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Association of severity of depression, paroxetine use and markers of liver damage with QT interval duration in patients with alcohol dependence

Udruženost težine depresije, upotrebe paroksetina i markera oštećenja jetre sa dužinom QT intervala kod zavisnika od alkohola

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Abstract

Background/Aim. Patients suffered from chronic alcoholic disease very often have depression and cardiomyopathy. Treatment with several antidepressants is associated with prolonged QT interval, ventricular arrhythmias and sudden death. The aim of this study was to investigate the relation between the severity of depression, serum levels of gamma-glutamyl transferase (GGT), as a marker of liver damage, and the possible influence of paroxetine use on duration of QT interval in patient who started treatment of chronic alcoholic dependence. **Methods.** The study included 147 male patients (older than 18 years of age) suffering from alcohol addiction, who were also diagnosed with depressive disorder on the basis of DSM-IV criterion and positive Hamilton Rating Scale for Depression (HRSD) at the beginning of hospitalization. Out of total number of patients, 49 were randomly selected to be treated with antidepressant paroxetine at a dose of 20 mg once daily during 20 days. The global QTc interval was automatically determined. **Results.** By applying the generalised linear model, the statistically significant positive correlation between the length of QTc interval and serum values of GGT, that is, intensity of alcoholism (p = 0.002) and values of the HRSD score, that is, intensity of depression (p = 0.021) was established in the sample of 147 depressed alcoholic patients before the application of paroxetine. In spite of the vulnerability of patients due to the heart damage and the liver dysfunction arising from alcohol consumption, as well as altered patients' drugs metabolism, no elongation of QTc interval resulting from the application of paroxetine was established. The length of QTc interval 20 days after paroxetine administration was 401.43 ms and before paroxetine administration it was 403.31 ms. The difference in QTc interval length (after and before paroxetine administration) was ΔQTc = -1.88 ms (p = 0.524). **Conclusion.** The results indicated that the severity of depression and GGT serum levels positively correlated with the length of QT interval. On the other hand, paroxetine after 20 days of usage did not prolong QT interval.

Key words:
alcoholism; alcohol-induced disorders; depression; comorbidity; long QT syndrome; paroxetine.

Apstrakt

Uvod/Cilj. Oboleli od hronične alkoholne bolesti vrlo često imaju depresiju i kardiomiopatiju. Lečenje sa nekim antidepresivima je povezano s produženim QT intervalom, ventrikularnim aritmijama i iznenadnom smrću. Cilj ove studije bio je da se utvrdi odnos između težine depresije, nivoa gama-glutamil transferaze (GGT) u serumu, kao markera oštećenja jetre, i mogućeg uticaja korišćenja paroksetina na trajanje QT intervala kod bolesnika kod kojih je započeto lečenje hronične alkoholne zavisnosti. **Metode.** U ispitivanje je bilo uključeno 147 osoba muškog pola, starijih od 18 godina, zavisnih od alkohola, kod kojih je na početku hospitalizacije na osnovu DSM-IV kriterijuma i pozitivne Hamiltonove skale za procenu depresije (HRSD) dijagnostikovan depresivni poremećaj. Od ukupnog broja ispitanika, njih 49 je metodom slučajnog izbora lečeno antidepresivom paroksetinom u dozi od 20 mg, jedanput dnevno, tokom 20 dana. Globalni QTc interval određivan je automatski. **Rezultati.** U uzorku od 147 depresivnih bolesnika sa alkoholnom zavisnošću, pre ordiniranja bilo kog antidepresivnog leka, primenom generalizovanog linearnog modela utvrđena je stati-

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stički značajna pozitivna korelacija između dužine QTc intervala i serumskih nivoa GGT, tj. intenziteta alkoholizma (p = 0.002), odnosno vrednosti HRSD skora, tj. intenziteta depresije (p = 0.021). I pored vulnerabilnosti bolesnika zbog oštećenja miokarda i poremećaja funkcionisanja jetre izazvanog konzumiranjem alkohola i, posledično, izmenjenog metabolizma lekova, nije utvrđeno produženje QTc intervala usled primene paroksetina. Dvadeset dana posle primene paroksetina dužina QTc interval iznosila je 401.43 ms, a pre njegove primene 403.31 ms. Razlika u dužini QTc intervala (nakon i pre ordiniranja paroksetina) iznosila je ΔQTc = -1.88 ms (p = 0.524). **Zaključak.** Rezultati pokazuju da težina depresije i nivoi GGT u serumu pozitivno korelišu sa dužinom QT intervala. Sa druge strane, paroksetin nakon 20 dana primene, nije produžio QT interval.

Ključne reči:
alkoholizam; poremećaji izazvani alkoholom; depresija; komorbiditet; sindrom produženog QT; paroksetin.

Introduction

Depression and alcoholism are particularly connected. Clinical picture of the comorbidity of depression and alcoholism is manifested by significantly more severe disorder symptoms, longer duration of illness, reduced psychosocial functioning and higher suicidal risk in such patients. Many patients suffering from depression may become alcohol addicts because they try to "cure" bad mood and anxiety by alcohol. On the other hand, many things in the life of an alcohol addict have an effect on the increase of depression and bad mood, which is why a vicious circle from which it is really hard to escape is created. Treatment of patients with dual diagnosis of alcoholism and depression is carried out in several stages. The acute stage is directed at detoxification and stabilisation of depression. The phase of continued treatment is directed at symptoms and change of lifestyle. The maintenance phase is oriented towards the reduction of risk of relapse. Pharmacotherapy is more efficient when combined with counselling and self-help programmes. Antidepressants from the group of selective serotonin reuptake inhibitors (SSRI, e.g. sertraline, fluoxetine, paroxetine, escitalopram, citalopram, and others) and mirtazapine have a positive effect on patients suffering from alcoholism and coexisting depressive disorder as well as comorbid anxiety disorders [1–3].

Epidemiological, clinical and pharmacological research that should help clarify depression and prevent undesired effects of the antidepressant therapy on QT interval have faced problems from the very beginnings, which is of crucial significance for the reduction of serious consequences that these disorders can lead to individuals, their families and community as a whole [4]. Application of an adequate psychopharmacological treatment represents the central part of the therapeutic process of depressed alcoholic persons.

It is described that there is a positive correlation of the dependence of ethanol and paroxetine dosage with the reversible blockage of the voltage-dependent potassium channels of Purkinje cells of the heart which are responsible for the third phase of repolarization of the action potential, thereby causing the prolongation of QT interval [5, 6].

The aim of this study was to examine influences of depression intensity determined by the Hamilton Rating Scale for Depression, serum levels of serum gamma-glutamyltransferase (GGT), as a biomarker of the liver function, and the antidepressant drug paroxetine on the length of QT interval in depressed alcoholic patients.

Methods

This study included 147 male patients, older than 18 years of age, suffering from alcohol addiction and treated at the Department of Addictive Diseases of the Psychiatric Clinic, University Clinical Center of the Republic of Srpska in Banja Luka, Bosnia and Herzegovina, and the Psychiatric Clinic of the University Clinical Center in Novi Sad, Serbia, in whom depressive disorder was diagnosed at the very start of hospitalization, on the basis of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criterion [7] and the positive Hamilton Rating Scale for Depression [8]. Out of these 147 patients, 49 (by a method of random selection) were treated by antidepressant paroxetine. Due to necessity of applying an anxiolytic in relieving and preventing symptoms of alcoholic abstinence syndrome in patients, a benzodiazepine anxiolytic bromazepam in a dose of 3 mg (1, 1, 2) was applied during the study. Serum levels of GGT, as an indirect indicator of the intensity of alcoholism and liver cell lesions, as well as electrolyte status (sodium, potassium, calcium and magnesium) and values of creatine kinase myocardial isoenzyme (CK-MB) were determined in these patients at the beginning of the study and on the day 20 upon admission to the treatment. These parameters were determined in the serum by applying Olympus AU680 chemical analyser (Olympus America Inc.; Centerville, Pa., USA).

In order to be included in the study, patients had to satisfy the following criteria: to have a clinically diagnosed alcohol addiction and to satisfy the criteria under DSM-IV for depressive disorder. It was also necessary for them to have normal referential values in electrolyte findings (Na^+, K^+, Ca^{++}, Mg^{++}), not to have heart rhythm disorders or diagnosed heart diseases. The referential values of electrolytes were the working referential values that are used at the University Clinical Center in Banja Luka: Na^+ 130–147 mmol/L; K^+ 3.2–5.2 mmol/L; Ca^{++} 2.2–2.7 mmol/L, and Mg^{++} 0.5–1.1 mmol/L.

Patients who did not satisfy the above stated criteria, namely patients with diagnosed congenital long QT syndrome, Brugada syndrome, acute infective diseases, autoimmune and malignant diseases, as well as patients who took drugs which prolong QT interval, were not included in the study.

The study was approved by the Ethics Committee of the University Clinical Center in Banja Luka, and patients gave their written consent for participating in the study.

The existence of alcohol addiction and depression was assessed on the basis of anamnestically obtained data and clinical observation. DSM-IV criteria were used for the purpose of diagnosing alcoholic addiction and depression [7]. The HRSD [8] was used for quantifying the severity of depression. The version containing 17 items was used. The severity of depression was determined according to the following scoring system: a) 0–7 score is an indicator that depression is not present; b) 8–15 score speaks in favour of existence of minor (slight) depression; c) score ≥ 16 speaks in favour of existence of major (high) depression.

Antidepressant therapy, that is, paroxetine was applied in 49 patients, in a single morning dose of 20 mg, recommended by the drug manufacturer, during 20 days.

Long QT interval represents a marker of the development of ventricular arrhythmia and sudden death. ECG finding, including measurements of the length of QT interval, as well as GGT serum levels and the HRSD score, were made in patients at the beginning of the study (before the application of paroxetine) at 11 a.m., and on the day 20 after the treatment with the drug, also at 11 a.m. The stated time for ECG check-ups was chosen due to circadian changes in the heart electrophysiology [9]. Due to the impact of the sinus rhythm on the length of QT interval and for the adequate comparison among subjects, QT interval was corrected by the value of the heart frequency (the so-called QTc interval) [10]. Because of deferred adaptation of QT interval to values of the heart frequency, ECG measurement was done following the establishment of a stable heart frequency [11]. Measurement was done with patients in the resting (lying) position in the course of 20 seconds.

In our study, global QTc interval (12 leads) [12, 13] was determined by an automatic application of ECG device, type "Schiller Cardiovit AT-1", which uses "SCHILLER ECG Measurement and Interpretation Software for Children and Adult ECGs" (developed by SCHILLER AG, Altgasse 68, CH-6341 Baar, Switzerland, see http://www.schiller.ch). Global QTc interval represents the interval with the earliest QRS onset and the latest T end in any lead. Global QRS complex in our study was shorter than 120 ms, which excludes the impact of extended depolarisation of ventricles on the length of QT interval. The analysis included patients with technically regular ECG findings (without interference, background noise, 'wondering' of isoelectric line). Examination of automatic measurement by the coincidence of heart frequencies in V3 lead using classical method was done. Patients with double and biphasic T waves were not included in the study, while T wave amplitude was greater than 0.2 mV [12].

Measured/empirical data values were statistically processed in SPSS 16.0 programme package for Windows and Excel 2016. The methods of descriptive statistics and methods of statistic testing of hypotheses were used. Parametric methods were used as the first choice, whereas in case of undermining of the assumptions about the normality of distribution and homogeneity of variance, the relevant non-parametric methods were used. Control of variability and confounding factors was done by means of repeated measures test and application of multifactorial regression models with determination of the degree of collinearity between the examined and set of independent variables.

For the purpose of examining the significance of differences in the length of QTc interval following the application of the antidepressant, paired-samples *t*-test was used. Dependence of the length of QTc interval on the serum levels of GGT and CK-MB, and values of the HRSD score was examined by means of multiple linear regression model, whereas in the case of undermined assumptions of the test, by means of generalised linear model of the subclass *LINEAR* and gamma with log link robust estimator. The effect of empirical values on the slope of the regression line (Cook's distance and leverage values) was also analyzed. Statistically significant conclusions were presented on the basis of 2-tailed *p*-values and the significance level $p < 0.05$.

Results

Descriptive values of examined parameters in depressed patients with alcohol dependence are shown in Table 1. By use of generalised linear mode, a statistically significant positive correlation between the length of QTc interval and the serum levels of GGT (Figure 1), that is, the intensity of alcoholism (regression coefficient B = 0.00007, $p = 0.002$), as well as values of the HRSD score, that is, the intensity of depression (regression coefficient B = 0.001, $p = 0.0021$) (Figure 2) was determined in 147 depressed alcoholic patients before administration of the antidepressant. We noticed statistically significant deviation of the residuals of multiple linear regression model from the normal distribution (Shapiro-Wilk test, $p = 0.041$, *skewness* = 0.261) as well as a mild heteroscedasticity of the residuals; therefore, we used a generalised linear model – subclass gamma with log link robust estimator. No statistically significant collinearity between independent variables (the lowest *eigenvalue* model value 0.080, the highest condition index 5.617) was observed. By removing the value with a high Cook distance and high *leverage* value from the generalised linear model, a statistically significant correlation was confirmed between the length of QTc interval and GGT serum levels (regression coefficient B = 0.00005, $p = 0.0029$) as well as with the HRSD score (regression coefficient B = 0.001, $p = 0.023$).

Table 1
Values of examined parameters in depressed patients with alcohol dependence

Parameter	Before paroxetine usage	After paroxetine usage
	mean ± SD	mean mean ± SD
HRSD score	18.51 ± 7.959	9.98 ± 5.234
GGT (U/L)	126.447 ± 63.1980	90.133 ± 44.1603
CK-MB (ng/L)	19.22 ± 2.816	19.66 ± 3.311

HRSD – Hamilton Rating Scale for Depression;
GGT – gamma-glutamyltransferase;
CK-MB – creatine kinase isoenzyme MB; SD – standard deviation.

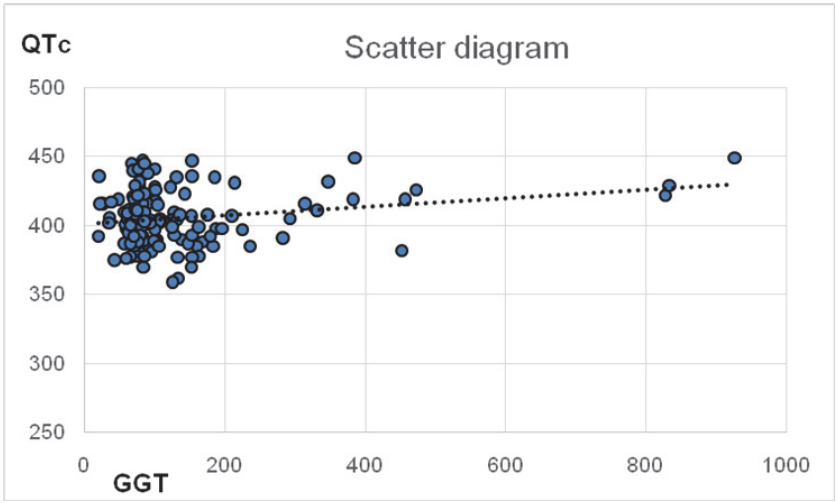

Fig. 1 – Scatter diagram showing correlation between values of gamma-glutamyl transferase serum levels (U/L) and QTc interval (ms).

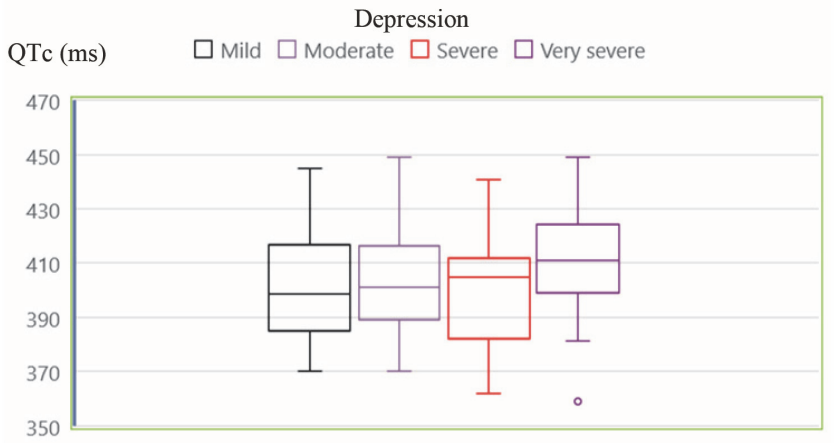

Fig. 2 – Association between QTc interval and severity of depression.

Despite the assumptions of the multiple linear regression model being undermined, statistically significant differences were determined by applying that model too, and the same was used in order to determine the size of the effect of examined variables (GGT serum levels: partial eta² = 0.040, HRSD score: partial eta² = 0.034). A somewhat greater effect of GGT serum levels on the length of the QTc interval was observed.

Since creatine kinase isoenzyme MB (CK-MB) residuals deviated from the normal distribution and showed a negative asymmetry (*skewness)*, they were transformed by reflection into positive asymmetry (gamma distribution). The reflection was done in the way that empirical values of CK-MB were detracted from the maximal value of CK-MB, increased by a single unit (max CK-MB + 1). By using the generalised linear model, subclass gamma with log link robust estimator, a negative correlation between the serum levels of GGT and reflected values of creatine kinase isoenzyme MB levels (R_CK-MB) before the application of paroxetine (regression coefficient B = -0.0011, $p < 0.001$) was determined. The same correlation was also confirmed after removing values with huge Cook distance and high *leverage* values ($p < 0.001$). Therefore, we could conclude that higher values of GGT serum levels were associated with higher degree of myocardium damage. No significant correlations between HRSD/R_CK-MB ($p = 0.925$), and HRSD/GGT ($p = 0.383$) were determined.

The length of QTc interval in 49 depressed alcoholic patients before the application of paroxetine was 403.31 ± 19.4 (362–441) ms.

No statistically significant deviation of the residuals of multiple linear regression model of dependence of the QTc interval length before the application of paroxetine from the normal distribution (n = 49, Shapiro-Wilk test, $p = 0.105$) was observed. Collinearity between the examined independent variables (the lowest *eigenvalue* 0.008, the highest condition index 21.113) was observed. Due to the present heteroscedasticity of residuals and low values of dependence of QTc interval on depression intensity ($p = 0.079$), the generalised linear model – subclass LINEAR with robust estimator was used. No statistically significant correlation between the length of QTc interval and serum levels of GGT (as a marker of alcoholism intensity) ($p = 0.983$), serum levels of CK-MB (as a marker of myocardium damage) ($p = 0.388$) was determined, but dependence on the HRSD score (as a marker of depression intensity) ($p = 0.045$) was established. However,

by inserting only one parameter into the stated model no statistically significant correlation between depression intensity and the length of QTc interval (p = 0.063) was confirmed, which was explained by the inflation of variance due to the collinearity of independent variables.

Due to the collinearity stated above, correlation between examined independent variables was analyzed in the group of patients who had not been taking paroxetine. Given that the assumptions related to the normality of distribution of the linear regression model residuals (Shapiro-Wilk test, p = 0.001, *skewness* = -1.258) were undermined, as well as because of the present heteroscedasticity, the generalised linear model, subclass gamma with log link robust estimator was used. A statistically significant negative correlation between the serum levels of GGT and R_CK-MB in these patients at the beginning of the study was established (regression coefficient B = -0.003, p = 0.010), that is, it was established that higher serum levels of GGT were associated (statistically significantly) with higher values of CK-MB. By excluding measured/empirical values with huge Cook distance and high leverage value (patients with GGT levels = 347.0 U/L and CK-MB levels = 19 ng/L), this correlation remained statistically significant and even greater (p < 0.001). No correlation between the HRSD score and R_CK-MB levels (p = 0.097), as well as the HRSD score and GGT levels (p = 0.413) was found.

The length of QTc interval in depressed alcoholic patients on the day 20 after the application of paroxetine was 401.43 ± 20.13 (366–446) ms.

No statistically significant deviation of the residuals of the multiple linear regression model of dependence of QTc interval length after the application of paroxetine from the normal distribution (n = 49, Shapiro-Wilk test, p = 0.605) was established. Collinearity between examined independent variables (the lowest *eigenvalue* 0.011, the highest condition index 18.066) was observed. Due to present heteroscedasticity of residuals, the generalised linear model, subclass *LINEAR* with robust estimator was used for the examination of the significance of differences. No statistically significant correlation between the length of QTc interval and serum levels of GGT (alcoholism intensity) (p = 0.144), as well as the HRSD score (depression intensity) (p = 0.345) was established, but the correlation between the length of QTc interval and serum levels of CK-MB (myocardium damage) (p = 0.027) was found. However, by inserting only one parameter into the stated model, no statistically significant correlation between the myocardium damage and the length of QTc interval (p = 0.154) was confirmed, which was explained by the inflation of variance due to the collinearity of independent variables.

Due to stated collinearity, the correlation between examined independent variables was analyzed. A statistically significant correlation between the serum levels of GGT (alcoholism intensity) and the serum levels of R_CK-MB (myocardium damage) in patients suffering from alcohol addiction after the application of paroxetine (regression coefficient B = -0.007, p < 0.001) was determined. In other words, it was established, just as in the case when paroxetine had not been applied, that higher serum levels of GGT were statistically significantly associated with higher levels of CK-MB. No undermining of the assumption about the normality of distribution of the linear regression model residuals (Shapiro-Wilk test, p = 0.130) was observed, but due to the present heteroscedasticity of residuals ("fan in"), the generalised linear model, subclass *LINEAR* robust estimator was used. After exclusion of the empirical value with huge Cook distance and high leverage value from the model (patients with the serum levels of GGT = 253.2 U/L and CK-MB = 23 ng/L), the correlation remained statistically significant (p < 0.001). No statistically significant correlation between the HRSD score and the serum levels of R_CK-MB (p = 0.501), as well as the HRD score and the serum levels of GGT (p = 0.988) was established.

No statistically significant deviation of differences in the length of QTc interval from the normal distribution, both before and after the application of paroxetine, was present (dif QTc Shapiro-Wilk test: p = 0.766), due to which the paired-samples t-test was used for the examination of the significance of differences. No statistically significant difference in the length of QTc interval, before and 20 days after the application of paroxetine was established (p = 0.524) (Figure 3).

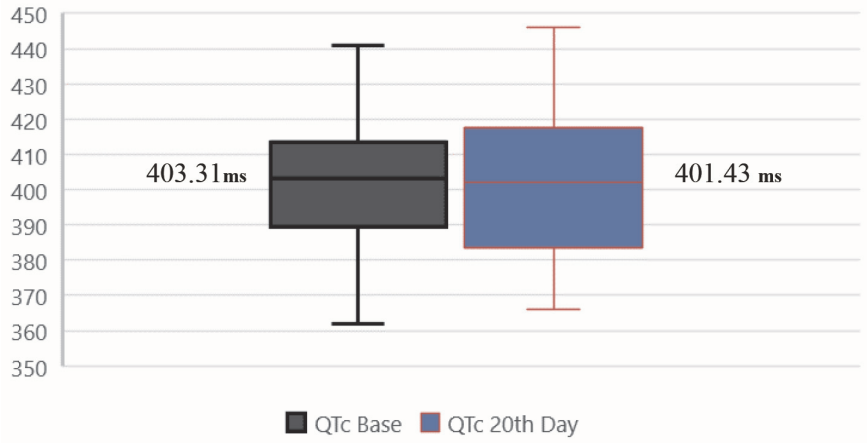

Fig. 3 – Influence of paroxetine administration during 20 days on the lenght of QTc interval in depressed patients with alcohol dependence.

Discussion

In our study, a statistically significant correlation between the HRSD score (depression intensity) and the length of QTc interval was established in 147 patients before the application of paroxetine. Therefore, we can claim that higher values of the HRSD score are statistically significantly associated with a longer QTc interval. In the same regression model, the statistically significant positive correlation between the length of QTc interval and the serum levels of GGT was also determined. These results were also confirmed after the exclusion of values with huge Cook distance and high leverage value from the model. A somewhat greater effect of the serum levels of GGT on the length of Qtc interval in relation to the HRSD score (GGT: partial eta² = 0.040, HRSD score: partial eta² = 0.034) was established.

The association of depression with higher values of QTc interval have also been determined in other studies [14, 15]. Besides higher values of QTc interval in patients with clinical depression, Minoretti et al. [15] point to higher values of QTc interval in healthy persons who are prone to the development of depression – with traits of neuroticism. This association has also been indirectly confirmed by observing higher death rates in depressed patients with acute coronary syndrome [16, 17]. Rainey et al. [14] did not notice longer values of QTc interval in patients suffering from depression and abusing psychoactive substances, whereas Whang et al. [17] established a longer QTc interval in depressed female persons with acute coronary syndrome (unstable angina pectoris and myocardial infarction without the elevation of ST segment), but not in men. Therefore, we would like to point out that our results of positive correlation of the HRSD score and the length of QTc interval refer to the population of patients who consume psychoactive substances (alcohol), as well as that the research pertains to male persons.

Even though the subject of our research is not to determine the frequency of the prolonged QT interval syndrome in persons suffering from alcohol addiction and depression in relation to healthy population, the correlation between the effect of alcohol and the extension of QTc interval has been confirmed by various studies. Thus, for example, Rossinen et al. [18] indicate that there is a direct effect of ethanol infusion on the extension of QTc interval independently from the presence of coronary arterial disease. A similar result is also stated by Gonzalez et al. [19] by presenting a case of QTc prolongation and heart rhythm disorder (*torsade de pointes*) in patients with acute alcoholic intoxication (F10.0). However, in that study, the associated/confounding factor was hypomagnesemia stated by authors. The correlation between alcoholism and extended QTc interval has also been confirmed by other studies [20–23]. In the study of Bär et al. [24], a statistically significant prolongation of QTc interval in male persons with the symptoms of alcoholic abstinence (n = 18) in relation to the "pair matched" control group was established, but not in the case of syndrome of dependence without the abstinence syndrome (n = 15). Authors explain the result in terms of extended repolarisation as a consequence of increased sympathetic tone or low levels of potassium, through which they point to the goals of adjuvant therapy of the alcoholic abstinence syndrome.The correlation between abstinence and extended QTc interval is also stated by Koide et al. [21]. The frequency of QTc prolongation in persons with chronic alcoholism (n = 90) in their study amounted to 22%. The examination was carried out in the period of abstinence, on average 35 days from the day of quitting alcoholic beverages, while QTc interval was not correlated with values of serum electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}). Main factors associated with extended QTc interval were greater daily consumption of alcohol and a longer period of abstinence. Even though the association of individual factors is not completely clear, authors assume that the damage of myocardium is the cause of extension of QTc interval. Krasemann [25] describes the phenomenon of ventricular tachycardia of a newborn delivered by a mother suffering from alcoholic addiction (on the third day upon birth). After a spontaneous normalisation of rhythm, extended QTc interval of the newborn (480 ms) was determined. Author concludes that the "abstinence syndrome of the newborn" is the cause of QTc interval extension.

Serum concentrations of GGT indirectly reflect the intensity of alcoholism. In our study, dependence of the QTc interval length on alcohol intensity (GGT serum levels) was determined in patients without abstinence syndrome, given that the same was controlled by applying drugs (bromazepam, a benzodiazepine anxiolytic). Dependence of QTc interval elongation on GGT serum levels are also stated by Borini et al. [20]. However, in their patients, disorders of electrolytes (hypokalemia) and hyperglycaemia were established. Authors point out that changes of ECG are a consequence of metabolic changes in persons with alcoholic dependence. We would like to remark that in our study the exclusion factors were disorders of electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}), by which we excluded the possibility of the effect of electrolyte disorders on the extension of QTc interval.

There are also studies that negate the correlation between alcoholism and the extension of QTc interval. Pomini et al. [26] did not notice significant differences in the lenght of QTc interval between persons suffering from chronic alcoholism and persons who did not consume alcohol. Authors indicate that arrhythmogenic effect due to acute alcohol ingestion is not significant, but that further studies are needed. In this way they do not close the problem of researching subclinical alcohol cardiomyopathy. However, limitation of this study is a relatively small sample of the study and the control group: 12 persons with chronic alcoholism and 10 persons who do not consume alcohol.

Various causes are stated as the etiological factor that extends QTc interval in persons suffering from alcoholic addiction. Certain authors (as has been stated above) emphasize the dysfunction of autonomous nervous system of the heart with extended repolarisation as the main factor [22, 24], while others point to damage of myocardium [21]. In our study, in the group of alcohol-addicted patients, initially, a correlation between the serum level of CK-MB, that is, the degree of myocardial demage and the lenght of QTc interval (p = 0.027) was established. The same was not confirmed by inserting only one parameter into the stated model (p = 0.154). This

finding we explained by the inflation of variance due to present collinearity with other two independent variables (GGT serum levels and HRSD score). We remark that we often used R_CK-MB in the analysis, given that residuals of CK-MB diverged from the normal distribution and showed skewness, which is why the same were transformed by means of reflection into positive asymmetry and gamma distribution. Also, because of that, we used generalised linear model, subclass gamma with log link, in the course of statistical analysis. Reflection was also considered when interpreting coefficients of independent variables that had R_CK-MB as the dependent variable. In regression models with R_CK-MB as the dependent variable, we did not reflect independent variables, and the correlation between independent and dependent variables remained linear. In the course of the said transformation we noticed that a statistically significant intercept was not often established, which meant that the interpretation and comparison of the results were made harder. Occasional instability of the regression model (GGT/R_CK-MB) and not getting statistically significant correlations after the exclusion of values with huge Cook distance and high leverage value, are the consequence of measured high values of GGT serum levels in the examined population of patients. The highest recorded serum value of GGT amounted to 926.0 U/L in this study. However, this finding is not strange, given that in clinical practice we have often come across four-digit values of GGT serum levels. This is why we do not advocate the exclusion of extreme values from the regression model, because those values often draw attention to significant phenomena and correlations. We remark that in our study the results were confirmed after the exclusion of extreme values, and sometimes even the significance was greater (e.g. the correlation between GGT and R_CK-MB serum levels in the group of patients who had not been taking paroxetine.

Data from the literature that pertain to the assessment of the effect of paroxetine on the length of QTc interval are contradictory. Krulewicz et al. [27] point out in a study that included 449 children aged 7–18 years (placebo, n = 207; paroxetine dose of 10–50 mg daily, n = 200; and imipramine, n = 42) that paroxetine did not statistically extend QTcB (Bazett formula) and QTcF (Fridericia formula) in relation to placebo, in contrast to imipramine that prolonged QTcB, both in relation to placebo and paroxetine. Nelson et al. [28] indicate that duloxetine (serotonin-norepinephrine reuptake inhibitor – SNRI) (n = 736) and paroxetine (n = 359) did not significantly influence the QTc interval length in relation to placebo (n = 371). Paroxetine was used in a dose of 20 mg, in the period from 8 to 26 weeks. Yeragani and Rao [29] state that, in contrast to nortriptyline which due to its stronger anticholinergic effect exercises an impact on QTc interval, paroxetine does not show that effect on QTc interval in patients with panic disorder (n = 16).

On the other hand, Lim et al. [30] indicate that paroxetine in combination with flecainide (Ic antiarrhythmic) in persons with CYP2D6*10 gene allele, which determines microsomal cytochrome P450 metabolic enzymes of the liver, significantly extends QTc interval. Their study confirmed genetic vulnerability of persons to effects of drugs that extend QTc interval. However, due to common administration with antiarrhythmic drugs, an isolated effect of paroxetine is not clear. It is also interesting to mention the study of Martin et al. [31], which undermines the previous result. Authors started with the assumption that paroxetine is a mild cytochrome P_{450} 3A4 (CYP3A4) inhibitor. The study examined combined effect of the drug with terfenadine (H1 antagonist) on the length of QTc interval. Terfenadine was used in a 60 mg dose, twice a day, and paroxetine was given in a 20 mg dose in the course of 15 days after the eighth day. QTcmax slightly changed the value (from 404 ms to 405 ms), and authors concluded that paroxetine did not change pharmacokinetics and cardiovascular effects of terfenadine. The limitation of this study could be a small sample: twelve male persons, and, as we know, terfenadine was discontinued due to extension of QTc interval. Gongadze et al. [6] indicate that due to a greater affinity for proteins of potassium channels coded by hERG gene, paroxetine extends QTc interval, whereas Erfurth et al. [33] show two cases of prolonged QTc interval syndrome and one case of severe bradycardia occurring due to application of paroxetine. There are indications that higher paroxetine doses (e.g. 50 mg) can cause QT elongation [34], but this question must be more explored. In our study, despite the vulnerability of patients due to heart damage and disorder of liver functioning due to alcohol consumption, as well as changed drug metabolism, no extension of QTc interval due to application of paroxetine was established. We found that the length of QTc interval 20 days after paroxetine administration was 401.429 ms and before paroxetine administration 403.307 ms. The average difference: global QTc on the day 20 – global QTc basic, amounted to -1.878 ms (95% confidence interval = -7.755 - 4.000 ms). Statistical probability of 2.5% that the increase in the length of QTc interval is greater than 4.0 ms after the application of paroxetine indicates that it is safe antidepressant in the examined population of patients (depressed alcoholic persons).

Conclusion

A statistically significant correlation of the HRSD score (depression intensity) and the length of QTc interval in patients suffering from alcohol addiction was established (higher values of the HRSD score were statistically significantly associated with longer QTc interval) as well as a statistically significant positive correlation of serum levels of GGT and the length of QTc interval.

Higher serum concentrations of GGT (as a parameter that indirectly reflects alcoholism intensity) were statistically significantly associated with higher serum levels of CK-MB, that is, the degree of myocardium damage.

Statistical probability of 2.5% that the increase in the length of QTc interval is greater than 4.0 ms after the application of paroxetine indicated that it is safe to apply this antidepressant in the examined population of patients (depressed alcoholic patients).

The presented results indicate that associated depression in patients suffering from alcohol addiction by far in-

creases the sensitivity of these patients to cardiotoxic effects of drugs that extend QTc interval. Because of that pharmacotherapy of depression should conduct with special attention in this population of patients. However, in this study paroxetine did not change the length of QTc interval in patients with alcohol dependence and associated depression.

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