ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

# The Effect of Antidepressants on Biochemical Parameters of the Blood of Patients with Opioid Dependence, Combined with Chronic Hepatitis C

**Pinskyy LL[1]*, Khaitovych NV[1], Ovcharenko NA[2], Koveshnykov AV[3] and Radchenko TN[4]**

[1]*National Medical University Named After O.O. Bogomolets, Kyiv, Ukraine*

[2]*Luhansk State Medical University, Rubizhne, Ukraine*

[3]*Lviv National Medical University Named After Danilo Galitskiy, Lviv, Ukraine*

[4]*Kharkiv National Medical University, Kharkiv, Ukraine*

***Corresponding Author**: Pinskyy LL, Department of Clinical Pharmacology and Clinical Pharmacy, National Medical University Named After O.O. Bogomolets, Kyiv, Ukraine.

**Received:** March 15, 2020; **Published:** March 28, 2020

## Abstract

The aim of the study is to analyze the effect of antidepressants (amitriptyline and fluoxetine) on the biochemical parameters of blood serum in drug-dependent patients with low activity of chronic hepatitis C (CHC). One hundred and twenty-two patients (98 men and 24 women aged from 21 to 49 years) with opioid dependence (OD) combined with low activity of chronic hepatitis C were under observation. Group 1 included 64 patients who were prescribed tricyclic antidepressant amitriptyline from 75 mg to 150 mg per day. The patients of group 2 (n = 58) were treated with fluoxetine in a daily dose of 20 to 40 mg in the early withdrawal period. Dynamic observation revealed that in group 1, when administering amitriptyline, the intensity of cytolytic syndrome in patients was significantly increased - with increased activity of ALT (2,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,8 - 2,9; P < 0,001 according to Wilcoxon) and AST (1,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,3 - 2,4; P < 0,001 according to Wilcoxon) correspondingly and these parameters significantly exceeded those of group 2 - ALT (1,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,0 - 1,7; P < 0,001 by Mann-Whitney) and AST (0,9 ± 0,1 mmol /l*h; $Q_{25}$-$Q_{75}$ = 0,7 - 1,4; P < 0,001 by Mann-Whitney).

Thus, the administering of amitriptyline has a significant effect on the biochemical parameters of cytolysis (P < 0,001) and cholestasis (P < 0,001) in drug-dependent patients with low CHC activity. The administering of fluoxetine had virtually no effect on the severity of the cytolytic syndrome ($F_{ALT}$ = 3,6; P > 0,1); $F_{AST}$ = 4,9; P > 0,1) and moderately increased the activity of cholestasis markers ($F_{GGTP}$ = 18,1; P < 0,01); $F_{ALP}$ = 15,4; P < 0,01). In further studies, the development of hepatoprotective therapy for the use of antidepressants in patients with opioid dependence and CHC is appropriate.

***Keywords:*** *Chronic Hepatitis C; Opioid Dependence; Cytolysis; Cholestasis*

## Introduction

The significant prevalence of opioid dependence (OD), which is accompanied by comorbid chronic hepatitis C (CHC), has become a significant medical and social problem in Ukraine [1,2]. More than 80 percent of drug-dependent patients are infected with CHC virus, which leads to an increase in the incidence of pseudo-withdrawal syndrome [3,4]. Significant shifts in the biochemical parameters of blood serum accompany the combined courses of OD and CHC in the early and late withdrawal periods [5]. All this requires from the clinician a careful selection of antidepressants with minimal hepatotoxic activity for the treatment of patients with OD and CHC [6-9]. The iatrogenic

increase in the activity of cytolysis and cholestasis, which is accompanied by asthenic-depressive syndrome in the late withdrawal period and the period of remission, can lead to an increase in the frequency of the pseudo-withdrawal syndrome, when the hepatotoxic effect of the drugs is regarded by patients as the onset of withdrawal and this provokes a new relapse of drug use [10-13]. In this clinical situation, it becomes urgent to conduct biochemical monitoring of the liver condition in drug-dependent patients with low activity of CHC with the administering of various groups of antidepressants.

## Aim of the Study

The aim of the study is to assess the effect of antidepressants of the group of non-selective monoamine reuptake inhibitors - amitriptyline and selective serotonin reuptake inhibitors - fluoxetine on the biochemical parameters of blood serum of patients with opioid dependence, combined with low activity of chronic hepatitis C.

## Materials and Research Methods

One hundred and twenty-two patients with OD combined with low CHC activity (98 men and 24 women aged from 21 to 49 years) were under medical observation in the Lugansk Regional Narcological Clinic (Rubezhnoye). Group 1 included 64 patients (51 men and 13 women aged from 21 to 47 years) who were prescribed tricyclic antidepressant amitriptyline (ATX code N06A A09) in the early (EWP) and late (LWP) withdrawal periods in the dose from 75 mg to 150 mg per day. Patients of group 2 (58 patients including 47 men and 11 women aged from 22 to 49 years) in the early period of abstinence were treated with fluoxetine (ATC code N06A B03) in a daily dose of 20 mg to 40 mg. The criteria for inclusion into the study was the diagnosis of OD according to the criteria of ICD-10 (F 11,30) and CHC based on a set of clinical and biochemical parameters, determination of anti-HCV antibodies and polymerase chain reaction - HCV-RNA. A group of healthy people included 53 blood donors.

Standard biochemical studies were carried out by unified methods and included the determination of enzyme activity - alanine aminotransferase (ALT, EC 2,6,1,2), aspartate aminotransferase (AST, EC 2,6,1,1), alkaline phosphatase (ALP, EC 2,3,2,4), gamma glutamyl transpeptidase (GGTP) (EC 2,3,2,2), serum bilirubin and its fractions, total protein, and protein fractions [14].

The results of biochemical analysis were statistically processed by using EXCEL 2010 spreadsheets and the STATISTICA 8,0 software package in the Windows 7 operating system [15]. In each of the observed groups, we determined the normality of the distribution of the variant according to the criteria of Kolmogorov-Smirnov, Lilliefors test and Shapiro-Wilk's W test. In case of discrepancy with the normality criteria, we calculated the median value (Me), its error (mMe), the lower (25%) and upper (75%) quartile ($Q_{25}$-$Q_{75}$) in each group. To assess the reliability of intergroup differences in unrelated groups, we used the Mann - Whitney test, to assess the dynamics of biochemical parameters we used the Wilcoxon test, as well as discriminant analysis with the determination of the coefficient F.

The studies conducted comply with the principles of clinical bioethics.

## Results and Discussion

Prior to the administration of antidepressant therapy, we compared the results of a biochemical investigation of patients of groups 1 and 2 during the period of acute intoxication (AI). When conducting a Mann-Whitney intergroup analysis, we found that there were no significant differences between the biochemical markers of cytolysis and cholestasis before the administration of amitriptyline and fluoxetine ($P > 0,1$). In both groups, there was a significant increase of AST activity in group 1 (0,6 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,4 - 0,9 mmol/l*h) and in group 2 (0,7 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,5 - 1,0 mmol/l*h), compared to the parameters of donors (0,27 ± 0,01 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,1 - 0,4 mmol/l*h) (Table 1). In the period of AI, there was also a significant increase in the activity of ALT in both groups to 1,2 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,8 - 1,7 mmol/l*h) in group 1 and to 1,1 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,7 - 1,6 mmol/l*h) in group 2, which was signifi-

cantly higher than the parameters of the donors' group - 0,37 ± 0, 01 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,2 - 0,5 mmol/l*h). Biochemical markers of cholestasis in the period of AI also exceeded the parameters of the donors' group. Thus, the activity of ALP was 1,7 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,3 - 1,9 mmol/l*h) in group 1 and 1,8 ± 0,2 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,4 - 2,1 mmol/l*h) in group 2, which exceeded the level of the donors' group (1,3 ± 0,01 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,1 - 1,4 mmol/l h) 1,3 and 1,4 times, correspondingly (Table 1).

| Groups | Donors (n = 53) | Periods of opioid dependence of group 1(n = 64) | | | Results of Wilcoxon analysis between AI and EWP parameters | Results of Wilcoxon analysis between EWP and LWP parameters |
|---|---|---|---|---|---|---|
| Biochemical parameters | | Period of acute intoxication (AI) | Early withdrawal period (EWP) | Late withdrawal period (LWP) | | |
| Total bilirubin, μmol/l | 5,1 ± 0,05 (2,9 - 5,8) | 7,2 ± 0,2* (4,5 - 8,9) | 9,0 ± 0,1* (4,9 - 11,3) | 11,6 ± 0,1* (5,3 - 16,1) | < 0,001 | < 0,001 |
| AST, mmol/l*h | 0,27 ± 0,01 (0,1 - 0,4) | 0,6 ± 0,1* (0,4 - 0,9) | 1,4 ± 0,1* (1,0 - 1,8) | 1,9 ± 0,1* (1,3 - 2, 4) | < 0,01 | < 0,01 |
| ALT, mmol/l*h | 0,37 ± 0,01 (0,2 - 0,5) | 1,2 ± 0,1* (0,8 - 1,7) | 1,9 ± 0,1* (1,4 - 2,2) | 2,4 ± 0,1* (1,8 - 2,9) | < 0,001 | < 0,001 |
| Alkaline phosphate mmol/l*h | 1,3 ± 0,01 (1,1 - 1,4) | 1,7 ± 0,1* (1,3 - 1,9) | 2,8 ± 0,1* (2,1 - 3,8) | 3,9 ± 0,1* (3,3 - 4,7) | < 0,001 | < 0,01 |
| GGTP, U/ml | 531,3 ± 1,9 (470 - 610) | 902,0 ± 53* (585 - 934) | 1240 ± 62* (670 - 2400) | 1520 ± 69* (720 - 2900) | < 0,001 | < 0,001 |
| Total protein, mmol/l | 72,6 ± 0,2 (71,0 - 77,8) | 71,0 ± 0,8 (61,0 - 75,9) | 71,2 ± 0,6 (64,1 - 76,2) | 72,1 ± 0,7 (6 5,8 - 79,1) | > 0,1 | > 0,1 |
| Albumin, g/l | 63,1 ± 0,2 (62,1 - 65,3) | 62,8 ± 0,7 (56,8 - 64,1) | 62,5 ± 0,8 (57,9 - 65,2) | 61,3 ± 0,9 (55,0 - 64,9) | > 0,1 | > 0,1 |

***Table 1:*** *Dynamics of biochemical parameters of blood serum in administering of amitriptyline in patients with opioid dependence combined with chronic hepatitis C.*

*Note: In this and other tables biochemical parameters are represented in median value (Me) and its error (mMe,) (± mMe, Me). In parentheses, in the second line 25% and 75% quartile ($Q_{25}$-$Q_{75}$) are shown.*

**: At P < 0,01 by Mann - Whitney in relation to the parameters of donors.*

When analyzing the parameters of protein-synthetic liver function, we found that there were no significant intergroup differences in groups 1 and 2 in the period of AI with those of donors' parameters (P > 0,1 according to Mann - Whitney, table 1).

After the beginning of administering of amitriptyline in group 1, there was a significant increase in the activity of AST in the EWP period by 2,3 times to 1,4 ± 0,1 mmol/ l*h ($Q_{25}$-$Q_{75}$ = 1,0 - 1,8 mmol/l*h) (P < 0,01 according to Wilcoxon) (Table 1). An increase in the activity of this enzyme also took place in the LWP period - up to 1,9 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,3 - 2,4 mmol l*h) (P < 0,01 according to Wilcoxon) (Table 1).

The hepatocyte cytolysis marker ALT significantly increased its activity in blood serum in early and late withdrawal periods (1,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,4 - 2,2 mmol/l*h and 2,4 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,8 - 2,9 mmol/l*h, correspondingly; P < 0,001 according to Wilcoxon) (Table 1). When administering amitriptyline in patients of group 1, the biochemical parameters of cholestasis significantly increased. Thus, the activity of GGTP in the period of EWP exceeded 1,4 times (1240 ± 62 U/ml ($Q_{25}$-$Q_{75}$ = 670 - 2400 U/ml) indicator of AI (902 ± 53 U/ml ($Q_{25}$-$Q_{75}$ = 585 - 934 U/ml) (P < 0,001 according to Wilcoxon) (Table 1). In late withdrawal period, this parameter continued to increase to (1520 ± 69 U/ml ($Q_{25}$-$Q_{75}$ = 720 - 2900 U/ml) (P < 0,001 according to Wilcoxon), exceeding the donors' parameters (531,3 ± 1,9 U/ml ($Q_{25}$-$Q_{75}$ = 470 - 610 U/ml) 2,9 times (P < 0,001 according to Mann-Whitney). Analyzing the parameters of protein-synthetic liver function, we found that in the dynamics of EWP and LWP, when administering amitriptyline, significant changes were not been marked in patients of group 1 (P > 0,1 according to Wilcoxon) (Table 1).

When analyzing the biochemical parameters of blood serum of group 2, we found that after the administering of fluoxetine in the treatment of OD patients with low CHC activity, there was no significant increase in the activity of AST and ALT compared with the parameters of the period of acute intoxication. Thus, the activity of AST in the early withdrawal period was 0,8 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,6 - 1,2 mmol/l*h) (P > 0,1 according to Wilcoxon), and in the late withdrawal period-0,9 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 0,7 - 1,4 mmol/l*h) (P > 0,1 according to Wilcoxon). The biochemical parameters of cholestatic syndrome, in particular the activity of serum GGTP, increased moderately from 712 ± 23 U/ml ($Q_{25}$-$Q_{75}$ = 510 - 955 U/ml) in the period of AI to 890 ± 17 U/ml ($Q_{25}$-$Q_{75}$ = 570 - 1030 U/ml) in EWP (P < 0,001 according to Wilcoxon) and reached 981 ± 22 U/ml ($Q_{25}$-$Q_{75}$ = 615 - 1190 U/ml) in the late withdrawal period (P < 0,001 according to Wilcoxon). When analysing ALP parameters in group 2, we found that early withdrawal period was not accompanied by significant changes of this enzyme activity compared with the stage of AI (1,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,5 - 2,2 mmol/l*h and 1,8 ± 0,2 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,4 - 2,1 mmol/l*h, correspondingly; P > 0,1 according to Wilcoxon) and increased slightly in the late withdrawal period 2,3 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,9 - 2,8 mmol/l*h, correspondingly; P < 0,01 according to Wilcoxon) (Table 2).

| Groups | Donors | Periods of opioid dependence of group 2 (n = 64) | | | Results of Wilcoxon analysis between AI and EWP parameters | Results of Wilcoxon analysis between EWP and LWP parameters |
|---|---|---|---|---|---|---|
| Biochemical parameters | (n = 53) | Period of acute intoxication (AI) | Early withdrawal period (EWP) | Late withdrawal period (LWP) | | |
| Total bilirubin, μmol/l | 5,1 ± 0,05 (2,9 - 5,8) | 7,1 ± 0,1* (4,4 - 8,7) | 7,3 ± 0,2* (4,5 - 8,9) | 7,6 ± 0,3* (4,7 - 9,4) | > 0,1 | > 0,1 |
| AST, mmol/l*h | 0,27 ± 0,01 (0,1 - 0,4) | 0,7 ± 0,1* (0,5 - 1,0) | 0,8 ± 0,1* (0,6 - 1,2) | 0,9 ± 0,1* (0,7 - 1,4) | > 0,1 | > 0,2 |
| ALT, mmol/l*h | 0,37 ± 0,01 (0,2 - 0,5) | 1,1 ± 0,1* (0,7 - 1,6) | 1,3 ± 0,1* (0,8 - 1,5) | 1,4 ± 0,1* (1,0 - 1,7) | > 0,1 | > 0,1 |
| ALP, mmol/l*h | 1,3 ± 0,01 (1,1 - 1,4) | 1,8 ± 0,2* (1,4 - 2,1) | 1,9 ± 0,1* (1,5 - 2,2) | 2,3 ± 0,1* (1,9 - 2,8) | > 0,1 | < 0,01 |
| GGTP, U/ml | 531,3 ± 1,9 (470 - 610) | 712 ± 23* (510 - 955) | 890 ± 17* (570 - 1030) | 98 1 ± 22* (615 - 1190) | < 0,001 | < 0,01 |
| Total protein, mmol/l | 72,6 ± 0,2 (71,0 - 77,8) | 70,3 ± 0,2* (67,3 - 76,3) | 69,8 ± 0,5 (62,1 - 72,9) | 69,5 ± 0,3 (64,2 - 75,8) | > 0,1 | > 0,1 |
| Albumin, g/l | 63,1 ± 0,2 (62,1 - 65,3) | 62,1 ± 0,2 (57,4 - 63,9) | 61,9 ± 0,2 (55,8 - 67,1) | 62,4 ± 0,3 (59,2 - 64,5) | > 0,1 | > 0,1 |

***Table 2:*** *Dynamics of biochemical parameters of blood serum in administering fluoxetine in patients with opioid dependence, combined with chronic hepatitis C.*

When analyzing the concentration of serum proteins, we found that there were no dynamic changes in the total protein content in patients of group 2. Thus, in early withdrawal, this parameter was 69,8 ± 0,5 mmol/l*h ($Q_{25}$-$Q_{75}$ = 62,1 - 72,9 mmol/l*h), and in the period of late withdrawal it was 69,5 ± 0 3 mmol/l*h ($Q_{25}$-$Q_{75}$ = 64,2 - 75,8 mmol/l * h) (P > 0,1 according to Wilcoxon), that did not significantly differ from the level of the total protein of the donors' group (63,1 ± 0,2 mmol/l*h; $Q_{25}$-$Q_{75}$ = 62,1 - 65,3 mmol/l*h) (P > 0,1 according to Mann-Whitney, see table 2).

When conducting Mann-Whitney intergroup analysis of biochemical parameters of blood serum in LWP, we found that the markers of hepatocyte cytolysis were significantly higher in group 1 when administering amitriptyline, than the parameters of group 2, AST activity in group 1 exceeded 2,1 times that of group 2 when administering fluoxetine (1,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,3 - 1,9 mmol/l*h and 0,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 0,7 - 1,4 mmol/l*h, correspondingly; P < 0,001 according to Mann-Whitney; table 3).

| Groups<br>Biochemical parameters | 1 group (n = 64) | 2 group (n = 58) | Results of Mann - Whitney analysis between groups 1 and 2 |
|---|---|---|---|
| Total bilirubin, µmol/l | 11,6 ± 0,1 (5,3 - 16,1) | 7,6 ± 0,3 (4,7 - 9,4) | < 0,001 |
| AST, mmol/l*h | 1,9 ± 0,1 (1,3 - 1,9) | 0,9 ± 0,1 (0,7 - 1,4) | < 0,001 |
| ALT, mmol/l*h | 2,4 ± 0,1 (1,8 - 2,9) | 1,4 ± 0,1 (1,0 - 1,7) | < 0,001 |
| Alkaline phosphate and per mmol/l*h | 3,9 ± 0,1 (3,3 - 4,7) | 2,3 ± 0,1 (1,9 - 2,8) | < 0,001 |
| GGTP, U/ml | 1520 ± 69 (720 - 2900) | 981 ± 22 (615 - 1190) | < 0,001 |
| Total protein, µmol/L | 72,1 ± 0,7 (65,8 - 79,1) | 69,5 ± 0,3 (64,2 - 75,8) | < 0,01 |
| Albumins, g/l | 61,3 ± 0,9 (55,0 - 64,9) | 62,4 ± 0,3 (59,2 - 64,5) | > 0,1 |

***Table 3:*** *Biochemical indicators of serum of blood 1 and 2 groups of patients in late withdrawal period.*

When administering amitriptyline, ALT activity exceeded 1,7 times this parameter of group 2 (2,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,8 - 2,9 mmol/l*h and 1,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,0 - 1,7 mmol/l*h, correspondingly; P < 0,001 according to Mann-Whitney; see table 3). In the LWP period, significant differences between the cholestasis parameters of groups 1 and 2 were verified. When administering fluoxetine, ALP activity was 1,7 times lower than that of patients of the group 1 (P < 0,001 according to Mann - Whitney), the GGTP activity was 1,5 times lower (P < 0,001 according to Mann - Whitney) (Table 3).

To objectify the differences in the effect of antidepressants of different pharmacological groups on the biochemical parameters of blood serum, we also conducted a discriminant analysis of the parameters of cytolysis and cholestasis in both groups of patients. We found that the coefficient F for ALT activity in the blood serum was 37,1 (P < 0,001) and 3,6 (P > 0,1) in group 1 and group 2, correspondingly and the coefficient F for AST was 33,8 (P < 0,001) with amitriptyline administering and 4,9 (P > 0,1) in the fluoxetine administering group (Figure 1). This analysis confirmed the significant and reliable effect of the tricyclic antidepressant amitriptyline on the intensity of hepatocyte cytolysis in patients with opioid dependence combined with low activity of CHC in the LWP period, as compared with fluoxetine.

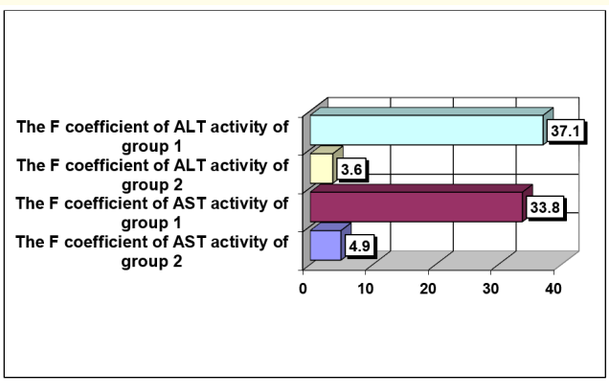


***Figure 1:*** *Results of discriminant analysis between biochemical parameters of cytolysis of early and late withdrawal.*

When conducting a discriminant analysis of biochemical parameters of cholestasis, we found that the F coefficient of GGTP activity of group 1 - 59,3 (P < 0,001) - was 3,3 times higher than that of group 2 (18,1; P < 0,01) (P < 0,001). Also, the discriminant coefficient F of ALP activity when administering amitriptyline (59,3; P < 0,001) was significantly higher than this parameter of group 2 (15,4; P < 0,01) (P < 0,001) (Figure 2). Thus, the administration of amitriptyline in drug-dependent patients with low activity of CHC had a significantly greater effect on cholestasis in the period of late withdrawal.

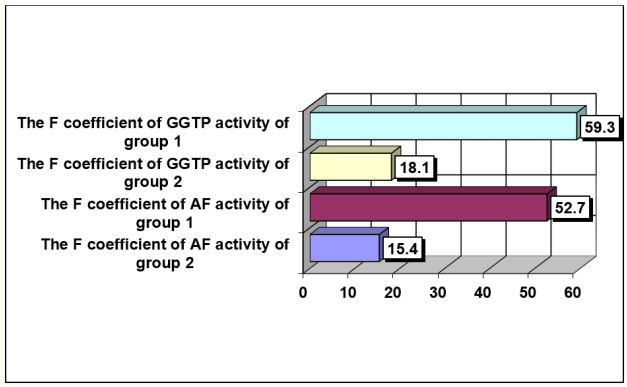


***Figure 2:*** *Results of discriminant analysis between biochemical parameters of cholestasis in early and late withdrawal periods.*

## Conclusion

1. During dynamic observation, we found that, when using amitriptyline in patients in the early withdrawal period, the intensity of the cytolytic syndrome significantly increased with the rising of ALT activity (2,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,8 - 2,9; P < 0,001 according to Wilcoxon) and AST activity (1,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,3 - 2,4; P < 0,001 according to Wilcoxon) in group 1 of drug-dependent patients with low CHC activity, and these parameters significantly exceeded those of group 2 (when administering fluoxetine)-ALT (1,4 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 1,0 - 1,7; P < 0,001 according to Mann-Whitney) and AST (0,9 ± 0,1 mmol/l*h; $Q_{25}$-$Q_{75}$ = 0,7 - 1,4; P < 0,001 according to Mann-Whitney).

2. When analyzing the parameters of cholestasis, it was found that the administration of tricyclic antidepressant amitriptyline significantly and reliably increased the activity of GGTP in blood serum. In patients of group 1, the activity of GGTP in the period of late withdrawal was 1520 ± 69 U/ml ($Q_{25}$-$Q_{75}$ = 720 - 2900 IU/ml), exceeding 1,5 times the parameters of group 2 (with fluoxetine) - 981 ± 22 U/ml ($Q_{25}$-$Q_{75}$ = 615 - 1190 U/ml; P < 0,001 according to Mann-Whitney). When analyzing the parameters of ALP, we found that in group 2, the activity of this enzyme slightly increased in the period of late withdrawal to 2,3 ± 0,1 mmol/l*h ($Q_{25}$-$Q_{75}$ = 1,9 - 2,8 mmol/l*h) and was significantly lower than the parameters of group 1 when administering amitriptyline (3,9 ± 0,1 mmol/l*h; $Q_{25}$ - $Q_{75}$ = 3,3 - 4,7 mmol/l*h; P < 0,001 according to Mann-Whitney).

3. When conducting the discriminant analysis, we found that the administering of fluoxetine in group 2 caused a moderate increase in the activity of GGTP (F = 18,1; P < 0,001) and ALP (F = 15,4; P < 0,001) and the parameters of discriminant analysis were significantly less than the values of the coefficient F of group 1 with administering of amitriptyline (F = 59,3; F = 52,7, correspondingly; P < 0,001).

Thus, the administering of amitriptyline had a significant effect on the biochemical parameters of cytolysis ($P < 0,001$) and cholestasis ($P < 0,001$) in drug-dependent patients with low HCV activity. The administering of fluoxetine had practically no effect on the severity of the cytolytic syndrome ($F_{ALT} = 3,6$; $P > 0,1$); $F_{AST} = 4,9$; $P > 0,1$) and moderately increased the activity of cholestasis markers ($F_{GGTP} = 18,1$; $P < 0,01$); $F_{ALP} = 15,4$; $P < 0,01$).

In further studies, it is advisable to develop hepatoprotective therapy with the administering of antidepressants in patients with opioid dependence and CHC.

## Bibliography

1. Sosin IK and Chuev Ju F. "Narkologija (monografija) [Narcology (monograph)]". Har'kov: Kollegium (2005): 800.

2. Sosin IK., *et al*. "Diagnosticheskaja znachimost 'funkcional'nyh prob pecheni pri narkozav i simyh toksicheskih gepatitah [Diagnostic significance of functional liver tests in drug-dependent toxic hepatitis]". Sovremenny Diagnostiki I Terapii Gepatitov 5.2 (1999): 128-132.

3. MO Ovcharenko., *et al*. "Vpliv aktivnosti komorbidnogo hronichnogo gepatitu S na neparamet-richni koreljacijni zv'jazki mizh koncentracieju prozapal'nih citokiniv ta po-kaznikami hemiljuminescenciї sirovatki krovi u hvorih na opioїdnu zalezhnist". *Zagal'na Patologija ta Patologichna Fiziologija* 5.1 (2010): 178-185.

4. Seidenberg A., *et al*. "Patients receiving opioid maintenance treatment in primary care: successful chronic hepatitis C care in a real world setting". *BMC Infectious Diseases* 13 (2013): 9.

5. Ovcharenko MO. "Rezul'tati dispersijnogo. diskriminantnogo ta kla-sternogo analizu v ocinci vplivu aktivnosti komorbidnogo hronichnogo gepatitu S na biohimichni sir pokazniki o vatki krovi u hvorih na opioїdnu zalezhnist". *Ukraïns'kij Zhurnal Klinichnoї Ta Laboratorno Medicini* 6.1 (2011): 203-209.

6. Billioti de Gage S., *et al*. "Antidepressants and Hepatotoxicity: A Cohort Study among 5 Million Individuals Registered in the French National Health Insurance Database". *CNS Drugs* 32.7 (2018): 673-684.

7. Elgebaly HA., *et al*. "Olive oil and leaf extract prevent fluoxetine-induced hepatotoxicity by attenuating oxidative stress. inflammation and apoptosis". *Biomedicine and Pharmacotherapy* 98 (2018): 446-453.

8. Gahr M., *et al*. "Drug-Induced Liver Injury Associated with Antidepressive Psycho-pharmacotherapy: An Explorative Assessment Based on Quantitative Signal Detection Using Different MedDRA Terms". *Journal of Clinical Pharmacology* 56.6 (2016): 769-778.

9. Adinolfi LE., *et al*. "Chronic Hepatitis C Virus Infection and Depression". *Clinical Liver Disease* 21.3 (2017): 517-534.

10. Chen JY., *et al*. "Tricyclic antidepressant use and the risk of fibrosis progression in hepatitis C-infected persons: Results from ER-CHIVES". *Journal of Viral Hepatitis* 25.7 (2018): 825-833.

11. Chiu WC., *et al*. "Mental Disorders and Interferon Nontreatment in Hepatitis C Virus Infection-a Population Based Cohort Study". *Psychiatry Investigation* (2020).

12. Senn O., *et al*. "Determinants of successful chronic hepatitis C case finding among patients receiving opioid maintenance treatment in a primary care setting". *Addiction* 104.12 (2009): 2033-2038.

13. Voican CS., *et al*. "Antidepressant-induced liver injury: a review for clinicians". *American Journal of Psychiatry* 171.4 (2014): 404-415.

14. Men'shikov VV. "Laboratornye metody issledovanija v klinike. Spravochnik [Laboratory research methods in the clinic. Reference book]". M: Medicina (1987): 368.

15. Borovnikov VP. "STATISTICA - Statisticheskij analiz i obrabotka dannyh v srede Wi n dows [STATISTICA - Statistical analysis and data processing in Windows]". M: Informacionno-izdatel'skij dom "Filin" (1997): 608.

**Volume 9 Issue 4 March 2020**