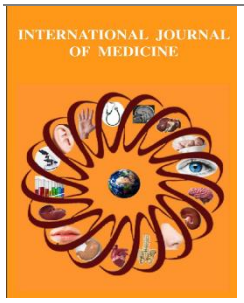
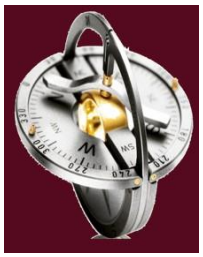


International Journal of Medicine

https://www.theinternationalmedicine.com



Research Article

Cardiac Screening as a Prerequisite: Insights from A Cross-Sectional Observational Study of Dementia Patients Treated With 5 mg versus 10 mg Donepezil

Dr Bawankar Niharika[1], Dr Kanwarjeet Singh[2], Sahiba Singh MD[3], Dr Paramjeet Singh[4], Dr Vipul Sharma[5], Surendra Kumar Dattatrey[6].

[1]*Junior Resident, Department of Psychiatry, SMS Medical College, Jaipur 302004, India*
[2]*Resident, Internal medicine, Brookdale university hospital and medical centre,Brooklyn 11212, NY*
[3]*Fellow, Division of geriatric and Palliative Medicine, Zucker School of Medicine at Hofstra/ Northwell Health, New York 11042, NY*
[4]*Senior Professor, Department of Psychiatry, SMS Medical College, Jaipur 302004, India*
[5]*Casualty Medical Officer, District Hospital and GMC, Sindhudurg 416812, Maharashtra*
[6]*Data scientist at dotecloud , ex S&P global, London, United Kingdom.*

Abstract

Objective: To evaluate the effect of donepezil on resting heart rate in elderly dementia patients and compare HR changes between those prescribed 5 mg and 10 mg daily doses. ***Method***: This cross-sectional observational study was conducted at the Geriatric OPD of the Department of Psychiatry of a tertiary healthcare centre in India from November 2024 to February 2025. Sixty dementia patients (≥60 years), who had been taking donepezil (5 mg or 10 mg daily) for at least one month, were included. Baseline HR (prior to starting donepezil) and follow-up HR were recorded. Patients were divided into two groups based on dose. Heart rate changes were compared within and between the groups. Subgroup analyses were performed based on age, sex, and co-morbidities. ***Results***: Both groups showed significant reductions in HR from baseline (5 mg: 4.04 ± 2.30 bpm; 10 mg: 6.51 ± 2.49 bpm; $p < 0.001$). The 10 mg group had a significantly greater reduction compared to the 5 mg group ($p = 0.002$). Age, sex, and co-morbidities did not significantly influence HR change. ***Conclusion***: Donepezil significantly reduces resting heart rate in a dose-dependent manner in elderly dementia patients. The drug appears safe and well-tolerated in routine outpatient care with appropriate monitoring.

Keywords: Autonomic function, Cholinesterase inhibitors, Donepezil, Dementia, Heart rate.

Introduction:

Dementia is a growing global health concern, with Alzheimer's disease (AD) being the most prevalent form, accounting for 60–70% of cases worldwide[1]. Pharmacological management primarily includes cholinesterase inhibitors (ChEIs), with donepezil being among the most widely prescribed agents due to its favourable safety and efficacy profile[2,3]. Donepezil enhances cholinergic transmission by inhibiting acetylcholinesterase, resulting in increased acetylcholine availability in the synaptic cleft, which improves cognitive symptoms in mild to moderate AD[4].

Despite its cognitive benefits, concerns have been raised regarding the cardiovascular safety of Donepezil. Because the heart contains cholinergic receptors, enhancing cholinergic tone can modulate cardiac autonomic balance, influencing heart rate (HR) and rhythm[5,6]. Donepezil has been associated with bradycardia, PR interval prolongation, and, rarely, ventricular arrhythmias including torsades de pointes (TdP) [7,8,9].

A number of studies have examined the electrocardiographic and autonomic impacts of donepezil. Wang et al.[10] reported a statistically significant reduction in mean HR and an increase in parasympathetic tone in elderly patients with ischemic heart disease and mild cognitive impairment (MCI) who were administered donepezil 5 mg daily for 4 weeks. Similarly, Pu et al.[11] demonstrated that donepezil administration in elderly Alzheimer's patients led to a significant decline in HR, especially at night, and enhanced parasympathetic modulation of cardiac function.

In contrast, McLaren et al.[12] observed a significant reduction in high-frequency (HF) HRV components, indicating reduced parasympathetic activity, in a small sample of dementia patients treated with donepezil. This disparity may reflect differences in dementia subtypes, measurement durations, and dosage. McLaren's cohort included patients with Lewy body dementia, which may exhibit distinct autonomic responses.

Case reports and population studies have emphasised donepezil's potential to induce bradyarrhythmias. Park-Wyllie et al.[7] documented increased hospitalisations for bradycardia in elderly patients prescribed ChEIs, and Tanaka et al.[8] described rare but serious events such as atrioventricular block and TdP associated with donepezil. Conversely, large-scale observational studies have proposed that donepezil may be cardioprotective, potentially reducing the risk of myocardial infarction and pacemaker insertion[13,14].

Address for Correspondence: Dr. Bawankar Niharika*, 1Junior Resident, Department of Psychiatry, SMS Medical College, Jaipur 302004, India, Rajasthan, India,*

DOI: 10.5455/im.9874139

Donepezil's vagotonic effects may restore autonomic balance, especially in dementia patients who often exhibit sympathetic

overactivity and vagal withdrawal[15,16,17]. Heart rate variability (HRV), as a non-invasive measure of autonomic modulation, has shown improved parasympathetic activity following donepezil in several trials[10,11,18].

Despite this body of evidence, limited data is available on dose-dependent effects of donepezil on heart rate. While clinical trials often report average group effects, outpatient data reflecting the cardiovascular responses to varying donepezil doses (5 mg vs. 10 mg) over time remain limited. Most prior studies employed pre-post intervention designs, and few have utilised cross-sectional observational methods to examine how real-life outpatient HR readings correlate with prescribed donepezil doses in patients with varying durations of use.

The aim of this cross-sectional study is to assess the heart rate profiles of dementia patients, all of whom had been taking donepezil (5 mg or 10 mg) for at least one month. Baseline HR (recorded prior to therapy initiation)is compared to their current HR upon outpatient follow-up to identify any dose-dependent HR changes. This approach adds to the growing literature on the autonomic and cardiovascular safety of donepezil in clinical practice

Materials and Methods

Study design

This prospective, observational study was conducted at the Geriatric Outpatient Department, Department of Psychiatry at tertiary healthcare centre in India. The study was conducted over a period of four months, from November 2024 to February 2025. Ethical approval was obtained from the Institutional Ethics Committee prior to the initiation of the study. All participants provided written informed consent after receiving detailed information regarding the study objectives, procedures, benefits, and potential risks. The study adhered to the principles outlined in the Declaration of Helsinki (2013 revision) regarding research involving human participants.

Participants

The sample size was calculated using the formula for comparing two independent means: $n = 2 (Z\alpha/2+Z\beta)2\sigma2 / \Delta2$, assuming a clinically meaningful difference in heart rate (Δ) = 5 beats per minute (bpm), standard deviation (σ) = 7 bpm based on previous literature [10,11], type I error (α) = 0.05 ($Z\alpha/2 = 1.96$), power ($1–\beta$) = 0.80 ($Z\beta = 0.84$). Using these parameters, the minimum required sample size was approximately 27 participants per group. To account for potential dropouts and measurement variability, a total of 60 dementia patients were enrolled, with 30 patients in each donepezil dose group (5 mg and 10 mg).

Participants were included if they were 60 years or older, had a clinical diagnosis of Major Neurocognitive disorder according to DSM-5 criteria, and had been taking donepezil (either 5 mg or 10 mg per day) consistently for a minimum of one month. They were required to have documented baseline heart rate data available from before the initiation of donepezil therapy and be physically stable for outpatient follow-up. Patients were excluded if they had pre-existing cardiac arrhythmias such as atrial fibrillation, a history of symptomatic bradycardia, a pacemaker, or any recent hospitalisation for cardiovascular events within the last three months, current use of medications known to affect heart rate, significant electrolyte disturbances, or lack of adequate clinical records.

Procedure

This study included individual who attended geriatric psychiatry outpatient department at Tertiary healthcare centre in India. After confirmation of eligibility and consent, demographic data, medical history, comorbidities, duration of dementia, duration of donepezil use, and concurrent medications were recorded using a structured case record form. Baseline heart rate values were obtained from documented pre-treatment medical records (recorded within one week prior to initiating donepezil). During the current outpatient visit, resting heart rate was measured manually using a standard acoustic stethoscope. The patient was seated comfortably and allowed to rest for at least 10 minutes in a quiet environment. The stethoscope was placed over the apex of the heart (fifth intercostal space, midclavicular line), and the number of heartbeats was counted over a full 60-second period to ensure accuracy. If the rhythm was irregular or if the clinician was uncertain, a second reading was taken and the average of the two was used. Patients were categorised into two groups based on the prescribed dose of donepezil, Group A (5 mg daily) and Group B (10 mg daily). The primary outcome variable was the change in heart rate from baseline to the follow-up visit across both groups.

Statistical analysis

All data were analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Normality of data was assessed using the Shapiro–Wilk test. Paired sample t-tests were used to assess within-group differences in heart rate (baseline vs. follow-up), while independent samples t-tests were applied to compare between the two dose groups. A p-value less than 0.05 was considered statistically significant. Additional subgroup analyses based on age, sex, and presence of co-morbidities were performed to evaluate potential confounding effects

Results

A total of 60 patients with clinically diagnosed dementia were enrolled in this cross-sectional observational study. Participants were equally distributed into two groups based on their prescribed dose of donepezil: 30 patients receiving 5 mg daily and 30 receiving 10 mg daily. All participants had been on donepezil therapy for at least one month, and complete baseline and follow-up heart rate data were available for analysis. The schematic representation of study participants is presented in Figure 1.

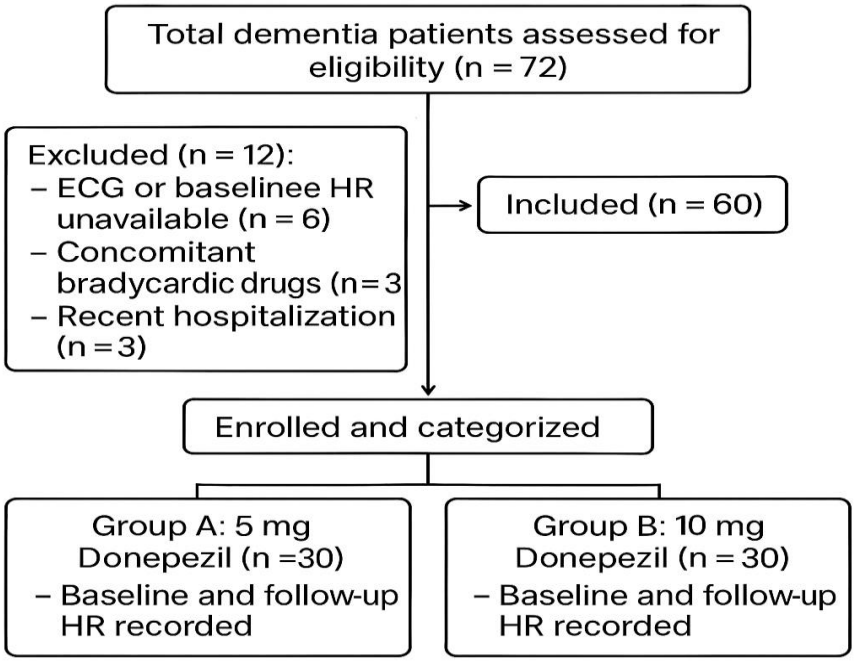


Figure 1. Schematic representation of the study population.

The demographic profile of the study population is presented in Table 1. The mean age in the 5 mg group was 71.9 ± 6.4 years, compared to 72.3 ± 7.1 years in the 10 mg group. Both groups had a comparable gender distribution, comorbidity profile (hypertension and diabetes mellitus), and mean duration of dementia and donepezil use. No statistically significant differences were observed between the two groups in terms of baseline characteristics, suggesting good comparability.

Table 1. Demographic and clinical characteristics of the study population

Variable	5 mg Group (n = 30) Mean ± SD/ N (%)	10 mg Group (n = 30) Mean ± SD/ N (%)	p-value
Age (years)	71.9 ± 6.4	72.3 ± 7.1	0.78a
Male sex	16 (53.3%)	17 (56.7%)	0.79b
Duration of dementia (months)	26.4 ± 8.7	27.1 ± 9.2	0.72a
Duration of donepezil use (days)	45.2 ± 11.6	47.0 ± 13.1	0.48a
Hypertension	5 (16.7%)	7 (23.3%)	0.59b
Diabetes mellitus	6 (20.0%)	8 (26.7%)	0.78b
a. Unpaired t-test b. Chi-square test			

The primary outcome variable was the change in resting heart rate from baseline to the outpatient follow-up visit. As shown in Table 2, the mean baseline heart rate was comparable between the two groups (78.04 ± 6.12 bpm in the 5 mg group and 78.99 ± 6.03 bpm in the 10 mg group; p = 0.51). Following at least one month of donepezil therapy, both groups demonstrated a significant reduction in heart rate. The mean reduction in HR was 4.04 ± 2.30 bpm in the 5 mg group and 6.51 ± 2.49 bpm in the 10 mg group. The between-group comparison of HR change was statistically significant (p = 0.002), indicating a dose-dependent effect of donepezil on heart rate (Figure 2).

Table 2. Heart rate comparison before and after donepezil use

Variable	5 mg Group (n = 30)	10 mg Group (n = 30)	Between-group p-value
Baseline HR (bpm)	78.04 ± 6.12	78.99 ± 6.03	0.51
Follow-up HR (bpm)	74.00 ± 6.09	72.49 ± 6.66	0.28
HR Change (bpm)	4.04 ± 2.30	6.51 ± 2.49	0.002
Within-group p-value	< 0.001	< 0.001	—

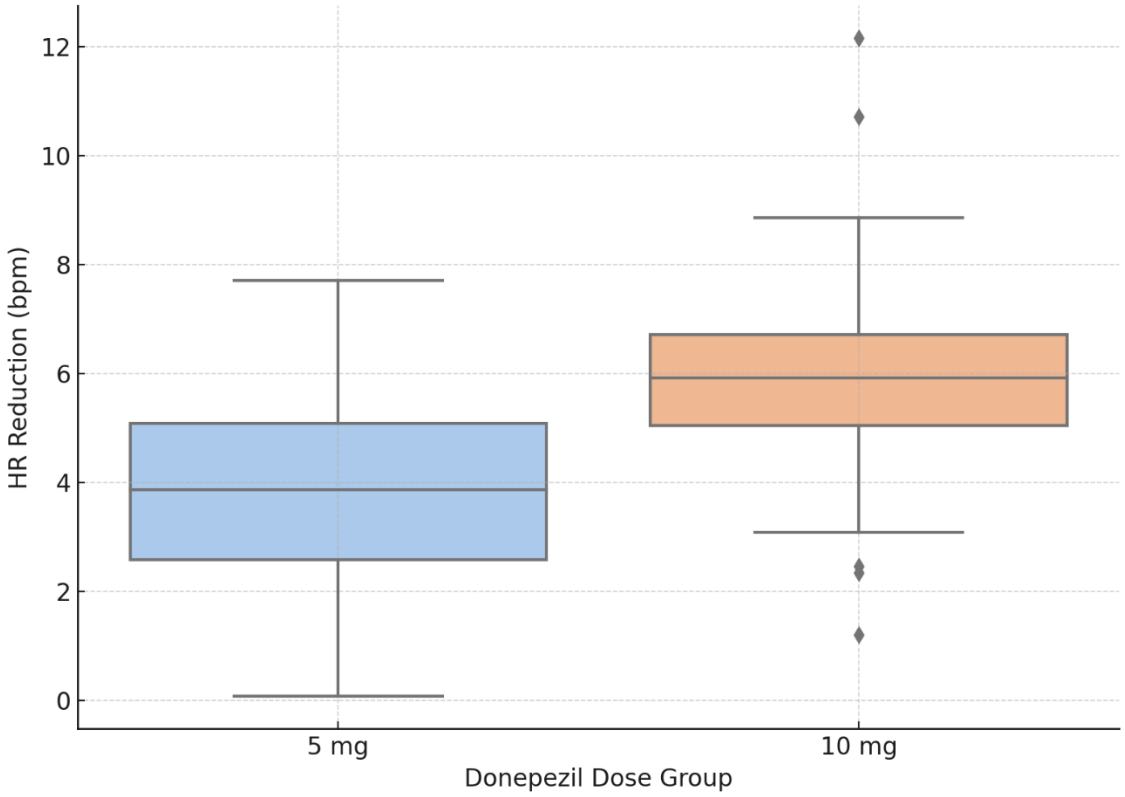


Figure 2. Heart rate changes after donepezil use.

None of the subgroup analyses demonstrated a statistically significant influence on the degree of heart rate change following donepezil administration (Table 3). This suggests that the effect of donepezil on heart rate appears consistent regardless of patient age, sex, or presence of hypertension or diabetes mellitus.

Table 3. Subgroup analysis of heart rate change after donepezil use

Subgroup	Category	N	HR Change (bpm) Mean ± SD	p-value
Age	≤75 years	42	5.21 ± 2.57	0.69
	>75 years	18	5.45 ± 2.60	
Gender	Male	33	5.38 ± 2.72	0.81
	Female	27	5.22 ± 2.42	
Hypertension	Present	12	5.13 ± 2.41	0.68
	Absent	48	5.43 ± 2.71	
Diabetes	Present	14	5.08 ± 2.64	0.59
	Absent	46	5.44 ± 2.52	

.

Discussion

The present study was conducted with the aim of evaluating the effect of donepezil on resting heart rate in elderly patients with dementia who had been on a stable dose of donepezil (either 5 mg or 10 mg daily) for at least one month. This study compare HR changes between the two dosage groups in a outpatient geriatric population. We hypothesised that higher doses of donepezil might lead to greater reductions in heart rate due to enhanced parasympathetic stimulation.

This study found that both 5 mg and 10 mg doses of donepezil were associated with statistically significant reductions in resting heart rate from baseline. The mean HR reduction in the 5 mg group was 4.04 ± 2.30 bpm, whereas the 10 mg group showed a significantly greater reduction of 6.51 ± 2.49 bpm ($p = 0.002$). Subgroup analyses further revealed that these effects were consistent across age groups, sexes, and the presence or absence of hypertension and diabetes, suggesting that the HR-lowering effect of donepezil is relatively uniform and dose-dependent.

These findings are in agreement with previous studies that have investigated the cardiovascular effects of donepezil. In a study by Wang et al. [10] involving elderly patients with ischemic heart disease and mild cognitive impairment, donepezil (5 mg daily for 4 weeks) led to a significant decrease in mean heart rate as well as increased parasympathetic tone, indicated by improvements in heart rate variability (HRV) metrics such as high-frequency (HF) power and reduced low-frequency/high-frequency (LF/HF) ratio. Similarly, Pu et al. [11] reported a significant reduction in heart rate, particularly during nighttime hours, in Alzheimer's disease patients on donepezil, along with favourable shifts in HRV, suggesting enhanced vagal modulation. Findings in this study are consistent with these results and further confirm that even under routine clinical conditions, donepezil exerts a measurable parasympathetic influence on cardiac autonomic function.

Contrary findings have been reported in earlier literature. McLaren et al. [12] observed a paradoxical reduction in HRV (specifically HF power) in a small group of patients with dementia, suggesting reduced parasympathetic modulation after donepezil administration. However, their study had a limited sample size (n = 15), included patients with different types of dementia (including Lewy body dementia, which is more prone to autonomic dysfunction), and used a short-duration ECG protocol (5-minute recording). In contrast, our study included a larger sample of patients with well-documented Alzheimer's or unspecified dementia, and measurements were taken in standardised outpatient conditions after adequate rest, which may offer a more stable assessment of resting HR.

In this study, a greater HR reduction in the 10 mg group aligns with the pharmacodynamic properties of donepezil. Donepezil is a reversible inhibitor of acetylcholinesterase that increases the availability of acetylcholine at both central and peripheral synapses. The cardiac effects are likely mediated via increased vagal stimulation, particularly at the sinoatrial node, which can decrease sinus rate. This vagotonic effect is more pronounced at higher plasma concentrations of the drug [5,8]. Therefore, a dose-dependent HR-lowering effect, as observed in our study, is a physiologically plausible outcome.

The cardiovascular safety of donepezil has been debated in the literature. Case reports have described instances of bradyarrhythmia, atrioventricular block, and even torsades de pointes in patients taking donepezil, especially in those with pre-existing cardiac conduction disorders or those on concurrent bradycardic medications [7,9]. Park-Wyllie et al. [7], in a large population-based study, found an increased risk of hospitalisation for bradycardia among elderly patients prescribed cholinesterase inhibitors. However, other large-scale studies have noted potential cardioprotective effects. For example, Nordström et al. [14] reported a reduced risk of myocardial infarction and all-cause mortality in patients with Alzheimer's disease taking donepezil, and Huang et al. [13] found a lower risk of pacemaker insertion among cholinesterase inhibitor users. These seemingly conflicting findings may be due to heterogeneity in patient populations, concomitant medications, and comorbid conditions.

In this study, no patients reported bradycardia-related symptoms such as dizziness, syncope, or fatigue, and there were no cases requiring treatment interruption or hospital referral. This suggests that, when used judiciously in appropriately selected patients, donepezil, even at 10 mg doses, appears to be hemodynamically well-tolerated.

Study limitation

Though this is a preliminary study, several limitations of this study should be acknowledged. First, the cross-sectional design limits causal inference, and it is possible that unmeasured confounders may influence the observed HR changes. Second, this study relied on recorded baseline HR values, which may have been subject to variability in measurement conditions. Third, continuous ECG or HRV monitoring was not performed, which would have provided deeper insights into autonomic modulation. Fourth, although we excluded patients on known bradycardic agents, other undetected drug interactions or comorbidities might have influenced HR. Lastly, the sample size, while adequate for the primary outcome, limits detailed subgroup analysis by dementia type or duration of treatment.

Conclusion

This cross-sectional observational study demonstrated that donepezil use in elderly dementia patients is associated with significant reduction in resting heart rate, with a greater decrease observed in those receiving the 10 mg dose as compared to 5 mg per day. No adverse cardiac events or symptomatic bradycardia were observed, indicating that donepezil is generally safe and well-tolerated in this patient population when used appropriately. However, careful screening is still advised in patients to avoid any harmful cardiovascular consequences.

References

1. World Health Organization. Dementia Fact Sheet. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia
2. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018;(6). https://doi.org/10.1002/14651858.cd001190.pub3

3. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008;3(2):211–25.
4. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the NIA-AA workgroups. Alzheimers Dement. 2011;7(3):263–9. https://doi.org/10.1016/j.jalz.2011.03.005
5. Howes LG. Cardiovascular effects of drugs used to treat Alzheimer's disease. Drug Saf. 2014;37(6):391–5. https://doi.org/10.1007/s40264-014-0161-z
6. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. Int J Clin Pharm. 2017;39(1):16–25. https://doi.org/10.1007/s11096-016-0414-2
7. Park-Wyllie LY, Mamdani MM, Li P, Gill SS, Laupacis A, Juurlink DN. Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study. PLoS Med. 2009;6(9):e1000157. https://doi.org/10.1371/journal.pmed.1000157
8. Tanaka A, Koga S, Hiramatsu Y. Donepezil-induced adverse side effects of cardiac rhythm: 2 case reports of atrioventricular block and Torsade de Pointes. Intern Med. 2009;48(14):1219–23. https://doi.org/10.2169/internalmedicine.48.2181
9. Bordier P, Garrigue S, Barold SS, Bressolles N, Lanusse S, Clémenty J. Significance of syncope in patients with Alzheimer's disease treated with cholinesterase inhibitors. Europace. 2003;5(4):429–31. https://doi.org/10.1016/s1099-5129(03)00080-1
10. Wang D, Wu Y, Wang A, Chen Y, Zhang T, Hu N. Electrocardiogram changes of donepezil administration in elderly patients with ischemic heart disease. Cardiol Res Pract. 2018;2018:9141320. https://doi.org/10.1155/2018/9141320
11. Pu Z, Xu W, Lin Y, Shen J, Sun Y. Donepezil decreases heart rate in elderly patients with Alzheimer's disease. Int J Clin Pharmacol Ther. 2019;57(2):94–100. https://doi.org/10.5414/CP203257
12. McLaren AT, Allen J, Murray A, Ballard CG, Kenny RA. Cardiovascular effects of donepezil in patients with dementia. Dement Geriatr Cogn Disord. 2003;15(4):183–8. https://doi.org/10.1159/000068781
13. Huang AR, Redpath CJ, van Walraven C. The influence of cholinesterase inhibitor therapy for dementia on risk of cardiac pacemaker insertion: a retrospective, population-based, health administrative databases study in Ontario, Canada. BMC Neurol. 2015;15:66. https://doi.org/10.1186/s12883-015-0325-1
14. Nordström P, Religa D, Wimo A, Winblad B, Eriksdotter M. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. Eur Heart J. 2013;34(33):2585–91. https://doi.org/10.1093/eurheartj/eht182
15. Nonogaki Z, Umegaki H, Makino T, Suzuki Y, Kuzuya M. Relationship between cardiac autonomic function and cognitive function in Alzheimer's disease. Geriatr Gerontol Int. 2017;17(1):92–8. https://doi.org/10.1111/ggi.12679
16. Kaushik V, Smith ST, Mikobi E, Raji MA. Acetylcholinesterase inhibitors: beneficial effects on comorbidities in patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2018;33(2):73–85. https://doi.org/10.1177/1533317517734352
17. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond). 2003;105(6):671–6. https://doi.org/10.1042/CS20030010
18. Igeta H, Suzuki Y, Tajiri M, Someya T. Cardiovascular pharmacodynamics of donepezil hydrochloride on the PR and QT intervals in patients with dementia. Hum Psychopharmacol. 2014;29(3):292–4. https://doi.org/10.1002/hup.2398.