Přehledový článek | Review article

Persistent Severe Bradyarrhythmia Following Donepezil Discontinuation in Dementia Patient: A Case Report and Literature Review

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SOUHRN

Kontext: Donepezil je inhibitor acetylcholinesterázy používaný v péči o nemocné s Alzheimerovou chorobou. Uvedená látka sice zmírňuje klinické symptomy, ale nese s sebou riziko vzniku ortostatické hypotenze a bradykardie. Pozornost je třeba věnovat nepříliš častému vzniku těžké bradyarytmie po vysazení donepezilu. Dosud nebyly publikovány žádné kazuistiky na téma těžkých bradyarytmií po vysazení donepezilu.
Popis případu: Uvádíme případ 33leté ženy s opakovanými mdlobami v anamnéze; trpí demencí a pravidelně užívá donepezil. Prodělala epizodu těžké bradyarytmie s hodnotou 45 úderů za minutu při aplikování dopaminu v dávce 5 μg/kg/min, která neodpovídala na podání atropinu. Vysazení donepezilu nevedlo k vymizení asymptomatické bradykardie. Protože použití dočasné kardiostimulace stav pacientky zlepšilo, byl jí implantován trvalý kardiostimulátor.
Závěry: Tento případ jednoznačně ukazuje na souvislost mezi užíváním donepezilu a těžkou bradyarytmií u pacientů s demencí. Kazuistika zdůrazňuje náročnost zvládání nežádoucích účinků a vyplývá z ní, že vysazení donepezilu a zahájení anticholinergní léčby nemusí vždy postačovat; v takovém případě je nutno pacientovi implantovat kardiostimulátor.

Keywords:
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Case report
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ABSTRACT

Background: Donepezil is an acetylcholinesterase inhibitor used in Alzheimer's disease management. It improves clinical symptoms but carries risks of orthostatic hypotension and bradycardia. Uncommon severe bradyarrhythmias post-discontinuation deserve attention. In addition, there have been no previous case reports regarding severe bradyarrhythmias post donepezil discontinuation.
Case presentation: We report a case of a 33-year-old woman with a history of recurrent fainting. She has dementia and regularly takes donepezil. She experienced severe bradyarrhythmia with heart rate of 45 beats per minute regular on dopamine 5 μg/kg/min and unresponsive to atropine. The discontinuation of donepezil did not improve asymptomatic bradycardia. The use of temporary pacemaker (TPM) improved the patient's condition, then permanent pacemaker (PPM) was implanted.
Conclusions: This case report highlights donepezil's link to severe bradyarrhythmia in dementia patients. It stresses the challenges in managing adverse effects, suggesting that stopping donepezil and anticholinergic therapy may not always be sufficient and pacemaker implantation may be required.

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Background

Donepezil is a commonly prescribed acetylcholinesterase inhibitor used in the management of Alzheimer's disease.[1] Its primary function is to enhance cholinergic neurotransmission by inhibiting the breakdown of acetylcholine, thereby improving cognitive function in patients with dementia.[2] The adverse reactions commonly experienced by more than 10% of individuals taking donepezil include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. On the other hand, less common adverse effects, occurring in 1–10% of cases, encompass insomnia, emesis, gastritis, hypertension, syncope, bradycardia, chills, generalized coldness, pain, dizziness, abnormal gait, confusion, fatigue, diaphoresis, abdominal pain, bloating, and constipation.[3] This case report highlights an unusual and previously unreported manifestation of donepezil-related adverse effects, involving the development of persistent severe bradyarrhythmia in a dementia patient following drug discontinuation.

Case presentation

A 33-year-old woman, referred from a local government hospital, came to the emergency room with complaints of frequent weakness for the last 5 months. The patient had a history of recurrent fainting. Prior to fainting, she experienced dizziness. The patient had never previously had similar symptoms. There were no complaints of shortness of breath, typical chest pain, palpitations, or similar previous episodes. The patient did not experience dyspnea on exertion (DOE), paroxysmal nocturnal disease (PND), orthopnea, or swelling. She had dementia and regularly took donepezil 5 mg, with no other medications. BMI was measured at 25.39, indicating overweight. The patient denied having hypertension, diabetes mellitus, heart disease, or neurological conditions. While at the referring hospital, the patient received 2 ampoules of Sulfas Atropine, but there was no change in the patient's heart rate and clinical conditions.

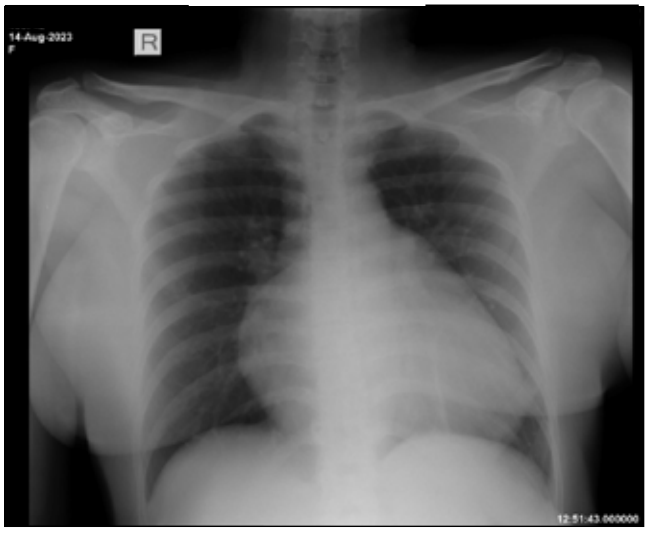

Fig. 1 – Chest X-ray on initial presentation showing prominent CTR 68%. CTR – cardiothoracic ratio.

On presentation, the patient had a GCS of 456, blood pressure of 111/67 mmHg, heart rate of 45 beats per minute regular on dopamine 5 µg/kg/min, respiratory rate of 18 breaths per minute, SpO_2 of 99% on room air, and a temperature of 36.5 °C. Upon auscultation of the heart, single regular S1 and S2 were heard, and no murmurs or gallops were found. Laboratory test results of the patient upon arrival at the emergency room are provided in **Table 1**.

The chest X-ray showed a prominent cardiothoracic ratio of 68% and no infiltrates were found (**Fig. 1**). The EKG results from the referring hospital revealed sinus arrest with junctional escape rhythm at 51 beats per minute, normal axis, and clockwise rotation with horizontal axis (**Fig. 2**). Transthoracic echocardiography (TTE) examination revealed dilatation in the left atrium and right atrium. Valve examination revealed qualitatively mild aortic

Table 1 – Laboratory work-up

Laboratory parameter	Patient's results	Normal range
Hb	14.7 g/dl	13–18
WBC	7.76 k/µL	4–11
Thrombocyte	221 k/µL	140–440
Natrium (Na)	140 mmol/l	135–145
Kalium (K)/potassium	3.2 mmol/l	3.5–5.0
Chloride (Cl)	107 mmol/l	98–107
Calcium (Ca)	9.1 mg/dL	8.5–10.5
Magnesium (Mg)	2.2 mg/dL	1.8–2.4
BUN	6.3 mmol/L	2.1–8.5
Creatinine	0.6 mg/dL	0.6–1.1
Random blood sugar	191 mg/dL	<200
SGOT	34 U/L	5–40
SGPT	14 U/L	7–56
Albumin	4.3 g/dL	3.4–5.4
CRP	1.16 mg/dL	<0.3
TSH	0.7530 µUI/mL	2–12 years: 0.64–6.27 12–18 years: 0.51–4.94 >18 years: 0.55–4.78
Free T4	0.99 ng/mL	1–23 months: 0.94–1.44 2–12 years: 0.86–1.4 13–20 years: 0.83–1.43
T3	0.63 ng/mL	0.35–1.93
Procalcitonin	0.02 ng/mL	<0.05: healthy ≥0.05 – <0.5: local infection ≥0.5 – <2: systemic infection ≥2 – <10: severe sepsis ≥10: septic shock
Blood sedimentation rate	9 mm	0–20
ANA test	15.7 AU/mL	<40.0: negative ≥40.0: positive
Anti ds.DNA	0.5 IU/mL	<30.0: negative ≥30.0: positive

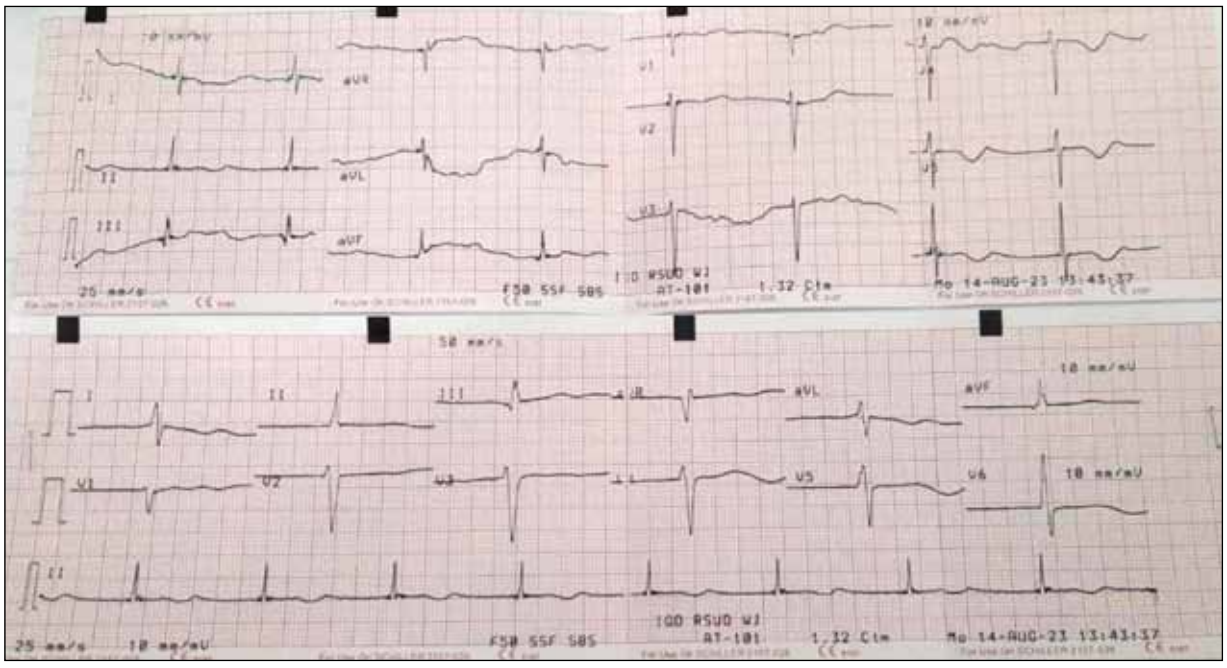

Fig. 2 – ECG on initial presentation.

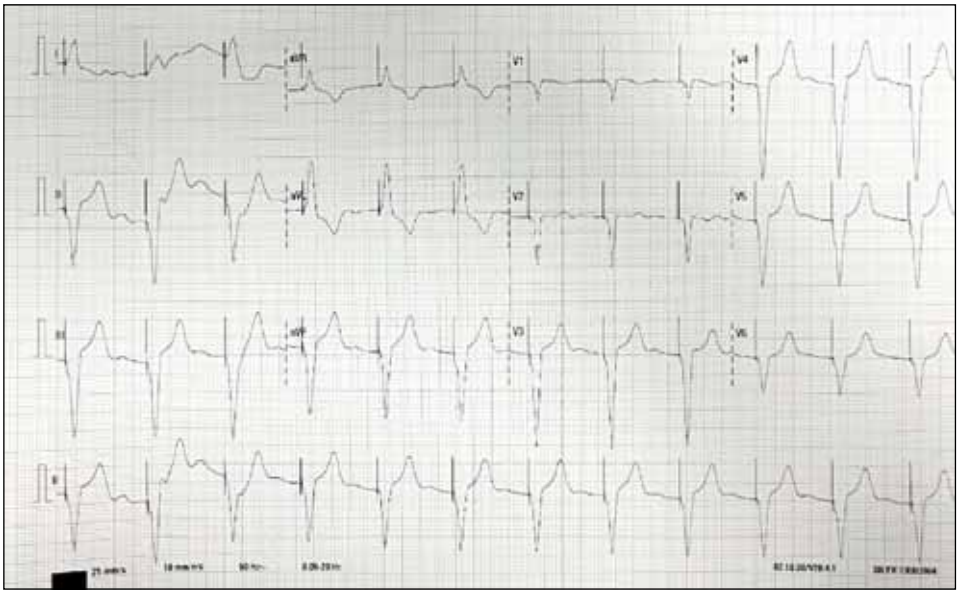

Fig. 3 – ECG after TPM installation.

regurgitation, trivial tricuspid regurgitation, and trivial pulmonary regurgitation. No signs of effusion or congestion were found.

The patient was diagnosed with symptomatic bradycardia, atrial fibrillation with slow ventricular response, and hypokalemia (3.1 mmol/l). The consumption of donepezil was also stopped and supervised by a nurse. A KCl drip of 40 mEq/100 cc over 3 hours via a central venous catheter (CVC) was administered to correct hypokalemia, but symptoms were still present. A temporary pacemaker (TPM) was implanted, and the dopamine pump was discontinued. After the TPM was placed, vital signs in normal limits with pacemaker rhythm, the patient had no symptoms and was under observation (**Fig. 3**).

However, asymptomatic bradycardia is persistent after 72 hours of donepezil discontinuation. After 72 hours of discontinuing donepezil consumption, the patient's heart rate did not change significantly. When attempting to remove the TPM, an EKG showed sinus arrest with junctional escape rhythm at 45 beats per minute, normal frontal axis, clockwise rotation of the horizontal axis, T-wave inversion in leads V_3–V_6 with prominent U wave (**Fig. 4**). The patient's potassium level became 3.7 mmol/l (normal). The patient experienced a weight loss of 10 kg

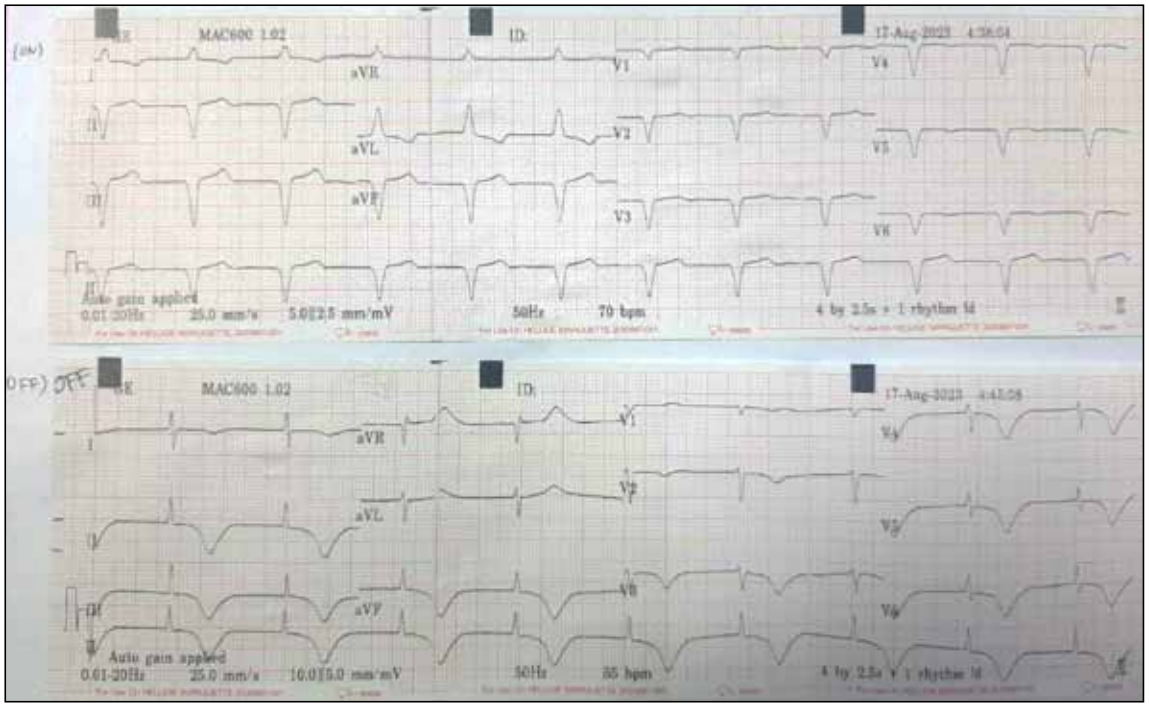

Fig. 4 – Comparison of ECG during TPM installation and TPM removal.

Table 2 – Similar published casereports

Number of cases or sex/age	Sign and symptoms	Donepezil dose	Treatment	Outcomes	Case link
Female/79	Letargy, vomiting, HR 56 bpm, pale skin, diaphoretic	50 mg	3 mg of atropine injection	Returned to baseline by day two in the hospital	Donepezil overdose: a tenfold dosing error - PubMed (nih.gov)[6]
Male/84	Nausea, vomiting, diarrhea, fatigue, excessive sweating, disorientation, HR 50 bpm, QTc prolongation	35 mg	0.5 mg of atropine injection	The patient's bradycardia and QTc prolongation resolved, and the patient returned home after six days in the hospital	Cardiotoxic overdose treated with intravenous fat emulsion and high-dose insulin in the setting of hypertrophic cardiomyopathy - PubMed (nih.gov)[7]
Female/74	Nausea, vomiting, drowsiness, flushing, diarrhea	45 mg	No treatment	Returned to baseline after stopping donepizil	Donepezil overdose - PubMed (nih.gov)[8]
Male/90	HR 36 bpm, advanced 2 : 1 atrioventricular block and QT prolongation	5–10 mg	The patient's donepezil was discontinued and 30 mg of orciprenaline was administered	By the fifth day, the patient's ECG and other symptoms had normalized	Donepezil-induced adverse side effects of cardiac rhythm: 2 case reports of atrioventricular block and Torsade de Pointes - PubMed (nih.gov)[9]
Female/87	Syncope, nausea, vomiting, HR 40 bpm, QT prolongation		30 mg of orciprenaline	On the fifth day, the donepezil was discontinued, and her heart rate increased to 55 BPM. On day 18, the QT prolongation resolved	Encephalopathy from unintentional donepezil and memantine ingestion - PubMed (nih.gov)[10]
Female/96	Difficult to awaken, diaphoretic, altered mental status, abdominal pain, HR 64 bpm	5–10 mg	Electrolyte correction, ciprofloxacin and metronidazole for colitis, 3 mg of glucagon injection	The patient was discharged on day six with two more days of antibiotic therapy (ciprofloxacin and metronidazole) and complete resolution for her symptoms	Suspected donepezil toxicity: A case report - PMC (nih.gov)[11]

(BMI 21.48). The patient was finally put on PPM because she remained symptomatic even though donepezil was discontinued. This decision took into consideration the patient's good quality of life and other health conditions. Patient was discharged from the hospital and had routine check-ups at the polyclinic in good condition for 2 months later.

Discussion

Bradyarrhythmias are characterized by an abnormally slow heart rate, fewer than 60 beats per minute (bpm).[4] Bradyarrhythmias can reflect normal physiologic responses, as in sleeping, or reveal a number of rhythm disorders, including sinus node dysfunction and AV conduction disturbances.[5] Common causes of bradyarrhythmias encompass intrinsic cardiac diseases, electrolyte imbalances, autonomic dysfunction, and pharmacological influences.[4] Although rare, bradyarrhythmias may occur in dementia patients taking donepezil at toxic and therapeutic doses, and all of them are elderly patients (>60 years) (**Table 2**). Bradycardia in older patients can occur due to the influence of an unstable autonomic nervous system so that donepezil causes bradycardia more easily in geriatrics, but uniquely in this case it occurred at a young age (33 years). This opens up insight that this condition can also occur at a young age.

The pathophysiological mechanisms underlying bradyarrhythmias in dementia patients following donepezil discontinuation remain elusive. It is postulated that donepezil's cholinergic enhancement may influence cardiac conduction pathways, potentially leading to abnormal rhythm disturbances.[12] The patient's bradycardia did not change even though donepezil had been stopped for 72 hours. The half-life of donepezil is 70 hours.[13] The altered pharmacodynamics of aging can cause up to a 17% decrease in clearance of donepezil in older adults and result in higher serum levels of donepezil.[14] In a randomized, open-label, real-world comparative trial, adverse effects accounted for 73.1% of discontinuations of donepezil, galantamine, and rivastigmine.[9] The adverse events listed as cardiovascular (CV) were "fast or slowed heart rate", and "irregular heartbeat", and the total CV adverse effects ranged from 6.5% for galantamine to 12.2% for rivastigmine. Other adverse events listed under other categories may have had, at least in part, an unrecognized CV contribution. Examples include fainting, dizziness, falls, and fatigue. The overall rates of discontinuation after the 18-week trial were 38.8% for donepezil, 53% for galantamine, and 58.7% for rivastigmine.[10]

Donepezil, by inhibiting acetylcholinesterase, increases synaptic levels of acetylcholine, thereby enhancing cholinergic signaling throughout the body. In dementia patients, this augmentation of cholinergic activity might exert a compensatory effect on cardiac autonomic regulation, potentially mitigating the occurrence of bradyarrhythmias. Conversely, abrupt cessation of donepezil could lead to a sudden decline in cholinergic tone, predisposing individuals to bradyarrhythmias. Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without underlying cardiac conduction abnormalities.[10] Additionally, potential interactions with other drugs commonly used in dementia management, such as antipsychotics or antiarrhythmic agents, could exacerbate the risk of bradyarrhythmias.[11] The patient did not complain of abdominal pain, but experienced weight loss. The weight loss and potential decrease in nutrition may have resulted in an increase in serum concentrations of donepezil as this medication has a large volume of distribution and is 96% protein bound.[3]

The patient was found to have low potassium levels (3.1 mmol/l). Potassium ions play a crucial role in maintaining the resting membrane potential and action potential of cardiac myocytes. Reduced extracellular potassium levels can lead to membrane hyperpolarization, which in turn prolongs the duration of the cardiac action potential. This prolongation can manifest as delayed depolarization of cardiac cells, resulting in slowed conduction through the cardiac conduction system and predisposing individuals to bradyarrhythmias.[12] However, after correction for potassium, bradycardia was still persistent.

Donepezil overdose has been shown to result in profound sinus bradycardia, which is reversible with atropine.[13] However, in this patient bradycardia still occurred after injection of 2 ampoules of atropine and potassium correction. So a TPM was installed with a regular heart rate of 70×/minute. The patient was treated for four days. When the TPM was removed, an ECG showed sinus arrest with junctional escape rhythm at 45 beats per minute, normal frontal axis, clockwise rotation of the horizontal axis, T-wave inversion in leads V_3–V_6 with prominent U wave. The use of TPM is continued to keep the patient's heart rate stable. Because the understanding of the development of bradycardia, syncope, and other adverse effects of AChE inhibitor use is incomplete, there are few guidelines regarding the management of patients on or being considered for placement on these agents.[14] The suggestions for managing possible AChE inhibitor CV side effects include monthly pulse checks and symptom monitoring. If bradycardia is noted (<50 bpm) or if syncope or seizures are reported, the investigation of all possible causes is recommended before attributing these signs to AChE inhibitors.[15]

This study has a limitation. It is important to note that study's findings are based on a single patient, limiting its generalizability to broader populations of dementia patients or those discontinuing donepezil therapy.

Conclusion

This case report highlights the relationship between donepezil consumption and the incidence of severe bradyarrhythmia in a young patient without any cardiovascular risk disease and risk factors, that are persistent even after discontinuation of donepezil. Permanent pacemaker (PPM) installation should be considered in cases with persistent severe symptoms. Further research is needed to understand better the mechanisms and improve treatment strategies for adverse events related to donepezil in dementia patients.

Conflict of interest
Nothing to declare

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Ethical statement
None.

Informed consent
The authors hereby grant permission to reproduce materials from our work for the purpose of dissemination, distribution, and academic or educational use. We have obtained consent from the patient to publish this information anonymously.

Availability of data and material
The authors confirm that the data supporting the findings of this study are available within the article.

Authors' contributions
OWF and BBD were responsible for drafting, literature review, and editing of the manuscript. RJ, CFA, PBT, and EP were responsible for literature review and editing. All authors approved the final version of paper.

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