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ORIGINAL RESEARCH

The Association Between Antidepressant Treatment and Heart Rate Deceleration Capacity in Patients With Mood disorders—A Potential New Predictor of Sudden Cardiac Death

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Purpose: Patients with mood disorders treated with antidepressants are at high risk of sudden cardiac death, and QT interval prolongation has been as an indicator of sudden cardiac death, however there is no clarity. Recently, a decreased heart rate deceleration capacity (DC) has been regarded as an accurate predictor of cardiac mortality. We attempted to reevaluate the risk of sudden cardiac death associated with antidepressant use assessed via DC.

Patients and Methods: We investigated the correlation of the DC of 107 patients with major depressive disorder (MDD) and bipolar disorder (BD), diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, with prescribed doses of antidepressants or other psychotropic drugs via linear regression analysis. We then compared the DC of 68 age- and sex-matched healthy controls with that of 68 MDD patients.

Results: DC was negatively correlated with both tricyclic antidepressant (TCAs) (PRC = −3.62, 95% CI= −5.69–-1,55, p<0.001) and non-tricyclic antidepressant (non-TCAs) use (PRC = −0.69, 95% CI= −1.34–-0.042, p<0.05) in a dose-dependent manner. Additionally, we found that MDD patients taking antidepressants had significantly lower DC compared to healthy controls (5.32 vs 7.60ms, p<0.001).

Conclusion: The use of TCAs would influence the decline in DC, and even the use of non-TCAs may influence the decline in DC when multiple medications are used. Evaluating DC may improve the predictive accuracy of sudden cardiac death in patients with mood disorders taking antidepressants.

Keywords: deceleration capacity, antidepressant, sudden cardiac death, heart rate variability, QT interval, mood disorder, major depressive disorder

Introduction

Antidepressant use has been associated with an increased risk of sudden cardiac death (SCD) in patients with mood disorders such as major depressive disorder (MDD) or bipolar disorder (BD).[1,2] Previously, antidepressants, especially tricyclic antidepressants (TCAs), have been reported to increase the incidence of SCD.[3–5] However, recent studies have reported that antidepressant use is associated with a lower risk of SCD and ventricular arrhythmias, indicating an inconsistency in the literature.[6–8]

A prolonged corrected QT interval (QTc) observed via electrocardiography (ECG) is a risk factor for torsade de pointes, which can cause SCD.[9] The use of TCAs in addition to some selective serotonin reuptake inhibitors (SSRIs) has previously been reported to prolong the QT interval.[10–13] Therefore, QT interval prolongation is routinely used as a surrogate marker of the risk of fatal arrhythmias in patients with mood disorders who are taking antidepressants. However, the QT interval is incomplete as a biomarker for proarrhythmic risk of inducing sudden cardiac death[14] because

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it shows diurnal variation[15] and has measurement errors even among cardiologists,[16] and the algorithms and correction equations used in automated ECG analysis differ depending on the model used.[17] It has even been reported that evidence for clinically meaningful QT prolongation in psychiatric drug treatment remains minimal.[18] Therefore, to correctly assess the risk of SCD due to antidepressant drugs, other more accurate, simple, and noninvasive markers are needed.

Decreased activity of the autonomic nervous system (ANS) is associated with an increased risk of SCD.[19,20] Heart rate variability (HRV) is considered an indicator of cardiac and ANS function, and it represents beat-by-beat variation in heart rate.[21] HRV decreases with increased sympathetic function and decreased parasympathetic function, and it has been associated with mortality in patients with heart failure, coronary artery disease, and acute myocardial infarction.[22,23] There are reports of decreased HRV in patients taking antidepressant medications.[24]

Indices of HRVs, including frequency domain components, such as low-frequency (LF) and high-frequency (HF) components, and time domain components, such as the standard deviation of normal-to-normal (SDNN) intervals or root mean square successive difference (RMSSD), have been developed, each with their own measurement method and physiological interpretation.[25,26] Thus, conventional measures of HRV have been shown to provide prognostic information linking reduced HRV with poor prognosis; however, their predictive power is variable and only moderate overall, and their clinical usefulness is low.[27]

A strong association between heart rate deceleration capacity (DC) and mortality has been reported in patients after myocardial infarction.[28] DC is believed to represent the parasympathetic nervous system's ability to regulate cardiovascular modulation and serves as a functional biomarker for parasympathetic capacity by analyzing the deceleration of the instantaneous heart rate.[28] DC values less than 2.5 ms, 2.6 to 4.5 ms, and greater than 4.5 ms represent high, moderate, and low risks of mortality, respectively. DC is more accurate than conventional measures of HRV, such as the SDNN. A reduction in DC results in a high risk of mortality, regardless of ventricular premature beats.[28]

Therefore, DC may represent a new and promising measure for noninvasive risk stratification to prevent cardiac death.[29] In the present study, we determined the DC of patients with mood disorders currently taking antidepressants and other psychotropic drugs to reevaluate their risk of SCD.

Material and Methods

Participants

Data from 112 Japanese patients with mood disorders such as MDD or bipolar disorder (BD) of mild to moderate severity (≦18 points on the Hamilton Depression Rating Scale (HAM-D)) treated with antidepressants or mood stabilizers at Dokkyo Medical University or Fudogaoka Hospital between 2019 and 2024 were collected. Psychiatric diagnoses were made on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. The medical history, pharmacotherapy status, and laboratory data of all patients were reviewed, ECGs were recorded, and blood pressure was measured to evaluate their physical condition. Among the 112 patients, the following patients were excluded because of factors known to affect heart rate and cardiac function: 2 patients with hypertension (systolic blood pressure at the time of measurement > 140 mmHg), 2 patients with hypotension (systolic blood pressure at the time of measurement < 100 mmHg) and 1 patient with hypokalemia (<3.5 mEq/L). Data from the remaining 107 patients (48 males; age range, 20–80 years; mean age, 53.6 ± 16.0 years) were analyzed in this study. Among the 107 patients, 94 were diagnosed with MDD, and 13 were diagnosed with BD. All 94 patients with MDD were taking one or more antidepressants. Additionally, 86 healthy volunteers among the staff at Dokkyo Medical University Hospital and Fudougaoka Hospital who provided consent were recruited. These healthy controls had no physical abnormalities or psychiatric abnormalities.

Measurement of DC

We used an instrument (Wireless Wearable Heart Rate Sensor®: Union Tool Co., Tokyo, Japan) to measure heart rate in an automatic and noninvasive manner by simply taping electrodes to the chests of patients, and DC was analyzed from the heart rate measured via RRI Analyzer® (Union Tool Co., Tokyo, Japan).

DC was calculated as described below. From the recorded waveforms of heart rate, the time series data of the R–R interval were extracted. Points in this time series where the R-R interval was longer than the previous interval were selected as anchors. All segments of the same size around the anchors were selected, and all selected segments were translated in the horizontal axis direction and overlaid with the anchor in the segment as the origin (X0). Then, the signals X within the aligned segments are averaged. DC was quantified via the following equation: DC = (1/4)[X(0)+X (1) - X(−1) - X(−2)]. X(0) and X(1) are the averages of the anchor points and the following R–R intervals, respectively, whereas X(−1) and X(−2) are the averages of the 2R–R intervals preceding the anchor points. This method thus followed Bauer et al's definition of phase-rectified signal averaging, which constitutes averaging the partial time series obtained under specific conditions such as increases or decreases (see also[28] 's report for a detailed description of the method).

All the measurements were obtained in the same order from 9:00 to 12:00 in a quiet, comfortable room. After appropriate skin preparation, the subjects were fitted with chest electrodes and allowed to rest for 5 minutes before the measurements were taken. After resting, DC and heart rate were recorded continuously for 10 minutes while the participants were in a seated position. During the measurement period, all the subjects were instructed to breathe 15 times per minute (cued with a metronome) to ensure that rhythmic variation in heart rate fluctuations was associated with respiration and not due to another source.

Determination of the QTc From ECG Data

All patients lay supine, and ECG data were recorded during the procedure. A standard 12-lead ECG device was used and recorded at a paper speed of 25 mm/s. The QT interval was measured manually following a previous report.[30] The end of the T wave was determined as the intersection between the tangent to the steepest downslope of the T wave and the isoelectric line. The QT interval was then corrected according to the heart rate. In the present study, we used Hodges' formula (QTc = QT interval+1.75 (heart rate – 60)) because it is considered more appropriate than Bazett's formula (QTc = QT interval/(RR interval)$^{1/2}$) in cases of tachycardia or bradycardia.[31–33]

Medications

Information on the drugs taken by patients with mood disorders was obtained from their medical records. The administered drugs remained unchanged for at least 1 week. The doses of antidepressants prescribed to participants were converted into imipramine-equivalent doses.[34] The antipsychotic drugs and benzodiazepines prescribed to participants were converted into chlorpromazine- and diazepam-equivalent doses, respectively.[34] The distribution of medications and dosages administered are shown in Table 1.

Table 1 Demographic Data of Patients Diagnosed With Mood Disorders and the Distributions of Medication and Dosage

	Total	
No. of patients	107 (48 men/59 women)	
Mean age (SD) Body mass index (SD) QTc (Hodges' formula) (SD), ms	53.6 (16.0) 23.3 (5.33) 0.42 (0.029)	
Administered drugs	No. of prescriptions (%)	Mean dose (SD), mg
Antidepressants	94 (87.8)	161.8 (113.0)
Clomipramine	5 (4.67)	68.0 (29.5)
Amitriptyline	3 (2.80)	100.0 (0.0)
Nortriptyline	2 (1.87)	100.0 (70.7)
Fluvoxamine	4(3.74)	100.0 (57.7)
Paroxetine	17 (15.9)	30.0 (10.6)

(*Continued*)

Table 1 (Continued).

	Total	
Sertraline	10 (9.35)	75.0 (28.9)
Escitalopram	18 (16.8)	14.7 (5.55)
Milnacipran	3 (2.80)	61.7 (37.5)
Duloxetine	15 (14.0)	47.3 (15.3)
Venlafaxine	10 (9.35)	124.5 (64.2)
Mirtazapine	21 (19.6)	33.9 (12.5)
Antipsychotics	34 (31.8)	220.7 (225.2)
Lithium	16 (15.0)	668.8 (202.4)
Carbamazepine	2 (1.87)	300.0 (141.4)
Sodium valproate	8 (7.48)	460.0 (237.1)
Benzodiazepines	69 (64.5)	15.2 (18.6)

Statistical Analysis

For the first analysis, linear regression analysis was applied to examine risk factors for DC. Age, sex, body mass index (BMI), and TCA (imipramine equivalent), non-TCA (imipramine equivalent), antipsychotic (chlorpromazine equivalent), benzodiazepine (diazepam equivalent), and mood stabilizer (lithium, sodium valproate, and carbamazepine) doses were entered as independent variables in the stepwise regression model (Model 1). The TCAs included clomipramine, amitriptyline, and nortriptyline. Non-TCAs include fluvoxamine, paroxetine, sertraline, escitalopram, milnacipran, duloxetine, venlafaxine, and mirtazapine. In the second analysis, age, sex, BMI and individual antidepressant doses were entered as independent variables in the stepwise regression Model 2. In the third analysis of the 94 patients with MDD who were taking antidepressants and 86 healthy controls, the propensity score was adjusted for age and sex. The mean heart rate and DC values were compared in 68 patients with MDD taking antidepressants adjusted for age and sex (33 males; mean age, 47.9±14.1 years) and 68 healthy subjects adjusted for age and sex (33 males; mean age, 46.7±12.8 years) via independent-samples t tests. All the statistical analyses were performed via SPSS version 29.0 (IBM Japan, Tokyo, Japan). All reported P values were two-tailed, and statistical significance was set at $p<0.05$, $p<0.01$, and $p<0.001$.

Ethics Approval

The protocol for this study was approved by the Bioethics Committee of Dokkyo Medical University (approval number: R-17-3J). This study was conducted in accordance with the Declaration of Helsinki. All clinical records used in this study were anonymized by removing any identifying information (such as name and registration number). Furthermore, the clinical data were collated and managed by one person. The person who performed the statistical analysis could not access the original data of each participant. Healthy controls underwent the examination voluntarily. Our study required written informed consent from each subject and healthy control, and data were collected only from consenting participants.

Results

Demographic Data

Demographic data are presented in Table 1. Among the 107 patients with mood disorders, 27 (25.2%) had a DC of <2.5 ms (mean DC: 1.44±0.63), 25 (23.4%) had a DC between 2.5 ms and 4.5 ms (mean DC: 3.59±0.58), and 55 (51.4%) had a DC over 4.5 ms (mean DC: 7.23±2.18). There were 94 patients with mood disorders who were taking antidepressants, 29 of whom were taking more than two kinds of antidepressants.

Correlation Between DC and Antidepressant Dose

In Model 1, age (partial regression coefficient (PRC) = −0.062, 95% confidence interval (CI) = −0.094–-0.030, $p<0.001$), TCA dose (PRC=−3.62, 95% CI= −5.69–-1,55, $p<0.001$) and non-TCA dose (PRC= −0.69, 95% CI= −1.34–-0.042, $p<0.05$) were

negatively correlated with DC in patients with mood disorders (Table 2). In Model 2, age (PRC=−0.070, 95% CI= −0.10–-0.037, p<0.001), clomipramine dose (PRC=−4.21, 95% CI= −8.24–-0.17, p<0.05) and amitriptyline dose (PRC=−5.65, 95% CI= −10.4–-0.94, p<0.05) were negatively correlated with DC in patients with mood disorders (Table 3).

Comparison Between Patients With MDD Prescribed Antidepressant Drugs and Healthy Controls

There was a significant difference in heart rate and DC between patients with MDD taking antidepressant medication and healthy controls (Figures 1 and 2). The mean heart rate was 80.2±12.8/min for patients with MDD in the antidepressant

Table 2 Effects of Distinct Psychotropic Drugs on DC

	DC	
	Forced entry PRC (95% CI)	**Stepwise selection PRC (95% CI)**
Age	−0.060 (−0.095–-0.025)***	−0.062 (−0.094–-0.030)***
Sex (risk in women)	−0.22 (−1.36–0.92)	
BMI	0.017 (−0.088–0.12)	
QTc (ms)	1.58 (−0.34–3.50)	
TCAs (150 mg)	−4.34 (−6.58–-2.10)***	−3.62 (−5.69–-1.55)***
Non-TCAs (150 mg)	−0.98 (−1.72–-0.24)*	−0.69 (−1.34–-0.042)*
Antipsychotics (100 mg)	−0.017 (−0.37–0.33)	
Lithium carbonate (100 mg)	−0.17 (−0.41–0.072)	
Sodium valproate (100 mg)	−0.055 (−0.48–0.37)	
Carbamazepine (100 mg)	−0.46 (−1.76–0.84)	
Benzodiazepines (5 mg)	0.11 (−0.064–0.29)	

Notes: Age, TCAs and non-TCAs were negatively correlated with DC. The doses of antidepressants prescribed to participants were converted into imipramine-equivalent doses. The doses of antipsychotics prescribed to participants were converted into chlorpromazine-equivalent doses. The doses of benzodiazepines prescribed to patients were converted into diazepam-equivalent doses. *p<0.05, ***p<0.001.
Abbreviations: QTc, corrected QT interval; DC, deceleration capacity; PRC, partial regression coefficient; CI, confidence interval; BMI, body mass index; TCA, tricyclic antidepressants.

Table 3 Effects of Individual Antidepressants on the DC of Patients With Mood Disorders

	DC	
	Forced Entry PRC (95% CI)	**Stepwise Selection PRC (95% CI)**
Age	−0.061 (−0.097–-0.025)**	−0.070 (−0.10–-0.037)***
Sex (risk in women)	−0.30 (−1.43–0.82)	
BMI	0.021 (−0.083–0.13)	
QTc	1.37 (−0.61–3.35)	
Clomipramine (120 mg)	−5.40 (−9.60–-1.20)*	−4.21 (−8.24–-0.17)*
Amitriptyline (150 mg)	−7.02 (−11.9–-2.16)**	−5.65 (−10.4–-0.94)*
Nortriptyline (75 mg)	−2.22 (−4.85–0.40)	
Fluvoxamine (150 mg)	0.040 (−3.76–3.85)	
Paroxetine (40 mg)	−1.43 (−3.38–0.53)	
Sertraline (100 mg)	0.73 (−1.65–3.10)	
Escitalopram (20 mg)	−0.40 (−2.36–1.56)	
Milnacipran (100 mg)	−0.97 (−5.68–3.74)	
Duloxetine (30 mg)	−0.69 (−1.65–0.27)	
Venlafaxine (150 mg)	−1.40 (−3.48–0.68)	
Mirtazapine (30 mg)	−1.16 (−2.34–0.014)	

Notes: Age and the doses of clomipramine and amitriptyline were negatively correlated with DC. *p<0.05, **p<0.01, ***p<0.001.
Abbreviations: DC, deceleration capacity; PRC, partial regression coefficient; CI, confidence interval; BMI, body mass index.

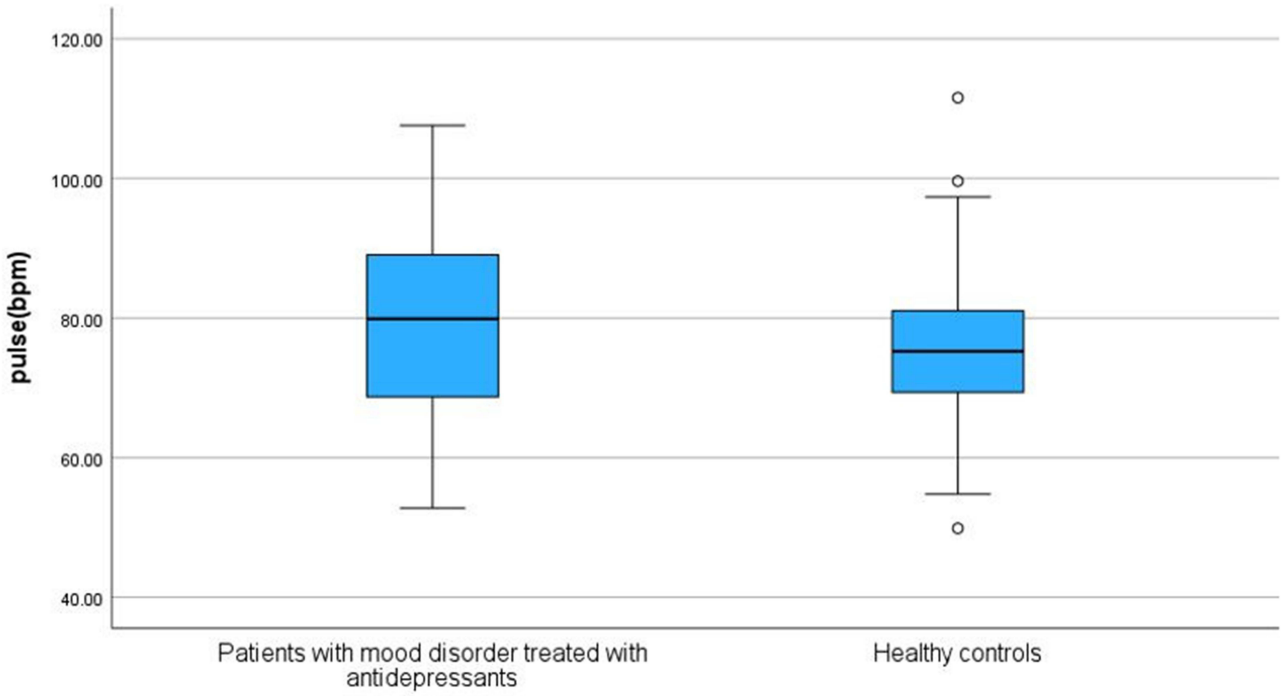

Figure 1 Comparison of pulse between patients treated with antidepressants and healthy controls.
Abbreviations: bpm, beat per minute.

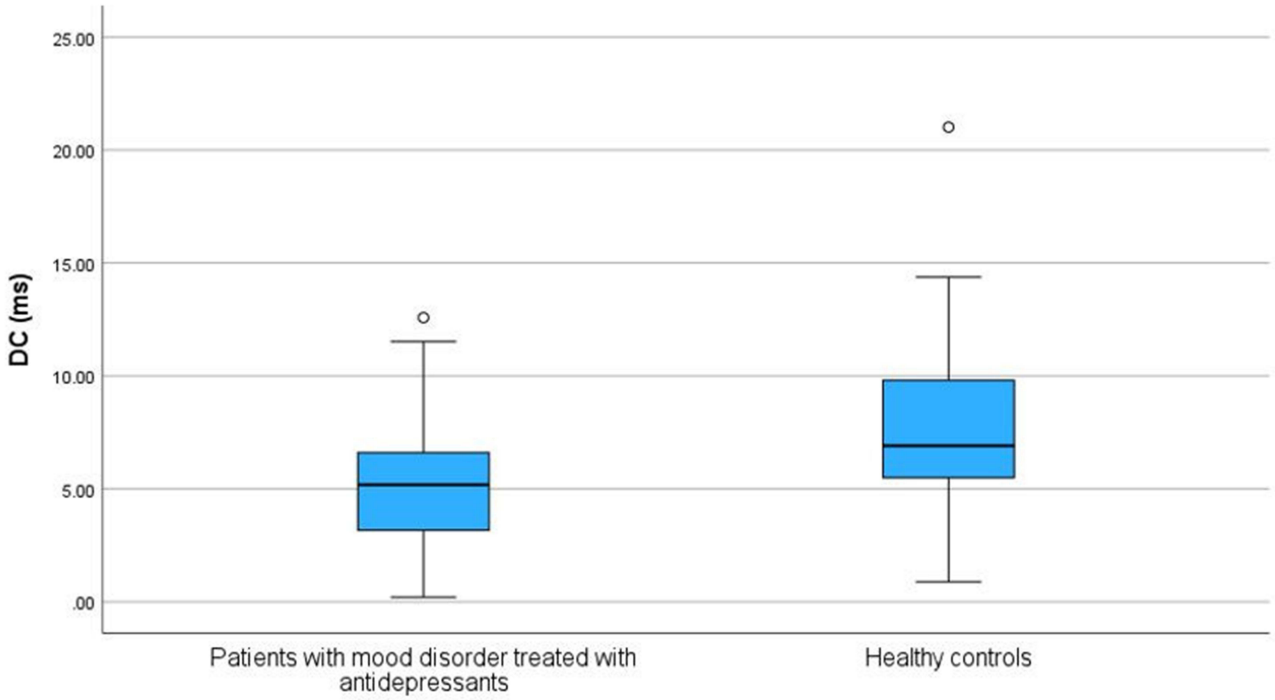

Figure 2 Comparison of DC between patients treated with antidepressants and healthy controls. Abbreviations: DC, deceleration capacity.

Table 4 Comparison of Heart Rate and DC Between Patients Treated With Antidepressants and Healthy Controls Adjusted for Age and Sex With Propensity Scores

Number	Patients with Mood Disorder	Healthy Controls	P value
	68	68	
	Mean (SD)	Mean (SD)	
Age (years)	47.9 (14.1)	46.7 (12.8)	0.61
Heart Rate (/min)	80.2 (12.8)	75.6 (10.9)	0.024*
DC (ms)	5.32 (2.97)	7.60 (3.44)	<0.001***

Notes: Significant differences in DC were found between patients and healthy controls. *p<0.05, ***p<0.001.

Abbreviations: DC, deceleration capacity, SD, standard deviation.

group, 75.6±10.9/min for those in the healthy control group (p<0.05) and the mean DC was 5.32±2.97 ms for the patients with MDD in the antidepressant group and 7.60±3.44 ms for those in the healthy control group (p<0.001) (Table 4).

Discussion

In our study, DC was negatively correlated with the TCA dose, especially for doses of clomipramine and amitriptyline. Although non-TCAs as a whole reduced DC in a dose-dependent manner, no association with DC was demonstrated for individual non-TCAs. Compared with healthy controls, patients with MDD on antidepressant medication presented decreased DCs. To our knowledge, there have been no reports on the association between DC and patients with mood disorders who received antidepressants.

We confirmed that the use of TCAs, particularly clomipramine and amitriptyline, was significantly associated with lower DC in a dose-dependent manner. Compared with those who did not use antidepressants, those who used TCAs had a dose-related increased risk of sudden cardiac death.[35] The use of TCAs is associated with decreased parasympathetic activity.[24] Previous reports have suggested that TCAs are significantly associated with several markers of reduced parasympathetic function.[36]

Our previous report revealed that the use of antipsychotics with wide-ranging receptor affinity profiles, such as olanzapine and clozapine, dose-dependently reduced DC in patients with schizophrenia.[37] TCAs such as clomipramine and amitriptyline exert relatively stronger blocking effects on muscarinic acetylcholine, adrenergic, and histamine receptors (such as olanzapine and clozapine) than do other types of antidepressants.[38,39] The effects of these drugs on DC may be due to their pharmacological properties, although more detailed validation is needed in the future.

Furthermore, TCAs have been identified as having arrhythmogenic effects, which are caused by strong blockade of cardiac sodium channels and arrhythmogenic activity in potassium channels.[38] The use of TCAs is also known to prolong the QT interval, which is considered a predictor of ventricular arrhythmias.[10]

Owing to their pharmacological profiles and arrhythmogenic activity, TCAs have potent and complex effects on the cardiovascular system, and these changes can occur at therapeutic levels or in overdose.[40]

Compared with TCAs, non-TCAs have relatively weaker effects on the ANS.[24] In particular, SSRIs have been reported in meta-analyses to have no significant association with conventional measures of HRV.[36,41] There are a few reports suggesting that serotonin–noradrenaline reuptake inhibitors (SNRIs) have the second strongest association with decreased HRV after TCAs[24] and that venlafaxine also decreases HRV.[42] The association between mirtazapine and HRV is not consistent across studies.[41,42] A recent systematic review revealed that no SSRIs had an adverse effect on mortality in heart failure patients.[43] Although an association with QT interval prolongation in escitalopram and citalopram has been reported,[44] there are reports of no excess risk of arrhythmia or sudden cardiac death,[11,45,46] and within a clinical dose range, most SSRIs have not been associated with a prolonged QT interval.[12] For SNRIs and mirtazapine, the risk of QT prolongation at therapeutic doses is considered lower.[47] In our present study, we found no association between individual

non-TCAs and DC. When considered together with previous reports, we suggest that there is little cardiac risk associated with using clinical doses of individual non-TCAs.

In contrast, the present study revealed a dose-dependent decrease in DC for non-TCAs overall. When antidepressant monotherapy is considered unresponsive, treatment with two antidepressants in combination is frequently performed, and combination treatment is considered a significantly superior treatment to monotherapy.[48] However, antidepressant polytherapy has been reported to be associated with an increased risk of ventricular arrhythmias and SCD.[49] Even the use of antidepressants other than TCAs may have an effect on cardiac function when used in combination with multiple drugs or in excess doses due to overmedication.

Additionally, it has been suggested that the risk of arrhythmias is increased in elderly individuals treated with any antidepressant.[50] In this study, age was significantly associated with lower DC, suggesting that antidepressant therapy may increase the risk of cardiac function decline in elderly individuals.

In our previous reports, we reported that antipsychotic use decreased DC in a dose-dependent manner.[37] However, in the present study, we did not detect a significant association between antipsychotic use and DC reduction. This could be because the patients in that study were patients with schizophrenia, the number of antipsychotic users among patients with mood disorders was lower, and the total use of antipsychotics among patients with mood disorders was lower than that among patients with schizophrenia.

Sodium valproate and carbamazepine are typically used as antiepileptic drugs. There have been several studies on antiepileptic drugs and conventional HRV, but the results have been inconsistent.[51,52] To our knowledge, there are no reports of lithium carbonate and its effects on the ANS. In this study, no significant association with DC was found for mood stabilizers; however, the number of patients taking carbamazepine, sodium valproate or lithium in this study was very small.

There was no significant association between DC and the use of benzodiazepines in this study. Similarly, our previous study revealed no association between benzodiazepine use and DC.[37]

In the present study, no significant association was detected between DC and QTc. These results were similar to those of our previous report.[37] Although it may not be directly comparable to the findings of previous studies of heart failure patients, DC has been reported to be an independent predictor of SCD.[53] Hence, DC may be considered an independent factor with respect to cardiac mortality, even in patients with mood disorders.

Limitations

This study has several limitations. First, given the variety of antidepressants used by the participants, the sample sizes of the groups were small. Second, because this study had a cross-sectional design, we could not evaluate changes in DC before and after medication use in the same patients. Third, the original method of Bauer et al involved calculating DC from a 24-hour ECG recording; in contrast, in the present study, the measurement time was only 10 minutes.[28] However, short ECG recordings have been reported to provide HRV data that are as useful as those obtained from an entire 24-hour period.[54,55] Finally, with respect to severity, all selected patients had a HAM-D of 18 or less at the time of DC measurement, but this is not a sufficient assessment of severity. Since there are reports that the severity of MDD and BD affects autonomic function,[56–58] detailed validation, taking severity into account, is needed in the future.

Conclusion

Although this research has several limitations, as mentioned above, we found that the use of antidepressants in patients with mood disorders was associated with decreased DC in a dose-dependent manner. Assessing DC might facilitate monitoring and identification of an increased risk of SCD in patients with mood disorders who are taking antidepressants. To increase the safety of antidepressant use, an evaluation of ANS function may be necessary. Future large-scale cohort studies or longitudinal studies are needed to clarify in detail the association between DC and SCD in patients with mood disorders receiving antidepressant treatment in the future.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. *Psychosom Med*. 2017;79(2):153–161. doi:10.1097/PSY.0000000000000382
2. Chen PH, Tsai SY, Pan CH, et al. Incidence and risk factors of sudden cardiac death in bipolar disorder across the lifespan. *J Affect Disord*. 2020;274:210–217. doi:10.1016/j.jad.2020.05.094
3. Sicouri S, Antzelevitch C. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. *Expert Opin Drug Saf*. 2008;7(2):181–194. doi:10.1517/14740338.7.2.181
4. Hamer M, Batty GD, Seldenrijk A, Kivimaki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish health survey. *Eur Heart J*. 2011;32(4):437–442. doi:10.1093/eurheartj/ehq438
5. Whang W, Kubzansky LD, Kawachi I, et al. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the nurses' health study. *J Am Coll Cardiol*. 2009;53(11):950–958. doi:10.1016/j.jacc.2008.10.060
6. Cao Y, Zhou M, Guo H, Zhu W. Associations of Antidepressants With Atrial Fibrillation and Ventricular Arrhythmias: a Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2022;9:840452. doi:10.3389/fcvm.2022.840452
7. Almuwaqqat Z, Jokhadar M, Norby FL, et al. Association of antidepressant medication type with the incidence of cardiovascular disease in the ARIC study. *J Am Heart Assoc*. 2019;8(11):e012503. doi:10.1161/JAHA.119.012503
8. Prasitlumkum N, Cheungpasitporn W, Tokavanich N, et al. Antidepressants and Risk of Sudden Cardiac Death: a Network Meta-Analysis and Systematic Review. *Medical Sciences*. 2021;9(2). doi:10.3390/medsci9020026.
9. Straus SMJM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47(2):362–367. doi:10.1016/j.jacc.2005.08.067
10. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*. 2000;355(9209):1048–1052. doi:10.1016/S0140-6736(00)02035-3
11. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75(5):e441–449. doi:10.4088/JCP.13r08672
12. Maljuric NM, Noordam R, Aarts N, et al. Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. *Br J Clin Pharmacol*. 2015;80(4):698–705. doi:10.1111/bcp.12681
13. Okayasu H, Ozeki Y, Fujii K, et al. Pharmacotherapeutic determinants for QTc interval prolongation in Japanese patients with mood disorder. *Pharmacopsychiatry*. 2012;45(7):279–283. doi:10.1055/s-0032-1308969
14. ICH steering committee. Is. ICH harmonized tripartite guideline. The clinical evaluation of QT/QTC interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. 2025. Available from: https://database.ich.org/sites/default/files/E14_Guideline.pdf. Accessed November 11, 2024.
15. Watanabe J, Suzuki Y, Fukui N, et al. Increased risk of antipsychotic-related QT prolongation during nighttime: a 24-hour holter electrocardiogram recording study. *J Clin Psychopharmacol*. 2012;32(1):18–22. doi:10.1097/JCP.0b013e31823f6f21
16. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol*. 2006;17(3):333–336. doi:10.1111/j.1540-8167.2006.00408.x
17. Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs*. 2011;25(6):473–490. doi:10.2165/11587800-000000000-00000
18. Beach SR, Celano CM, Sugrue AM, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018;59(2):105–122. doi:10.1016/j.psym.2017.10.009
19. Sessa F, Anna V, Messina G, et al. Heart rate variability as predictive factor for sudden cardiac death. *Aging (Albany NY)*. 2018;10(2):166–177. doi:10.18632/aging.101386
20. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. Heart rate variability from 24-hour electrocardiography and the 2-year risk for sudden death. *Circulation*. 1993;88(1):180–185. doi:10.1161/01.CIR.88.1.180
21. van Ravenswaaij-Arts CM, Kollée LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. *Ann Intern Med*. 1993;118(6):436–447. doi:10.7326/0003-4819-118-6-199303150-00008

22. Van Hoogenhuyze D, Weinstein N, Martin GJ, et al. Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1991;68(17):1668–1676. doi:10.1016/0002-9149(91)90327-H
23. Bigger JT Jr, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP. Components of heart rate variability measured during healing of acute myocardial infarction. *Am J Cardiol*. 1988;61(4):208–215. doi:10.1016/0002-9149(88)90917-4
24. Kemp AH, Brunoni AR, Santos IS, et al. Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: an ELSA-Brasil cohort baseline study. *Am J Psychiatry*. 2014;171(12):1328–1334. doi:10.1176/appi.ajp.2014.13121605
25. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. 2017;5:258. doi:10.3389/fpubh.2017.00258
26. Sammito S, Böckelmann I. Reference values for time- and frequency-domain heart rate variability measures. *Heart Rhythm*. 2016;13(6):1309–1316. doi:10.1016/j.hrthm.2016.02.006
27. Priori SG, Aliot E, Blømstrom-Lundqvist C, et al. Task force on sudden cardiac death, European society of cardiology. *Europace*. 2002;4(1):3–18. doi:10.1053/eupc.2001.0214
28. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet*. 2006;367(9523):1674–1681. doi:10.1016/S0140-6736(06)68735-7
29. Kreuz J, Lickfett LM, Schwab JO. Modern noninvasive risk stratification in primary prevention of sudden cardiac death. *J Interv Card Electrophysiol*. 2008;23(1):23–28. doi:10.1007/s10840-008-9264-8
30. Charbit B, Samain E, Merckx P, Funck-Brentano C. QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. *Anesthesiology*. 2006;104(2):255–260. doi:10.1097/00000542-200602000-00009
31. Bazet H. An analysis of the time-relations of electrocardiograms. *Heart*. 1920;7:353–370.
32. Hodges M, Salcrmo D, Erlien D. Bazett's correction reviewed-Evidence that a linear QT correction for heart is better. *J Am Coll Cardiol*. 1983;1:694.
33. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol*. 2004;37 Suppl:81–90. doi:10.1016/j.jelectrocard.2004.08.030
34. Inada T, Inagaki A, Inada T, Inagaki A. Psychotropic dose equivalence in J apan. *Psychiatry Clin Neurosci*. 2015;69(8):440–447. doi:10.1111/pcn.12275
35. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther*. 2004;75(3):234–241. doi:10.1016/j.clpt.2003.09.019
36. Fiani D, Campbell H, Solmi M, Fiedorowicz JG, Calarge CA. Impact of antidepressant use on the autonomic nervous system: a meta-analysis and systematic review. *Eur Neuropsychopharmacol*. 2023;71:75–95. doi:10.1016/j.euroneuro.2023.03.013
37. Okayasu H, Shinozaki T, Takano Y, et al. Effect of antipsychotic use by patients with schizophrenia on deceleration capacity and its relation to the corrected QT interval. *Gen Hosp Psychiatry*. 2023;81:15–21. doi:10.1016/j.genhosppsych.2023.01.005
38. Thanacoody HK, Thomas SH. Tricyclic antidepressant poisoning: cardiovascular toxicity. *Toxicol Rev*. 2005;24(3):205–214. doi:10.2165/00139709-200524030-00013
39. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol*. 2007;151(6):737–748. doi:10.1038/sj.bjp.0707253
40. Jefferson JW. A review of the cardiovascular effects and toxicity of tricyclic antidepressants. *Psychosom Med*. 1975;37(2):160–179. doi:10.1097/00006842-197503000-00006
41. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry*. 2010;67(11):1067–1074. doi:10.1016/j.biopsych.2009.12.012
42. Terhardt J, Lederbogen F, Feuerhack A, et al. Heart rate variability during antidepressant treatment with venlafaxine and mirtazapine. *Clin Neuropharmacol*. 2013;36(6):198–202. doi:10.1097/WNF.0b013e3182a76fbb
43. Hedrick R, Korouri S, Tadros E, et al. The impact of antidepressants on depressive symptom severity, quality of life, morbidity, and mortality in heart failure: a systematic review. *Drugs Context*. 2020;9. doi:10.7573/dic.2020-5-4
44. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288.
45. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. High-dose citalopram and escitalopram and the risk of out-of-hospital death. *J Clin Psychiatry*. 2017;78(2):190–195. doi:10.4088/JCP.15m10324
46. Hasnain M, Howland RH, Vieweg WV. Escitalopram and QTc prolongation. *J Psychiatry Neurosci*. 2013;38(4):E11. doi:10.1503/jpn.130055
47. Jasiak NM, Bostwick JR. Risk of QT/QTc prolongation among newer non-SSRI antidepressants. *Ann Pharmacother*. 2014;48(12):1620–1628. doi:10.1177/1060028014550645
48. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: a systematic review and meta-analysis. *JAMA Psychiatry*. 2022;79(4):300–312. doi:10.1001/jamapsychiatry.2021.4313
49. Wu CS, Tsai YT, Hsiung CA, Tsai HJ. Comparative risk of ventricular arrhythmia and sudden cardiac death across antidepressants in patients with depressive disorders. *J Clin Psychopharmacol*. 2017;37(1):32–39. doi:10.1097/JCP.0000000000000631
50. Biffi A, Rea F, Scotti L, et al. Antidepressants and the risk of cardiovascular events in elderly affected by cardiovascular disease: a real-life investigation from Italy. *J Clin Psychopharmacol*. 2020;40(2):112–121. doi:10.1097/JCP.0000000000001189
51. Hallioglu O, Okuyaz C, Mert E, Makharoblidze K. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. *Epilepsy Res*. 2008;79(1):49–54. doi:10.1016/j.eplepsyres.2007.12.020
52. Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia*. 2012;53(2):272–282. doi:10.1111/j.1528-1167.2011.03361.x
53. Arsenos P, Manis G, Gatzoulis KA, et al. Deceleration capacity of heart rate predicts arrhythmic and total mortality in heart failure patients. *Ann Noninvasive Electrocardiol*. 2016;21(5):508–518. doi:10.1111/anec.12343
54. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation*. 1993;88(3):927–934. doi:10.1161/01.CIR.88.3.927
55. Faber TS, Staunton A, Hnatkova K, Camm AJ, Malik M. Step wise strategy of using short- and long-term heart rate variability for risk stratification after myocardial infarction. *Pacing Clin Electrophysiol*. 1996;19(11):1845–1851. doi:10.1111/j.1540-8159.1996.tb03238.x

56. Ding J, Wu Y, Wang B, Sun Z. The relationship between depression severity and heart rate variability in children and adolescents: a meta-analysis. *J Psychosom Res*. 2024;182:111804. doi:10.1016/j.jpsychores.2024.111804
57. Chang H-A, Chang -C-C, Tzeng N-S, Kuo TBJ, Lu R-B, Huang S-Y. Heart rate variability in unmedicated patients with bipolar disorder in the manic phase. *Psychiatry Clin Neurosci*. 2014;68(9):674–682. doi:10.1111/pcn.12178
58. Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W. Heart rate variability in bipolar mania and schizophrenia. *J Psychiatr Res*. 2010;44(3):168–176. doi:10.1016/j.jpsychires.2009.07.011