

Effect of Fluoxetine and Escitalopram on Heart Rate Variability (HRV) and Serum Potassium Level in Patients of Depression and Anxiety Disorders

Journal of Pharmacology and
Pharmacotherapeutics
14(3) 231–237, 2023
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions-india
DOI: 10.1177/0976500X231213153
journals.sagepub.com/home/pha

Truptiben R Machhi¹, Chetna R. Patel², Sajal K. Pandya² and N. D. Kantharia²

Abstract

Background: The present study was conducted to generate data regarding the effect of fluoxetine as an anti-depressant and escitalopram as an antianxiety agent on heart rate variability (HRV). There is a scarcity of data regarding the correlation between selective serotonin reuptake inhibitors (SSRIs) and serum potassium levels.

Purpose: To find out the effect of SSRIs on HRV, and whether it is either dependent or independent of serum potassium level.

Materials and Methods: In this prospective, open-label, observational study, 70 participants were enrolled and divided into two groups, the fluoxetine group ($n = 35$) and the escitalopram group ($n = 35$) suffering from depression and anxiety, respectively. Parameters, like HRV, serum potassium level, heart rate, respiratory rate, and blood pressure, were measured baseline and after the first, second, and third months of treatment. HRV was calculated by root mean square deviation of successive differences between adjacent RR intervals (RMSSD). ECG (electrocardiogram) was recorded by Physio Pac Digital Polygraph software. All values were expressed as mean $\pm$ SD, and statistical analysis was done by using the repeated measure analysis of variance (ANOVA) test with Greenhouse–Geisser correction, *post hoc* analysis with Bonferroni correction, and SPSS 20.0 software.

Results: Among a total of 70 participants, *post hoc* tests using the Bonferroni correction showed a statistically significant difference between the HRV of the pretreatment group and after the second, and third month of fluoxetine therapy ($p < .05$). In the escitalopram group, the Bonferroni correction showed a significant difference between the HRV of the pretreatment and third-month value ($p < 0.05$). Repeated measure ANOVA with Greenhouse–Geisser correction showed no statistical significance of serum potassium at different time points ($p > 0.05$). There were also no significant changes in heart rate, respiratory rate, and blood pressure at different points of time in both groups. Pearson's correlation coefficient test for a relationship between HRV and serum potassium was negative at different time points.

Conclusion: Fluoxetine significantly increased HRV from the pretreatment value to the second and third months of treatment, whereas in the escitalopram group of participants, the third-month value of HRV was increased compared to the first month. The effect of SSRIs on HRV was independent of serum potassium levels at different time points suggesting that the effect of SSRIs on HRV was independent of serum potassium level.

Keywords

Heart rate variability (HRV), RMSSD, fluoxetine, escitalopram, selective serotonin reuptake inhibitors (SSRIs), serum potassium

Received 22 August 2023; **revised** 14 August 2023; **accepted** 19 October 2023

Introduction

Heart rate variability (HRV) is the rate of variability between each heartbeat with respect to time. HRV is primarily used to analyze the autonomic nervous system (ANS) which consists of the sympathetic nervous system and the parasympathetic

¹Vaccines Partnership Market Europe, Sanofi, Paris, France

²Department of Pharmacology, Government Medical College, Surat, Gujarat, India

Corresponding author:

Chetna R. Patel, Department of Pharmacology, Government Medical College, Surat, Gujarat 395001, India.

E-mail: drchetnapatel2012@yahoo.com



nervous system. ANS is a control system used to modulate the body's unconscious actions, such as cardiac, respiration, blood pressure, digestion, and urination.¹

The heart is highly innervated by autonomic nerves. Impaired vagal function and various potassium channels stimulated by sympathetic activity affecting the HRV are possibly the mechanisms linking to brain disorders.^{2,3} HRV is a classical biomarker, an informative indicator of the brain-body integration, pathological states, or concomitant health.⁴ By the neurovisceral integration (NVI) model, a reduction in activation of the central autonomic network (CAN) may affect the decreased level of HRV. The CAN modulates the neuroendocrine, visceromotor, and behavioral systems, and has a connection with the sinoatrial node of the heart via the stellate ganglion through the vagus nerve.⁵ The heart rhythm is coordinated with the cardiac action potential generation by the SA node, depolarization, and repolarization of myocyte by intricate flows of ions primarily sodium, calcium, and potassium across myocyte cell membranes. ANS is a major modulator of cardiac electrophysiology and particularly potassium current.³

Autonomic, cardiovascular, neuronal, psychological factors, and pathological states do affect HRV. Depression and anxiety disorders have low HRV and an increased risk of future cardiovascular disease and mortality, which can be identified by HRV and HRT (heart rate turbulence).^{4,6-9} Improvement in low HRV may cure major depressive disorder (MDD) and anxiety. HRV effects are considered by clinicians while selecting a medication for a depressed patient who has a low cardiac vagal tone.^{8,10} The previous study results showed that psychotherapy improves HRV; a CBT (cognitive-behavioral therapy) with a breathing relaxation exercise could significantly increase SDNN (standard deviation of NN intervals) and decrease the LF/HF ratio. Pharmacotherapy with tricyclic anti-depressants (TCAs) (imipramine, doxepin, and amitriptyline) results showed a decrease in most measures of HRV along with an increase in heart rate.¹¹⁻¹³ Fluoxetine, sertraline, or agomelatine could increase HF while mirtazapine or venlafaxine has no significant effect on HRV.¹¹ SSRIs (selective serotonin reuptake inhibitors) are prescribed for depression and anxiety due to selectivity, effectiveness, and relatively low toxic profile as compared to their predecessors, the monoamine oxidase inhibitors, TCAs, and antianxiety agents.¹⁴ Still, the effect of SSRIs (fluvoxamine, fluoxetine, and paroxetine) on HRV is less clear.¹³

Fluoxetine is a longer-acting bicyclic compound used as an anti-depressant and escitalopram an active S-enantiomer of the racemic mixture of RS-citalopram widely used as an antianxiety drug at tertiary care teaching hospital of South Gujarat.

The effect of fluoxetine on cloned human ether-a-go-go-related gene (hERG) potassium channels expressed in *Xenopus* oocytes suggests that hERG potassium channels are blocked by the fluoxetine. The effects of escitalopram on hERG channels expressed in human embryonic kidney cells,

suggest that escitalopram blocked hERG currents.¹⁵⁻¹⁷ In clinical medicine, changes in K⁺ homeostasis, either hypokalemia or hyperkalemia reveal pathophysiologic consequences due to reduced dietary K⁺ intake.^{18,19} Adrenaline is released more in anxiety and depression which causes an increased potassium uptake into the cells via Na⁺/K⁺ ATPase system-modulated beta-adrenoceptors.^{20,21}

There is a scarcity of data regarding the effect of SSRIs on HRV. So, this study was planned to check the effect of fluoxetine and escitalopram on HRV and serum potassium levels in patients of depression and anxiety and to find out the correlation between the effect of these two drugs on HRV, whether dependent on serum potassium level or not.

Materials and Methods

This was a prospective, open-label, observational study designed as per STROBE guidelines, conducted after approval of the institutional ethical committee (NO.MCS/STU/ETHICS/APPROVAL/22662/16). Enrollment of the 70 participants was done as per the inclusion and exclusion criteria at the psychiatry department of the tertiary care teaching hospital of south Gujarat and written informed consent was taken.

Inclusion criteria:

1. Patients of either gender between the ages of 20 and 65 years.
2. Newly diagnosed patients of depressive and anxiety disorders as per DSM-5 (diagnostic and statistical manual of mental disorders) criteria, not exposed to earlier SSRI or any psychotropic drugs for at least last 6 months.²²

Exclusion criteria:

1. Patients with cardiovascular disease.
2. History of substance abuse within a last year.
3. Patients with suicidal tendencies, schizoaffective disorder or bipolar disorder, seizure disorder, concurrent major illness, or systemic dysfunction involving hepatic and renal system.
4. Pregnant and lactating women.
5. H/O allergy to any of the medications mentioned above.

The individuals participating in this study were divided into the following two groups:

1. Fluoxetine group (*n* = 35)
2. Escitalopram group (*n* = 35)

Dosages of the drug:

Fluoxetine = 20 mg/day

Escitalopram = 10 mg/day

Control: Pretreatment value of the same patient.

The individuals participating in this study were compared for pretreatment and posttreatment parameters at 4, 8, and 12 weeks.

Parameters: HRV, serum potassium, heart rate, respiratory rate, blood pressure HRV was calculated by root mean square deviation of successive differences between adjacent RR intervals (RMSSD). ECG (electrocardiogram) was recorded by Physio Pac Digital Polygraph software for 5 minutes after 20 minutes of rest.²³

Blood pressure (systolic + diastolic) was measured by the auscultatory method according to the recommendations VIII Joint National Committee (JNC VIII). At least two measurements were taken, and the average was recorded.²⁴ Along with that, heart rate and respiratory rate were also recorded.

For the estimation of serum potassium level, 2 mL venous blood sample was collected in plain vacuity and subjected to electrolyte analysis was done in a biochemistry laboratory by ion selective electrode technique and recorded.

All statistical analysis was done using SPSS 20.0 software.

All values were expressed as mean $\pm$ SD.

Statistical analysis was done by repeated measure analysis of variance (ANOVA) test with Greenhouse–Geisser correction and *post hoc* analysis with Bonferroni correction.

p-Value < 0.05 was taken as statistically significant.

Results

A total of 23 male and 10 female participants were prescribed fluoxetine. A total of 17 male and 14 female participants were prescribed escitalopram (Figures 1 and 2).

Effects of Fluoxetine (*n* = 33) on HRV Measured During Follow-Up Visits with Those at Baseline

Repeated measures ANOVA with a Greenhouse–Geisser correction determined that HRV differed statistically significantly between time points ($F(2.52, 10362.57) = 15.61$,

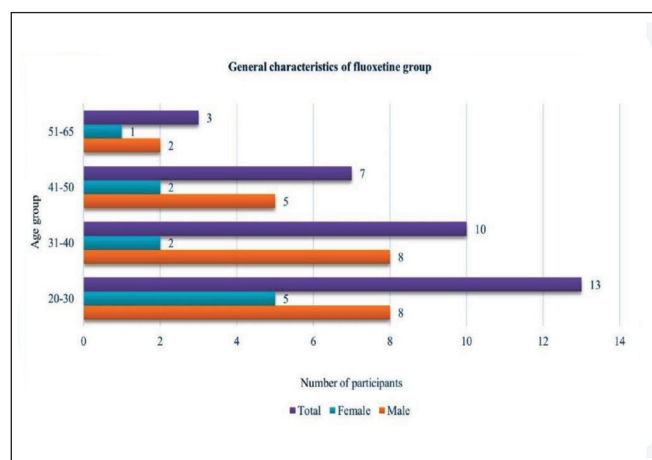


Figure 1. General Characteristics of the Fluoxetine Group.

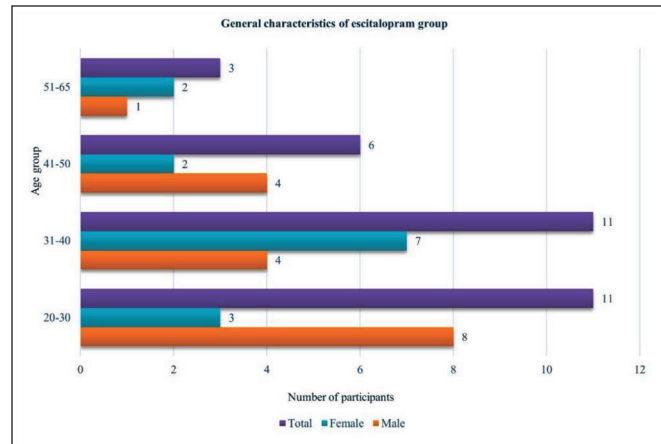


Figure 2. General Characteristics of the Escitalopram Group.

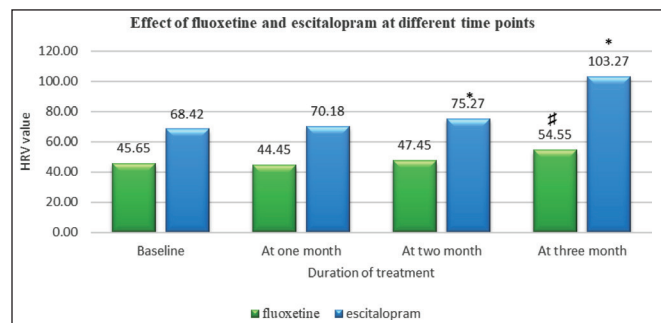


Figure 3. Comparison of Effects of Fluoxetine and Escitalopram on HRV (ms) Measured During Follow-Up Visits with Those at Baseline (*n* = 64).

* *p* < .05 vs baseline; # *p* < 0.05 vs baseline.

Abbreviations: HRV, heart rate variability.

p = 0.000). *Post hoc* tests using the Bonferroni correction revealed that there was a significant difference between HRV of a pretreatment group (68.42 ± 39.863) and HRV after 2 months of fluoxetine therapy (75.27 ± 41.93), HRV of a pretreatment group (68.42 ± 39.863) and HRV after 3 months of fluoxetine therapy (103.27 ± 41.59) (*p* < 0.05).

Effects of Escitalopram (*n* = 31) on HRV Measured During Follow-Up Visits with Those at Baseline

Repeated measures ANOVA with a Greenhouse–Geisser correction determined that HRV not differed statistically significantly between time points ($F(2.22, 858.20) = 1.35$, *p* = 0.266). *Post hoc* tests using the Bonferroni correction revealed that there was a significant difference between the HRV of a pretreatment group (45.65 ± 32.68) and HRV after 3 months of escitalopram therapy (54.55 ± 37.8) (*p* < 0.05) (Table 1 and Figure 3).

Repeated measure ANOVA with Greenhouse–Geisser correction reveals serum potassium did not differ statistically significantly at different time points ($p > 0.05$) (Table 2).

The correlation between HRV and serum potassium was checked by the Pearson Correlation Coefficient test which is significant at the 0.05 (2-tailed) level. In the Fluoxetine

group of patients, Pearson's correlation coefficient pretreatment ($r = 0.017$), after the first month ($r = 0.1$), after the second month ($r = 0.3$), and after the third month ($r = 0.3$). In the escitalopram group of patients Pearson's correlation coefficient pretreatment ($r = 0.017$), after the first month ($r = 0.1$), after the second month ($r = 0.3$), and after the third month ($r = 0.3$).

Table 1. Effects of Fluoxetine ($n = 33$) and Escitalopram ($n = 31$) on HRV Measured During Follow-Up Visits with Those at Baseline ($n = 64$).

Variable	Pre-treatment HRV (ms)	Post-treatment HRV (ms)		
		After the First Month of Treatment	After the Second Month of Treatment	After the Third Month of Treatment
Fluoxetine	68.42 ± 39.86	70.18 ± 33.44	*75.27 ± 41.93	*103.27 ± 41.59
Escitalopram	45.65 ± 32.68	44.45 ± 28.12	47.45 ± 29.2	#54.55 ± 37.8

* $p < 0.05$ vs baseline; # $p < 0.05$ vs baseline.

Table 2. Effects of Fluoxetine ($n = 33$) and Escitalopram ($n = 31$) on Serum Potassium Measured During Follow-Up Visits with Those at Baseline ($n = 64$).

Variable	Pre-treatment Serum Potassium (meq/L)	Post-treatment Serum Potassium (meq/L)		
		After the First Month of Treatment	After the Second Month of Treatment	After the Third Month of Treatment
Fluoxetine	4.15 ± 0.36	4.03 ± 0.17	4.15 ± 0.36	4.30 ± 0.46
Escitalopram	4.42 ± 0.50	4.06 ± 0.35	4.10 ± 0.39	4.03 ± 0.48

Table 3. Effects of Fluoxetine and Escitalopram on Heart Rate Measured During Follow-Up Visits with Those at Baseline ($n = 64$).

Variable	Pre-treatment Heart Rate	Post-treatment Heart Rate		
		After the First Month of Treatment	After the Second Month of Treatment	After the Third Month of Treatment
Fluoxetine	77.21 ± 8.83	79.64 ± 8.13	81.03 ± 7.28	82.00 ± 9.64
Escitalopram	80.97 ± 11.84	80.90 ± 10.57	82.52 ± 8.85	82.29 ± 8.32

Table 4. Effects of Fluoxetine and Escitalopram on Respiratory Rate Measured During Follow-Up Visits with Those at Baseline ($n = 64$).

Variable	Pre-treatment Respiratory Rate	Post-treatment Respiratory Rate		
		After the First Month of Treatment	After the Second Month of Treatment	After the Third Month of Treatment
Fluoxetine	19.09 ± 1.23	19.39 ± 1.06	19.27 ± 1.11	19.45 ± 1.03
Escitalopram	19.48 ± 1.23	19.68 ± 1.05	19.42 ± 1.06	19.16 ± 1.13

Table 5. Effects of Fluoxetine and Escitalopram on Systolic and Diastolic Blood Pressure Measured During Follow-Up Visits with Those at Baseline ($n = 64$).

Drug	Variable	Pre-treatment	Post-treatment		
			After the First Month of Treatment	After the Second Month of Treatment	After the Third Month of Treatment
Fluoxetine	SBP (mm of Hg)	118.24 ± 5.9	116.72 ± 5.2	117.21 ± 5.5	118.48 ± 5.3
	DBP (mm of Hg)	77.87 ± 5.4	76.36 ± 4.8	76.36 ± 4.8	77.87 ± 4.8
Escitalopram	SBP (mm of Hg)	119.16 ± 6.7	117.29 ± 5.5	117.93 ± 5.1	118.90 ± 4.8
	DBP (mm of Hg)	77.74 ± 4.2	77.29 ± 4.4	77.09 ± 4.6	78.06 ± 4.01

Repeated measure ANOVA with Greenhouse–Geisser correction reveals heart rates did not differ statistically significantly at different time points ($p > 0.05$) (Table 3).

Repeated measure ANOVA with Greenhouse–Geisser correction reveals respiratory rate did not differ statistically significantly at different time points ($p > 0.05$) (Table 4).

Repeated measure ANOVA with Greenhouse–Geisser correction reveals systolic and diastolic blood pressure (SBP and DBP) was not statistically significant at different time points ($p > 0.05$) (Table 5).

Discussion

As far back as 1965, the clinical importance of HRV was noted when it was found that alterations in HRV without any changes occurred in heart rate itself in fetal distress.¹⁰ Over the span of years, the assessment of HRV has increased in various research areas. The fact that HRV is noninvasive and reproducible—if carried out under standardized conditions.²⁵

Mathematical chaos can be described as complex patterns of variability exhibited in a healthy biological system. Time domain variables can be calculated directly from R–R intervals, and frequency domain variables are generated from ECG spectral analysis. By observing variation in these parameters after administering ANS antagonists, relative contributions of ANS have been inferred. Although the total power of the spectrum represents the general level of autonomic activation, low-frequency activity (<0.15 Hz) is mainly due to baroreceptor reflex modulation, related to both vagal and sympathetic influence, and high-frequency activity is mainly aligned with vagal activity. Low to high-frequency ratio is accepted to indicate the balance between both systems; however, this interpretation fails to take account of effects such as different temporal patterns of sympathetic and parasympathetic components and cardiac pacemaker sensitivity.¹⁰ The HRV LF band primarily reflects the vagally stimulated slow response, which is transmitted between the medulla and heart. ultra low frequency (ULF) and very low frequency (VLF) rhythms are associated with overall health status based on 24-hour monitoring.

In this study, total of 23 male and 10 female participants were prescribed fluoxetine and a total of 17 male and 14 female participants were prescribed escitalopram. Two patients from the fluoxetine group and four patients from the escitalopram group were excluded due to loss of follow-up.

Repeated measures ANOVA with a Greenhouse–Geisser correction determined that HRV differed statistically significantly between time points ($F(2.52, 10362.57) = 15.61$, $p = .000$) and *post hoc* tests using the Bonferroni correction revealed that there is a significant difference between HRV of pretreatment group (68.42 ± 39.863) and HRV at second-month of fluoxetine therapy (75.27 ± 41.93), HRV of pretreatment group (68.42 ± 39.863) and HRV after third-month of fluoxetine therapy (103.27 ± 41.59) ($p < 0.05$).

However, there is no significant difference between the HRV of the pretreatment group (68.42 ± 39.863) and HRV after the first month of fluoxetine therapy (70.18 ± 33.44) ($p > .05$). Repeated measures ANOVA with a Greenhouse–Geisser correction determined that HRV not differed statistically significantly between time points ($F(2.22, 858.20) = 1.35$, $p = 0.266$) and *post hoc* tests using the Bonferroni correction revealed that there is a significant difference between HRV of pretreatment group (45.65 ± 32.68) and HRV after third month of escitalopram therapy (54.55 ± 37.8) ($p < 0.05$).

In this study, a significant difference was present between HRV of pretreatment and after the second month of treatment with SSRIs, HRV of pretreatment, and after three months of treatment with SSRIs. A previous study conducted by Srivastava and Kantharia suggests that amitriptyline has produced a statistically significant effect on HRV after two and four weeks of treatment as compared to pretreatment values in diabetic patients.²⁶

In contrast, the short-term recordings of patients treated with SSRIs showed a marginally significant increase only in SDNN. Again, it is difficult to comment on these results as the long-term studies were markedly contradictory.¹³

Repeated measure ANOVA with Greenhouse–Geisser correction reveals serum potassium levels did not differ statistically significantly at different time points ($p > .05$).

In the present study, the correlation between HRV and serum potassium was checked by the Pearson correlation coefficient test which is significant at the 0.05 (2-tailed) level. In the Fluoxetine group of patients, Pearson's correlation coefficient was not significant at pretreatment ($r = 0.017$), after the first month ($r = 0.1$), after the second month ($r = 0.3$), and after the third month ($r = 0.3$). Similarly in the escitalopram group of patients, Pearson's correlation coefficient was not significant at pretreatment ($r = 0.017$), after the first month ($r = 0.1$), after the second month ($r = 0.3$), and after the third month ($r = 0.3$).

SSRIs are unlikely to cause cardiovascular adverse events when used in recommended dosage ranges, in a similar way, present study results reveal that heart rates do not differ statistically significantly before and after treatment with fluoxetine and escitalopram.^{11,27}

There is a significant decrease in HR associated with the treatment in all five studies, and the change in HR was much smaller.¹³ Nyström et al. results showed that in 18-week treatment with liraglutide, compared with glimepiride, in combination with metformin, there was significantly increased diurnal variation in hourly mean HR followed by an increase in mean day-time HR, with no effects on HRV.²³ The reduction of sinus tachycardia obtained by short-term treatment with propranolol in hyperthyroidism may be independent of the modification of HRV.²⁸

Respiratory sinus arrhythmia is a phenomenon, HRV is a result of pulmonary stretch receptors as a part of the parasympathetic input which synapse in the central nervous

system before acting on the SA node.²⁹ Results showed that RR does not differ significantly at pretreatment and at different time points of treatment. Individuals using SSRIs had more frequent apneas and hypopneas during NREM sleep compared to non-medicated and those taking non-serotonergic anti-depressants.³⁰

Schroeder et al. suggest that there is a decline in HRV relatively early in the development of hypertension. HRV has emerged as a tool to quantitatively investigate cardiac autonomic dysregulation in hypertension. Results showed that fluoxetine and escitalopram had no significant effect on blood pressure in this study.³¹

Controversy exists regarding the established frequency domain and time domain when it comes to their physiological interpretation and their psychometric properties like reliability, validity, and the sensitivity to cardiovascular properties of the variety of parameters seem to be a topic for further research.²⁵

Conclusion

Fluoxetine significantly increased HRV from baseline pretreatment value to the second and third months of treatment, whereas in the escitalopram group of participants, the third-month value of HRV increased compared to the first-month value of HRV. There is no statistically significant correlation between the HRV and serum potassium level at different time points suggesting that the effect of SSRIs on HRV was independent of the serum potassium level.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Study was conducted after approval of the institutional ethical committee (NO.MCS/STU/ETHICS/APPROVAL/22662/16).

Informed Consent

The participant has consented to the submission of the article to the journal.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Chetna R. Patel  <https://orcid.org/0000-0003-4134-3280>

References

1. Ishaque S, Khan N and Krishnan S. Trends in heart-rate variability signal analysis. *Front Digit Health* 2021; 3: 639444. DOI: 10.3389/fdgh.2021.639444
2. Singla S, Jhamb S, KD Singh, et al. Depression affects the autonomic system of the body? Yes, it does! *J Edu Health Promot* 2020; 9: 217. DOI: 10.4103%2Fjehp.jehp_627_19
3. Tomson TT and Arora R. Modulation of cardiac potassium current by neural tone and ischemia. *Card Electrophysiol Clin* 2016; 8(2): 349–360. DOI: 10.1016/j.ccep.2016.01.007
4. Calvi A, Fischetti I, Verzicco I, et al. Antidepressant drugs effects on blood pressure. *Front Cardiovasc Med* 2021; 8: 704281. DOI: 10.3389/fcvm.2021.704281
5. Choi KW and Jeon HJ. Heart rate variability for the prediction of treatment response in major depressive disorder. *Front Psychiatry* 2020; 11: 607. DOI: 10.3389/fpsy.2020.00607
6. O'Regan C, Kenny RA, Cronin H, et al. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from The Irish Longitudinal Study on Ageing (TILDA). *Psychol Med* 2015; 45(3): 623–636. DOI: 10.1017/S0033291714001767
7. Trimmel, K, Sacha, J, Huikuri, HV, eds. *Heart rate variability: clinical applications and interaction between HRV and heart rate* Lausanne: Frontiers Media, 2015. DOI: 10.3389/978-2-88919-652-4
8. Yeh T-C, Kao L-C, Tzeng N-S, et al. Heart rate variability in major depressive disorder and after antidepressant treatment with agomelatine and paroxetine: findings from the Taiwan Study of Depression and Anxiety (TAISDA). *Prog Neuropsychopharmacol Biol Psychiatry* 2016; 64: 60–67. DOI: 10.1016/j.pnpbp.2015.07.007
9. Iwamoto Y, Kawanishi C, Kishida I, et al. Dose-dependent effect of antipsychotic drugs on autonomic nervous system activity in schizophrenia. *BMC Psychiatry* 2012; 12: 199. DOI: 10.1186/1471-244x-12-199
10. McCraty R and Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Glob Adv Heal Med* 2015; 4(1): 46–61.
11. Chen S, Wang H, Yue J, et al. Intervention methods for improving reduced heart rate variability in patients with major depressive disorder: a systematic review and meta-analysis. *Compr Psychiatry* 2022; 119: 152347. DOI: 10.1016/j.comp-psych.2022.152347
12. Gorman JM and Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J* 2000; 140(4): S77–S83. DOI: 10.1067/mhj.2000.109981
13. van Zyl LT, Hasegawa T and Nagata K. Effects of antidepressant treatment on heart rate variability in major depression: a quantitative review. *Biopsychosoc Med* 2008; 2(1): 12. DOI: 10.1186/1751-0759-2-12
14. Bruggeman C and O'Day CS. Selective serotonin reuptake inhibitor toxicity. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2022.
15. Thomas B, Gut G, Wendt-Nordahl J, et al. The antidepressant drug fluoxetine is an inhibitor of human ether-a-go-go-related gene (HERG) potassium channels. *J Pharmacol Exp Ther* 2002; 300(2): 543–548.
16. Chen C, Wang L, Rong X, et al. Effects of fluoxetine on protein expression of potassium ion channels in the brain of chronic mild stress rats. *Acta Pharm Sin B* 2015; 5(1): 55–61. DOI: 10.1016/j.apsb.2014.12.004

17. Borsoatto M, Veyssiere J, Moha ou Maati H, et al. Targeting two-pore domain K⁺ channels TREK-1 and TASK-3 for the treatment of depression: a new therapeutic concept. *Br J Pharmacol* 2015; 172(3): 771–784.
18. Mrug S, Orihuela C, Mrug M, et al. Sodium and potassium excretion predict increased depression in urban adolescents. *Physiol Rep* 2019; 7(16): e14213. DOI: 10.14814/phy2.14213
19. Sica DA, Struthers AD, Cushman WC, et al. Importance of potassium in cardiovascular disease. *J Clin Hypertens* 2002; 4(3): 198–206. DOI: 10.1111/j.1524-6175.2002.01728.x
20. Hong E. Hypokalemia and psychosis: a forgotten association. *Am J Psychiatry Resid J* 2016; 11(11): 6–7.
21. Hatta K, Takahashi T, Nakamura H, et al. Hypokalemia and agitation in acute psychotic patients. *Psychiatry Res* 1999; 86(1): 85–88. DOI: 10.1016/s0165-1781(99)00018-9
22. Regier DA, Kuhl EA and Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry* [Internet]. 2013; 12(2): 92–98. DOI: 10.1002/wps.20050
23. Nyström T, Santos-Pardo I, Fang X, et al. Heart rate variability in type 2 diabetic subjects randomized to liraglutide or glimepiride treatment, both in combination with metformin: a randomized, open, parallel-group study. *Endocrinol Diabetes Metab* 2019; 2(2): e00058. DOI: 10.1002/edm2.58
24. Institute for Quality and Efficiency in Health Care (IQWiG); 2006. What is an electrocardiogram (ECG)? Cologne, Germany; 2019
25. Yacorzaynski, GK. *Frontiers of psychology* New York: Philosophical Library; 1963.
26. Srivastava R and Kantharia ND. Effect of amitriptyline and pregabalin on heart rate variability and electrolytes in neurotrophic pain in diabetic patients. *Int J Basic Clin Pharmacol* 2021; 11(1): 52. DOI: 10.18203/2319-2003.ijbcp20214889
27. Yekehtaz H, Farokhnia M and Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. *J Tehran Heart Cent* 2013; 8(4): 169–176.
28. Tankeu AT, Azabji-Kenfack M, Nganou C-N, et al. Effect of propranolol on heart rate variability in hyperthyroidism. *BMC Res Notes* 2018; 11(1). DOI: 10.1186/s13104-018-3224-x
29. MacDonald DM, Mkorombindo T, Ling SX, et al. Heart rate variability on 10-second electrocardiogram and risk of acute exacerbation of COPD: a secondary analysis of the BLOCK COPD trial. *Chronic Obstr Pulm Dis* 2022; 9(2): 226–236. DOI: 10.15326/jcopdf.2021.0264
30. Robillard R, Saad M, Ray LB, et al. Selective serotonin reuptake inhibitor use is associated with worse sleep-related breathing disturbances in individuals with depressive disorders and sleep complaints: a retrospective study. *J Clin Sleep Med* 2021; 17(3): 505–513. DOI: 10.5664/jcsm.8942
31. Schroeder EB, Liao D, Chambless LE, et al. Hypertension, blood pressure, and heart rate variability: the atherosclerosis risk in communities (ARIC) study. *Hypertension* 2003; 42(6): 1106–1111. DOI: 10.1161/01.HYP.0000100444.71069.73