syncope, exertional breathlessness, or palpitations), an ECG should be conducted and cardiology advice sought.

hospitalisation for bradycardia; however, no increased risk was found in patients with existing cardiac disease, or those on negative chronotropic drugs.⁴⁸

Given this evidence, although cholinesterase inhibitors carry a low risk of cardiac side-effects—even in patients with cardiac comorbidities—they do reduce heart rates and new symptomatic bradycardia can occur. Patients should therefore be monitored for bradycardia. Strategies such as agent selection (with evidence for safety of transdermal rivastigmine),^{42,49} slow titration, and monitoring if indicated by lower initial pulse rates are recommended. This cautious approach could be chosen over blanket avoidance in patients with dementia with Lewy bodies who have borderline cardiac risk.

Although cholinesterase inhibitors increase parasympathetic tone at the sinoatrial and atrioventricular nodes and can cause bradycardia, QT interval prolongation, heart block, and hypotension, increased vagal tone can also have protective cardiovascular effects. However, most data suggesting this effect are from observational studies, which could be affected by confounding indication bias. In a Taiwanese series of more than 6000 patients with Alzheimer's disease who had been treated with donepezil, incidence of cardiovascular events was lower in donepezil-treated patients than in non-users.³⁰ A reduced risk of myocardial infarction or death was also seen in a Swedish study of more than 7000 patients treated with cholinesterase inhibitors.⁵¹ A meta-analysis of 31 studies including 258 540 patients with dementia (mostly Alzheimer's disease, but also mixed dementia) found an increased proportion of patients with bradycardia (2%, 95% CI 1–6%) and PR interval prolongation in patients treated with cholinesterase inhibitors.⁵² Despite this increase, these patients had a significantly lower risk of cardiovascular events (eg, stroke, myocardial infarction, or death;

HR 0.63, 95% CI 0.45–0.88). The risk of major cardiovascular events might even be reduced in patients with Alzheimer's disease and a history of myocardial infarction. An observational Swedish study of 3198 patients with Alzheimer's disease or mixed dementia and previous myocardial infarction found that treatment with cholinesterase inhibitors was associated with a 19% reduction in all-cause mortality, with no increased risk of bradycardia or cardiovascular death.⁵³ Similarly, use of cholinesterase inhibitors in patients with Alzheimer's disease (n=221) was associated with a 2% incidence of major cardiovascular events, compared with 5% in untreated patients,⁵⁴ highlighting a possible cardioprotective effect for cholinesterase inhibitors. A similar potential cardioprotective effect of cholinesterase inhibitors is seen in studies of patients with dementia with Lewy bodies. In Sweden, a large retrospective study of 1095 patients with dementia with Lewy bodies compared use of cholinesterase inhibitors (predominantly rivastigmine) with memantine or no dementia-specific treatment.³⁸ Cognitive decline was significantly slower in those prescribed cholinesterase inhibitors (n=814; mean MMSE decline 0.4 points per year) than in those given memantine or no treatment (n=281; 2.5 points per year). Importantly, despite an increased incidence of bradycardia, no significant rise in major adverse cardiovascular events was observed. Instead, patients treated with cholinesterase inhibitors had a reduced risk of death within the first year after diagnosis (adjusted HR 0.66, 95% CI 0.46–0.94).³⁸

Additional studies support a possible survival benefit of cholinesterase inhibitors. In a UK observational cohort, patients with dementia with Lewy bodies who were treated with cholinesterase inhibitors showed a 33% reduction in mortality compared with untreated patients, as well as shorter periods of unplanned hospital admissions for physical disorders.⁵⁵ Similarly, a propensity-matched analysis from the US National Alzheimer's Coordinating Centre involving 3054 patients, including people with Lewy body dementia, found a 40% reduction in all-cause mortality in those treated with cholinesterase inhibitors compared with those who were not, with benefits sustained over nearly 8 years.⁵⁶

However, the decision to start treatment with cholinesterase inhibitors usually includes assessment of cardiac risk. In these studies, patients treated with cholinesterase inhibitors might have already had lower cardiovascular risk than those not receiving treatment, and differences between groups could therefore be due to this indication bias confounder, rather than to any protective cardiac action of the treatment.

Initiating cholinesterase inhibitors in people with dementia with Lewy bodies and conduction abnormalities

The evidence we have described supports the safe use of cholinesterase inhibitors to improve cognition in people

Panel 1: Contraindications to cholinesterase inhibitors

Absolute contraindication

- Known history of second-degree or third-degree atrioventricular block and no pacemaker
- Bradycardia <50 BPM with conduction abnormalities on ECG
- Symptomatic bradycardia

Relative contraindication (ie, administration feasible with monitoring*)

- Asymptomatic bradycardia (resting pulse <60 BPM)
- Left bundle branch block
- Rate-limiting drugs (eg, β blockers, digoxin, amiodarone, diltiazem, or verapamil)
- Sick sinus syndrome and other supraventricular conduction abnormalities (including first-degree atrioventricular block)
- QT prolongation or already taking medications known to prolong QT interval

Not contraindicated

- Atrial fibrillation
- Pacemaker

BPM=beats per min. *Suggested monitoring: consider 24 h Holter monitoring before starting acetylcholinesterase inhibitors, and repeat Holter monitoring once during treatment.⁵⁸

with dementia with Lewy bodies (figure 2). However, evidence is scarce regarding how to start treatment in patients with cardiac conduction abnormalities (see panel 1 for absolute and relative contraindications). Current guidelines do not recommend routine pre-treatment ECG screening or cardiac monitoring in all patients, as atypical ECG findings do not reliably predict adverse events, and cardiovascular events can occur in people with typical ECGs.⁵⁷ Similarly, short-term (24–48 h) cardiac monitoring is insensitive for detecting arrhythmias; however, in light of reports of clinically significant bradycardia, some clinicians might favour a cautious approach with ECGs to exclude underlying conduction abnormalities before starting treatment with cholinesterase inhibitors.^{59,60}

There is also no evidence supporting routine discontinuation of other medications that reduce heart rate before initiating cholinesterase inhibitors,^{52,57} but clinicians should be aware of the potential additive effects with negative chronotropes.

Before starting treatment with cholinesterase inhibitors, guidelines recommend checking a patient's pulse rate at baseline, monthly during dose titration, and every 6 months thereafter.⁵⁷ In some patients, the risk of bradyarrhythmia is too high to initiate treatment.

Although evidence is scarce, a qualitative case study described the potential benefits of pacemaker implantation for people with dementia with Lewy bodies, and their caregivers, with reductions in syncope and falls, and improved confidence for social engagement.⁶¹ However, these benefits should also be balanced with risks associated with placement of pacemakers, including procedural risks and potential for cognitive effects of sedation.

If bradycardia is identified (even if asymptomatic), it should be investigated. For asymptomatic mild bradycardia, more frequent monitoring is advised. In patients taking cholinesterase inhibitors who experience syncope or seizures, medication should be stopped while the underlying cause is evaluated. Treatment can be resumed if no causal relationship is established or if a pacemaker is implanted.

Choice of cholinesterase inhibitor

Evidence on which to base the choice of cholinesterase inhibitor is scarce, with no head-to-head randomised controlled trial comparisons of rivastigmine versus donepezil for people with dementia with Lewy bodies. In Alzheimer's disease, arrhythmogenic effects did not differ between donepezil, rivastigmine, and galantamine.⁶²

Panel 2: Two case studies of cholinesterase inhibitor use in patients with dementia with Lewy bodies

Case 1: pre-existing bradycardia

A 76-year-old man was diagnosed with probable dementia with Lewy bodies based on insidious cognitive decline with early executive and visuospatial dysfunction, recurrent visual hallucinations, and evidence of motor parkinsonism. Sleep was disrupted by dream enactment suggestive of rapid eye movement sleep behaviour disorder. His diagnosis was supported by an atypical dopamine transporter scan.

He was noted to be bradycardic at rest, and ECG showed sinus bradycardia (ventricular rate 54 BPM). He had no symptoms of syncope or dizziness. A 24 h Holter monitor revealed daytime bradycardia, including during a nap, but preserved chronotropic response with activity. After discussion with cardiology, low-dose rivastigmine (4.6 mg/24 h) transdermal patch was initiated with advice on home heart-rate monitoring. His pulse was checked daily (by himself and his partner), and Holter monitoring 3 weeks after treatment initiation with rivastigmine confirmed an average heart rate of 60 BPM (range 46–111 BPM), with preserved chronotropic reactivity and no symptomatic bradycardia. At a follow-up call at 6 weeks, the patient noted improvement in cognition and no adverse effects. After discussion with cardiology, the dose was increased to 9.5 mg/24 h under continued monitoring of his pulse at home, and Holter monitoring 3 weeks after the dose increase. This 24 h monitoring again confirmed preserved chronotropic reactivity and an average heart rate of 58 BPM. The patient and his wife noted an improvement in cognitive function, with reduced frequency and intensity of visual hallucinations.

Case 2: concurrent β blockers

An 80-year-old woman presented with a 2-year history of progressive memory decline, recurrent visual hallucinations, and cognitive fluctuations. These symptoms interfered with her daily functioning: she was missing medical appointments, had difficulty managing her medications, and required assistance with cooking. On examination, she had a rest tremor and parkinsonian gait. Neuropsychological testing revealed deficits in memory, executive function, and visuospatial abilities. She met criteria for probable dementia with Lewy bodies.

Her medical history included hypertension, treated with atenolol, and hyperlipidaemia, managed with atorvastatin. She had no history of myocardial infarction or heart failure.

Before initiating treatment with rivastigmine, her heart rate was 55 BPM and her blood pressure was 125/80 mm Hg. ECG showed a typical sinus rhythm. Given the risk of bradycardia with cholinesterase inhibitors in patients already on β blockers, her general practitioner was consulted and atenolol was switched to a thiazide diuretic—an appropriate option for uncomplicated hypertension in older adults. Following this change, her heart rate improved to 60–65 BPM.

Rivastigmine was initiated using a 4.6 mg transdermal patch, titrated to 9.5 mg after 1 month, with continued pulse monitoring at home.

Panel 3: Pragmatic, expert-informed recommendations for initiating cholinesterase inhibitors in patients with dementia with Lewy bodies and bradycardia or arrhythmia

- Review medication for negative chronotropic effects and consider stopping it if appropriate.
- Check baseline pulse to identify patients with heart rates below 60 BPM. Pulse rate should be checked first in a sitting position after 5 min of sitting, and then recorded after 3 min of standing.⁶⁶
- For patients with heart rates less than 50 BPM, an ECG should be done and advice sought from cardiology, especially if conduction abnormalities are found. Avoid cholinesterase inhibitors and consider memantine.
- For mild bradycardia (50–60 BPM), conduct an ECG. If no conduction abnormalities are found, consider following up with 24 h Holter monitoring. If mild sinus bradycardia without conduction block is confirmed, cholinesterase inhibitors can be used with close monitoring (consider repeat 24 h Holter monitoring after dose changes). If conduction abnormalities are found on ECG, arrange 24 h Holter monitoring and consult cardiology before starting cholinesterase inhibitors.
- For patients with heart rate greater than 60 BPM, if no symptoms of presyncope are present, cholinesterase inhibitors can be started with standard monitoring (ie, pulse checks after dose change). If symptoms of presyncope are found, an ECG should be done and 24 h Holter monitoring should be considered to rule out conduction abnormalities before initiating treatment.

Baseline and periodic ECG monitoring is prudent in patients with known conduction abnormalities or who are taking other medications that reduce heart rates. BPM=beats per min.

Meta-analyses and a Cochrane review showed increased side-effects for rivastigmine than for placebo, compared with donepezil versus placebo.^{33,34} However, these trials only examined oral rivastigmine.

The pharmacological and pharmacokinetic properties of each drug should be considered. Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase receptors, compared with donepezil, which only inhibits acetylcholinesterase.⁶³ The preference for transdermal patches over capsules of rivastigmine is based on their pharmacokinetics; for capsules, the median time to peak concentration is 1 h, with a peak concentration up to 29.3 ng/mL for 6 mg doses, and a half-life of 1.3–2 h. By contrast, transdermal patches reach peak concentration in 8 h, have a mean peak concentration of 19.5 ng/mL for the 13.3 mg patch, and a half-life of 3.4 h,⁶⁴ which could explain its better side-effect profile.

Concurrent β blockers

Before starting a cholinesterase inhibitor, a medication review might be prudent to confirm whether a β blocker or other rate-slowing drug is necessary, and to consider an alternative to β blockers or rate-slowing drugs.⁵⁷ However, β blockers should not be stopped when there is a compelling indication. In heart failure with reduced ejection fraction and for heart rate control in atrial fibrillation, β blockers confer mortality and morbidity benefit and are recommended.⁶⁵ In such cases, cardiac monitoring can be appropriate. Clinicians should seek cardiology advice if the indication is unclear (panel 2).

Search strategy and selection criteria

We searched PubMed for studies evaluating the cardiovascular safety and efficacy of cholinesterase inhibitors in Lewy body dementias, with a particular focus on randomised controlled trials (RCTs) and any head-to-head comparisons of rivastigmine and donepezil. The search covered the period from Jan 1, 2020, to April 26, 2026, and used a combination of medical subject heading terms and free-text keywords across three conceptual domains:

- 1 Lewy body dementia and related disorders: "Lewy body dementia" OR "LBD" OR "Dementia with Lewy bodies" OR "DLB" OR "Parkinson's disease dementia" OR "PDD" OR "Parkinson's dementia" OR "Lewy body disease" OR "Synucleinopathies"
- 2 Cholinesterase inhibitors: "cholinesterase inhibitors" OR "acetylcholinesterase inhibitors" OR "rivastigmine" OR "donepezil" OR "galantamine"
- 3 Cardiac effects and autonomic dysfunction: "cardiac" OR "cardiology" OR "bradycardia" OR "bradyarrhythmia" OR "arrhythmia" OR "tachycardia" OR "cardiac conduction" OR "autonomic" OR "heart rate variability" OR "QT prolongation" OR "pacemaker" OR "syncope" OR "Holter monitoring"

Search terms were combined using Boolean operators to identify studies addressing the intersection of cholinesterase inhibitor use, Lewy body dementia, and cardiovascular or autonomic considerations. Filters were applied to prioritise RCTs, head-to-head comparisons, and high-quality observational studies. We also hand-searched the reference lists of key publications for additional relevant articles.

To specifically identify comparative efficacy and safety data between rivastigmine and donepezil, additional terms such as "head-to-head", "comparative", "randomised", and "direct comparison" were used in combination with the drug names.

Non-English language articles were included when translation was feasible. The final reference list was curated based on scientific rigour, clinical relevance, and contribution to understanding the safety and therapeutic role of cholinesterase inhibitors in Lewy body dementia.

A pragmatic, expert-informed approach to initiating cholinesterase inhibitors

In this Personal View, we present a pragmatic approach to initiating cholinesterase inhibitors in patients with dementia with Lewy bodies and cardiac conduction abnormalities, aiming to balance their cognitive benefits with their potential to cause or worsen cardiac side-effects (panel 3). We consider existing evidence and previous guidance⁵⁷ adapted to address the needs of patients with dementia with Lewy bodies, who are more likely to have cardiac conduction abnormalities than patients with other dementias. We incorporate the multidisciplinary expertise at our centres, including input from neurology, psychiatry, and cardiology (figure 2). Key differences in our approach

compared with previous guidance are: reduced emphasis on presence of symptomatic versus asymptomatic bradycardia, which can be difficult to interpret in those with dementia with Lewy bodies; and use of ECGs and Holter monitoring to support decisions for patients with a pulse of 50–60 beats per min. We emphasise that our proposed pathway is based on multidisciplinary clinical experience in the context of scarce prospective evidence. Pulse-rate thresholds for guiding monitoring and investigations are based on pragmatic clinical convention, due to the dearth of evidence supporting particular thresholds.

Conclusions and future directions

Available evidence supports cholinesterase inhibitors as effective and generally safe treatments for cognitive and neuropsychiatric symptoms in people with dementia with Lewy bodies. The balance of data favours an approach of cautious prescribing with monitoring rather than avoidance, even in patients with cardiovascular comorbidities. Future studies with longer follow-up periods, inclusion of higher-risk cardiac populations, and cardiovascular endpoints as primary outcomes are needed to clarify longterm safety and confirm observed associations of improved survival in patients with dementia with Lewy bodies treated with cholinesterase inhibitors. Such studies would also help establish whether these associations reflect true cardioprotective effects of cholinesterase inhibitors.

Contributors

The manuscript was conceptualised by RSW, SK, and JS. All authors (RSW, SK, JS, RB and CA) planned the manuscript and contributed to the figures. SK and JS conducted the literature search. RSW, SK, CA, and JS wrote the first draft of the manuscript. RSW, SK, CA, JS, and RB reviewed and edited the manuscript.

Declaration of interests

RSW has received speaking and writing honoraria from Bial, Omrix Pharma, GE Healthcare, Arvinos, and Britannia; consultancy fees from Therakind and Accenture; and is the principal investigator for a CervoMed neflamapimod trial. CA has received honoraria as speaker from F Hoffmann–La Roche, Zambon, Nutricia, and Schwabe Farma Ibérica; is a consultant for BioArtic; and is a member of the Board of Directors of the Lewy Body Dementia Association. All other authors declare no competing interests.

Acknowledgments

RSW is supported by a Wellcome Career Development Fellowship (225263/Z/22/Z) and has received grant funding and support from Rosetrees, the Lewy Body Society, Parkinson's UK (G-2404), Michael J Fox Foundation, the University College London Hospitals NHS Foundation Trust Biomedical Research Centre and University College London Partners. CA is supported by the Spanish Institute of Health Carlos III Juan Rodés grant JR25/00034 and has received support from the ARISTOS programme, co-funded by the European Union's Horizon Europe research and innovation programme under the Marie Skłodowska-Curie grant agreement number 101081334 and the Susan and Charles Berghoff Foundation. SK is supported by an Alzheimer's Research UK Clinical Research Fellowship (ARUK-CF2024A-005).

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