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# THE ISOLATION OF TRAZODONE FROM THE BIOLOGICAL FLUIDS

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ІНФОРМАЦІЯ

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АНОТАЦІЯ

**The aim of the work** – to optimize the method for Trazodone isolation from blood and urine by liquid-liquid extraction technique.
**Materials and Methods.** The study was carried out with model samples of human biofluids spiked with Trazodone. The antidepressant was isolated from the blood and urine by the liquid-liquid extraction technique with methylene chloride from the alkaline aqueous medium at pH 9 at the presence of ammonium sulphate as a salting-out agent. The biological impurities were previously removed by extraction with diethyl ether from the acidic medium at pH 1. The erythrocyte mass of the blood was pre-precipitated with the help of 5% trichloroacetic acid. The resulting extracts were additionally purified using TLC technique. Quantitative determination of Trazodone in the extracts was carried out with the help of UV spectrophotometry.
**Results and Discussion.** Trazodone was detected in the biological extracts by UV spectra which coincided with standard methanol solution of the analyte and had the principal peak at wavelength of 251±2 nm. Quantitative determination of the drug in the extracts was performed with the help of calibration curve described by the equation $y=(0.0230\pm1\times10^{-4})\times x$, which showed linearity in the range of analyte concentration 2.5–50.0 μg/mL. Recovery values of the developed sample preparation methods were determined in the range of the drug concentrations of 10–50 μg/mL and 4–20 μg/mL for blood and urine respectively.
**Conclusions.** Effective methods for Trazodone isolation from blood and urine using liquid-liquid extraction in the presence of ammonium sulphate as a salting-out agent have been developed. It has been established that liquid-liquid extraction in the presence of electrolytes provided more effective Trazodone isolation from the biological fluids than under optimized conditions without salting-out agents. The recovery of the optimized methods was 52±3% for blood and 91±3% for urine that provided sufficient extraction yield of the antidepressant for its determination within the level of the expected acute concentrations in the biological fluids. The ability of UV spectrophotometry as an analytical method for determination of Trazodone in biological fluids has been proven by a range of validation parameters. The obtained results can be used for forensic toxicological examinations in cases of acute and fatal intoxications by antidepressants.

**Introduction.** Trazodone (2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-tri-azolo[4,3-a]-pyridin-3(2H)-one hydrochloride) is atypical antidepressant exercising complex agonistic/antagonistic effects on the serotonergic system and moderate antagonist effect on the histamine receptors [1; 2]. It is FDA-approved for the treatment of depression [3] and has proven effective in in major depressive disorder (MDD), particularly in those difficult to treat cases of MDD which accompanied with such symptoms as insomnia, anxiety, dementia and manic symptoms [4]. The usual prescribed daily dose is in the range between 150 and 600 mg [5]. At lower doses, Trazodone is used frequently to treat insomnia due to its sedative effect [6], Alzheimer's disease [7], obstructive sleep apnea [8], depression disorders with multiple chronic comorbidities [9]. Although it does not have FDA approval in management of insomnia, anxiety and a range of other mental disorders [10] because of possible undesirable side effects of this drug. Such complications of Trazodone therapy have been registered in a few case reports: Trazodone-induced parkinsonism [11], delirium [5], risk of extrapyramidal acute events [1], oromandibular dystonia [12], restless legs syndrome [2], hepatotoxicity manifested with acute reversible liver injury [13].

Several Trazodone acute and fatal intoxications have been reported [14–16]. The maximal ingested dose reported in the case of acute poisoning by Trazodone was 4500 mg [15]. According to the pharmacokinetic study after oral administration, Trazodone is mostly distributed in blood and excreted urinary with the total clearance of 6.85±2.80 mL/min/kg, volume of distribution of 1.06±0.07 L/kg, and elimination half-life of 8.58±1.88 hours [17].

Most of the bioanalytical methods developed recent decade for Trazodone refer to plasma samples. The following analytical techniques were used for the antidepressant determination: liquid chromatography-tandem mass spectrometry (LC-MS/MS) [18–20], HPLC-fluorescence detector [21; 22], voltammetry with a non-enzymatic biosensor [23]. Here protein precipitation with acetonitrile [19], capillary microsampling [20], liquid-liquid extraction (LLE) by methyl tert-butyl ether after alkalinization with ammonia [22], the thin film-solid phase microextraction (TF-SPME) [23] were used as sample preparation techniques.

Isolation of Trazodone from whole blood by liquid-liquid microextraction using ionic liquids as extraction solvents followed by LC-MS/MS determination was performed in the research [24]. The conditions for analysis of whole blood and urine for the presence of Trazodone are insufficiently covered in the literature. Thus, analytical aspects of Trazodone toxicology have not been developed completely.

The aim of this study was to optimize the method for Trazodone isolation from blood and urine by liquid-liquid extraction technique.

**Materials and Methods.** Reagents and Equipment. Trazodone basic form was extracted from commercially available tablets Trittico (150 mg) containing Trazodone hydrochloride which were purchased from Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F.S.p.A (Italy, Rome). Twenty tablets were weighted, placed into porcelain mortar and crushed, then 80 mL of chloroform was added to the tablet mass and the mixture was filtered into porcelain cup. The organic solvent was evaporated on a water bath at a temperature not higher than 40°C. The dry residue was transferred to a paper filter and washed with 40 mL of diethyl ether followed by discarding the organic solvent phase. The residue on the filter was dried and weighed. The purity of the drug extracted was ascertained by TLC, UV spectra and HPLC.

All other chemicals were of analytical grade or better. Light absorption of the solutions in UV region of spectrum was measured using spectrophotometer (SF-46), spectral measurement range was 190–1100 nm. A pH-meter 5123 (Elvro, Wroclaw, Poland). A water-bath LW-4 (Bytom, Poland). Merck chromatographic plates (Silica gel 60 F254, size 10×20 cm, Germany). A volumetric flasks of 10.00 mL, 25.00 mL, 100.00 mL; volumetric pipettes, Class A (Simax, Czech Republic).

*Method of Trazodone isolation from blood.* Module whole blood samples containing the drug were prepared. For this purpose, 10 mL of donor blood aliquots were spiked with 1 mL of aqueous solutions, containing from 100 to 500 μg of Trazadone hydrochloride and left for 24 h. Then 10 mL of 5% trichloroacetic acid solution was added to the model samples, left for 2 h and centrifuged for 10 min at 3000 rpm. The resulting centrifuge was separated, and 5 mL of 5% trichloroacetic acid was added again to the residue remaining in the centrifuge beaker. The contents of the beaker were stirred and centrifuged again under the conditions described above. The resulting centrifuges were combined and transferred to a separating funnel followed by triple extraction of biological impurities with 10 mL diethyl ether aliquots each time. The organic layer was separated and discarded, the aqueous layer was alkalified with 25% ammonium hydroxide solution to pH 9, 5 mL of saturated ammonium sulphate solution was added, then Trazadone was triple extracted with 10 mL of methylene chloride each time. The resulting extracts were combined and filtered through a filter containing 0.5 g of anhydrous sodium sulphate into a 25 mL volumetric flask and made up to the mark with methylene chloride. Blank sample was obtained at the same conditions. The resulting extracts were subjected to TLC purification as describe bellow.

*Method of Trazodone isolation from urine.* Module urine samples containing the drug were prepared. For this purpose, 50 mL of urine samples were spiked with 1 mL of aqueous solutions containing from 200 to 1000 μg of the drug, and left for 24 h. Then 0.1 M solution hydrochloric acid solution was added to the model samples adjusting to pH 1–2 and they were shaken with 20 mL of diethyl ether followed by discharging the organic layer. Then the aqueous layer was alkalified with 25% ammonium hydroxide solution to pH 9, 5 mL of saturated ammonium sulphate solution was added followed by the drug triple extraction with 15 mL methylene chloride aliquots. The emulsions were destroyed by

centrifugation. The centrifugate was filtered through a paper filter with 0.5 g of anhydrous sodium sulphate into a 25 mL volumetric flask and made up to the mark with methylene chloride. Blank sample was obtained at the same conditions. The resulting extracts were subjected to TLC purification as describe bellow.

*TLC purification of the extracts.* Aliquots of the 1/10 part of the biological extract and blank sample were concentrated to ~0.05 mL minimum volume and spotted on a baseline of TLC plate. Then 10 µL of 1.0 mg/mL reference solution of the drug in methanol was spotted next using a microsyringe. The rest of the biological extract and blank sample were evaporated to the volume of ~0.05 mL and applied as a band on a baseline. Then the zone in the chromatogram corresponding to these bands were not treated by the location reagent.

Chromatogram was developed in two mobile phases sequentially: first in chloroform followed by the development using methanol-25% ammonia solution mobile phase (100:10.5) placed into rectangular glass chambers (25×25×12 cm). UV light and Dragendorff-Mounier reagent were used for visualization. Then analyte was eluted from the area of the TLC plate untreated by the location reagent with 4 mL of methanol (the elution yield was of 99.5%), the eluate was filtered through a blue band paper filter. Eluate from the blank sample was obtained same way.

*UV spectrophotometric determination of Trazodone in the eluate.* Detection and quantitative determination of Trazodone in the extracts obtained after the drug isolation from the biological fluids was performed using UV spectrophotometry. UV-spectrum of Trazodone in the methanol eluate was measured over 200–350 nm wavelength range, 10 mm light pathway cuvette was used. Quantitative determination was carried out at 251 nm by the calibration curve. The reference solution was the blank sample.

Construction of the calibration curve. Standard solution (SS) of the drug was prepared by dissolving 0.00550 g of Trazodone hydrochloride (it corresponded to 0.00500 g of basic form of the drug) in methanol using a 100.00 mL volumetric flask; resulted concentration was 50 µg/mL of the drug basic form. To prepare working standard solutions (WSS) aliquots of 0.50; 1.00; 2.00; 3.00; 4.00; 6.00; 7.00; 8.00 and 9.00 mL of SS were placed into 10 mL volumetric flasks and adjusted by methanol to appropriate volume. Resulted concentration of WSS were 2.5; 5.0; 10.0; 15.0; 20.0; 30.0; 35.0; 40.0 and 45.0 µg/mL. Light absorption of SS and nine WSS was measured against methanol as reference solution. The linear regression model described in the general form as $y=b\times x+a$ was applied to obtain the equation of the calibration curve.

**Results and Discussion.** The optimal conditions for isolation of Trazodone from blood and urine were based on the preliminary study of the extraction yield of the drug depending on the pH of the aqueous solutions, kinds of organic solvents and salting-out agents. A wide range of organic solvents, sodium sulphate and ammonium sulphate as salting-out agents were tested at the aqueous phase pH ranging from 1 to 12. It has been found that the maximum extraction yield (87–89%) occurred for methylene chloride at pH 8–9 at the presence of ammonium sulphate as a salting-out agent. The lowest amount of the analyte (9%) was extracted with diethyl ether at pH 1, the last condition was chosen for the purification of the extracts from the biological impurities.

Methanol-25% ammonia solution mobile phase (100:10.5) was used for TLC purification of the extracts, the drug was detected on the resulting chromatogram using UV light by blue fluorescence spots (sensitivity 1.0 µg per a sample) and Dragendorff-Mounier reagent by orange spots on a yellow background (sensitivity 1.0 µg per a sample). $R_f$ values of Trazodone in the biological extracts and the drug in the reference solution coincided and were 0.59±0.03 (the mean of five measurements). Blank extracts did not give the spots with the corresponding $R_f$ values.

UV-spectra of the biological extracts and standard methanol solutions of Trazodone coincided and had the principal peak at wavelength of 251±2 nm (fig. 1). UV-spectrum of the blank sample did not have the principal peak at the specified wavelength.

Quantitative determination of Trazodone in the eluates was performed using calibration curve, which was described by the equation $y=(0.0230\pm1\times10^{-4})\times x$ ($r=0.999$; $S_0^2=1\times10^{-4}$; $S_a=0{,}0043$). The significance of the intercept in a regression model was checked using the *F*-test and the conclusion was drawn that it was possible to transfer to the equation in the form of $y=b'\times x$. The calibration curve was linear in the concentration range of 2.5–50 µg/mL. Limit of Detection (*DL*) and Limit of Quantification (*QL*) were calculated from the standard deviation of *y*-intercept $S_a$ and a slope *b* [25]; they were, respectively, 0.6 µg/mL and 1.9 µg/mL.

The results of the quantitative determination of Trazodone in the extracts obtained after drug isolation from blood using sample preparation method developed at five concentrations in the range of 10–50 µg/L are shown in table 1; the average recovery was 52±3%.

Recovery of the sample preparation method developed for isolation of Trazodone from urine was 91±3% in the 4–20 µg/L concentration range of the drug in the specified biological fluid (table 2). Thus, liquid-liquid extraction in the presence of electrolytes provided more effective Trazodone isolation from the biological fluids than under optimized conditions without salting-out agents when the recovery was 35±4% and 78±4% for blood and urine respectively [26].

The working range of the selected analytical procedure depending on the sample preparation method was established. The approach which is based on the standard deviation of the blank was applied [25]. In this case the lower range limits can be calculated with the following formula: $DL=3.3\times S/b$ and $DL=10\times S/b$, where *S* is a standard deviation of magnitude of background response of an appropriate number of blank samples; *b* is a slope of a calibration curve of a selected instrumental method of the analysis (table 3).

Thus, the lower limits of the working range of the UV spectrophotometric method for Trazodone determination

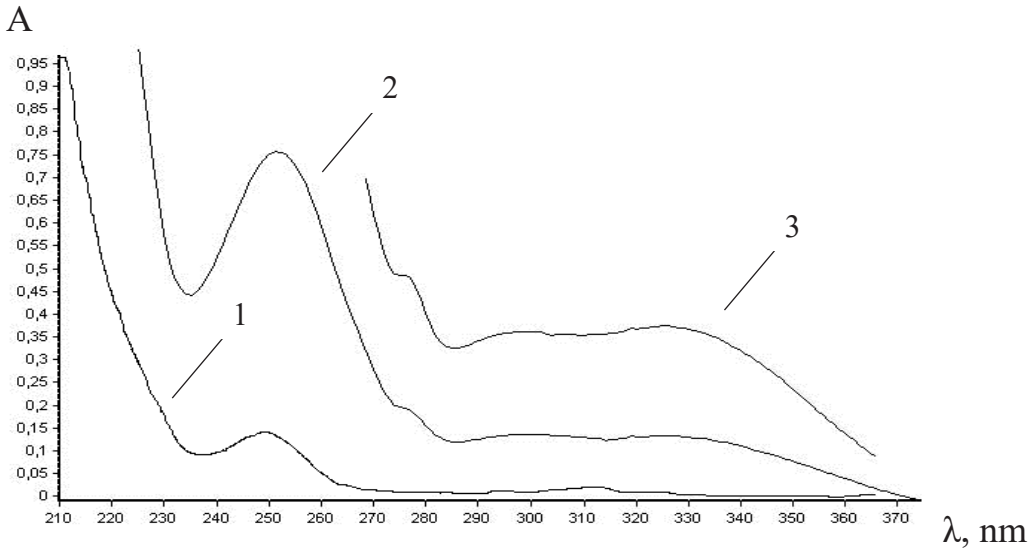


**Fig. 1.** UV spectrum of Trazodone standard solution in methanol
(1 – $1.5\times10^{-5}$ mol/L; 2 – $8\times10^{-5}$ mol/L; 3 – $5\times10^{-4}$ mol/L)

**Table 1**
Recovery of the isolation method for Trazodone from blood by solvent extraction technique in the presence of a salting-out agent

| Trazodone added to 10 mL of blood, μg | Trazodone extracted | | Metrological characteristics |
|---|---|---|---|
| | μg | % | |
| 100 | 53.2 | 53.2 | $\overline{X} = 52$ |
| 200 | 96.6 | 48.3 | $S = 2.858$ |
| 300 | 150.6 | 50.2 | $S_{\overline{X}} = 1.278$ |
| 400 | 225.6 | 56.4 | $\Delta\overline{X} = 3$ |
| 500 | 259.0 | 51.8 | $\varepsilon = 5.7\%$ |

**Table 2**
Recovery of the isolation method for Trazodone from urine by solvent extraction technique in the presence of a salting-out agent

| Trazodone added to 50 mL of urine, μg | Trazodone extracted | | Metrological characteristics |
|---|---|---|---|
| | μg | % | |
| 200 | 176.2 | 88.1 | $\overline{X} = 91$ |
| 400 | 368.8 | 92.2 | $S = 2.701$ |
| 600 | 549.6 | 91.6 | $S_{\overline{X}} = 1.208$ |
| 800 | 760.8 | 95.1 | $\Delta\overline{X} = 3$ |
| 1000 | 894.0 | 89.4 | $\varepsilon = 3.3\%$ |

**Table 3**
Detection and quantification limits of the UV spectrophotometric method calculated from the light absorption data of the blank ($A_{min}$)

| The biological fluid | ($A_{min}$) | S | RSD, % | $\Delta A_{min}$ ($n$=10; $P$=0.95) | ε | $DL$, μg/mL | $QL$, μg/mL |
|---|---|---|---|---|---|---|---|
| Blood | 0.0080 | 0.0010 | 12.5 | 0.0007 | 8.9 | 0.1 | 0.4 |
| Urine | 0.029 | 0.0030 | 10.3 | 0.002 | 8.9 | 0.4 | 1.3 |

in the biological fluids did not exit the corresponding validation characteristics calculated from the parameters of the calibration curve constructed using working standard solutions. This implies the lack of biological impurities influence on the selected analytical procedure and suitability of the sample preparation method

developed with a sufficient recovery of the antidepressant for its determination within the level of the expected acute concentrations in the biological fluids.

**Conclusions.** Effective methods for Trazodone isolation from blood and urine using liquid-liquid extraction in the presence of ammonium sulphate as a salting-out agent have been developed. It has been established that liquid-liquid extraction in the presence of electrolytes provided more effective Trazodone isolation from the biological fluids than under optimized conditions without salting-out agents. The recovery of the optimized methods was 52±3% for blood and 91±3% for urine that provided sufficient extraction yield of the antidepressant for its determination within the level of the expected acute concentrations in the biological fluids. The ability of UV spectrophotometry as an analytical method for determination of Trazodone in biological fluids has been proven by a range of validation parameters. The obtained results can be used for forensic toxicological examinations in cases of acute and fatal intoxications by antidepressants.

**Conflicts of interest:** authors have no conflict of interest to declare.

**Конфлікт інтересів:** відсутній.

## ІЗОЛЮВАННЯ ТРАЗОДОНУ З БІОЛОГІЧНИХ РІДИН

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**Мета дослідження** – розробка методу ізолювання тразодону з крові та сечі методом рідинно-рідинної екстракції.
**Матеріали і методи.** Дослідження проводили з модельними пробами біорідин людини, до яких було додано тразодон. Антидепресант виділяли з крові та сечі методом рідинно-рідинної екстракції метиленхлоридом із лужного водного середовища за pH 9 у присутності сульфату амонію як висолювача. Біологічні домішки попередньо видаляли екстракцією діетиловим етером із кислого середовища за pH 1. Еритроцитарну масу крові попередньо осаджували 5% трихлорацетатною кислотою. Отримані екстракти додатково очищували методом ТШХ. Кількісне визначення тразодону в екстрактах проводили за допомогою УФ-спектрофотометрії.
**Результати й обговорення.** Тразодон виявляли в біологічних екстрактах за УФ-спектрами, які співпадали зі стандартним розчином аналіту в метанолі та мали максимум світлопоглинання за довжини хвилі 251±2 нм. Кількісне визначення препарату в екстрактах проводили за допомогою калібрувального графіка, що описувався рівнянням $y=(0{,}0230\pm1\times10^{-4})\times x$, який був лінійним у діапазоні концентрацій аналіту 2,5–50,0 мкг/мл. Ступінь ізолювання розроблених методів пробопідготовки визначали в діапазонах концентрацій препарату 10–50 мкг/мл та 4–20 мкг/мл для крові та сечі відповідно.
**Висновки.** Розроблено ефективні методи ізолювання тразодону з крові та сечі за допомогою рідинно-рідинної екстракції у присутності амоній сульфату як висолювача. Встановлено, що рідинно-рідинна екстракція у присутності електролітів забезпечувала більш ефективне виділення тразодону з біологічних рідин, ніж за оптимізованих умов без висолювачів. Ступінь ізолювання оптимізованих методик становив 52±3% для крові та 91±3% для сечі, що забезпечувало достатню кількість антидепресанту для визначення його в межах очікуваних концентрацій у біологічних рідинах у разі гострих отруєнь. Придатність УФ-спектрофотометрії як аналітичного методу для визначення тразодону в біологічних рідинах була доведена низкою валідаційних параметрів. Отримані результати можуть бути застосовані для проведення судово-токсикологічних експертиз у разі гострих та смертельних отруєнь антидепресантами.
**Ключові слова:** тразодон, біологічні рідини, ізолювання, ТШХ, УФ спектрофотометрія.

**References**

1. Yajnik K, Thakar N, Chovatiya H, Desai S. Trazodone-Associated Extrapyramidal Syndrome: a Case Report and Review of Literature. Ann. Indian Acad. Neurol. 2024;27(1):85–87. DOI: 10.4103/aian.aian_774_23.
2. Yilbaş B. Restless Legs Syndrome Due to the Use of Trazodone: a Case Report. Turk. Psikiyatri Derg. 2022;33(1):70–72. DOI: 10.5080/u25787.
3. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. Postgrad. Med. 2017;129(1):140–148. DOI: 10.1080/00325481.2017.1249265.
4. Fagiolini A, Amodeo G, Goracci A, Blardi P. Trazodone Contramid® nella pratica clinica: strategie per la personalizzazione dell'intervento antidepressivo [Trazodone Contramid® in clinical practice: personalizing antidepressant intervention]. Riv. Psichiatr. 2016;51(4):123–128. DOI: 10.3389/fpsyt.2021.704847.
5. Pereira AT, Mota D, Ribeiro L, Rodrigues JD. Trazodone-induced delirium: case report. Rev. Colomb. Psiquiatr. (Engl Ed). 2020;49(3):199–201. DOI: 10.1016/j.rcp.2018.10.006.
6. Wichniak A, Wierzbicka AE, Jarema M. Treatment of insomnia-effect of trazodone and hypnotics on sleep. Psychiatr. Pol. 2021;55(4):743–755. DOI: 10.12740/PP/125650.
7. Kanamori T, Kaneko Y, Yamada K, Suzuki M. Successful Combination Therapy of Trazodone and Fluvoxamine for Pica in Alzheimer's Disease: a Case Report. Front. Psychiatry. 2021;12:704847. DOI: 10.3389/fpsyt.2021.704847.

8. He X, Lang Q, Pei ZM, Yan HY. Successful treatment of auto-trilevel positive airway pressure plus trazodone for obstructive sleep apnea complicated by anxiety disorder: a case report. J. Int. Med. Res. 2023;51(8):3000605231193924. DOI: 10.1177/03000605231193924.
9. Rosso G, et al. Personalizing the use of trazodone in real-world patients: a study of three cases of depression with comorbidities. Front. Psychiatry. 2024;15:1362221. DOI: 10.3389/fpsyt.2024.1362221.
10. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. Postgrad. Med. 2017;129(1):140–148. DOI: 10.1080/00325481.2017.1249265.
11. Ali HT, et al. Trazodone-induced parkinsonism in a middle-aged male: a case report. Afr. Health Sci. 2024;24(1):206–212. DOI: 10.4314/ahs.v24i1.25.
12. Skarmeta NP, et al. Tardive Oromandibular Dystonia Induced by Trazodone: a Clinical Case and Management from the Perspective of the Dental Specialist. Toxins (Basel). 2022;14(10):680. DOI: 10.3390/toxins14100680.
13. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. Am. J. Gastroenterol. 2000;95(2):532–535. DOI: 10.1111/j.1572-0241.2000.t01-1-01780.x.
14. Mannocchi G, et al. Forensic Aspects of a Fatal Intoxication Involving Acetaminophen, Citalopram and Trazodone: a Case Report. Toxics. 2022;10(8):486. DOI: 10.3390/toxics10080486.
15. Warnant A, Gerard L, Haufroid V, Hantson P. Coma Reversal After Intravenous Lipid Emulsion Therapy in a Trazodone-Poisoned Patient. Clin. Neuropharmacol. 2020;43(1):31–33. DOI: 10.1097/WNF.0000000000000376.
16. Potměšil P, Kostýlková L, Kopeček M. Increased amisulpride serum concentration in a patient treated with concomitant pregabalin and trazodone: a case report. Ther. Adv. Psychopharmacol. 2022;12:20451253221136754. DOI: 10.1177/20451253221136754.
17. Knych HK, et al. Pharmacokinetics and selected pharmacodynamics of trazodone following intravenous and oral administration to horses undergoing fitness training. Am. J. Vet. Res. 2017;78(10):1182–1192. DOI: 10.2460/ajvr.78.10.1182.
18. Ruggieri A, et al. Investigations on dose proportionality and drug-drug interaction for a fixed-dose combination of trazodone and gabapentin. Int. J. Clin. Pharmacol. Ther. 2021;59(1):71–86. DOI: 10.5414/CP203845.
19. Ding J, et al. Development of a Novel Analytical Method for Determining Trazodone in Human Plasma by Liquid Chromatography Coupled with Mass Spectrometry Coupled with Automatic 2-Dimensional Liquid Chromatograph-Mass Spectrometer Coupler 9500 and Its Application to Therapeutic Drug Monitoring. Ther. Drug Monit. 2022;44(3):465–473. DOI: 10.1097/FTD.0000000000000921.
20. Olivieri S, et al. Juvenile rat and pediatric trazodone studies: how to gain extra sensitivity to overcome bioanalytical challenges. Bioanalysis. 2019;11(1):21–22. DOI: 10.4155/bio-2018-0236.
21. Ragab GH, Bahgat EA. Development of HPLC method coupled with fluorescence detection for simultaneous determination of donepezil HCl and trazodone HCl in spiked human plasma and tablets dosage forms. Ann. Pharm. Fr. 2019;77(4):286–294. DOI: 10.1016/j.pharma.2019.02.003.
22. Li-Bo D, et al. Quantitative analysis of trazodone in human plasma by using HPLC-fluorescence detector coupled with strong cation exchange chromatographic column: application to a pharmacokinetic study in Chinese healthy volunteers. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2014;944:43–48. DOI: 10.1016/j.jchromb.2013.11.013.
23. Kashi F, Ebrahimzadeh H, Nejabati F. Development and characterization of a non-enzymatic electrochemical biosensor for rapid determination of sorbent-based extracted trazodone and doxepin in complicated samples. Anal. Chim. Acta. 2024;1317:342902. DOI: 10.1016/j.aca.2024.342902.
24. De Boeck M, et al. Fast and easy extraction of antidepressants from whole blood using ionic liquids as extraction solvent. Talanta. 2018;180:292–299. DOI: 10.1016/j.talanta.2017.12.044.
25. ICH Harmonised Guideline. Validation of Analytical Procedures Q2(R2) [Electronic resource]. 2022. 39 p. Available from: ich-guideline-q2r2-validation-analytical-procedures-step-2b_en.pdf.
26. Karpushyna SA, Baiurka SV, Merzlikin SI. Laboratory toxicological diagnosis of trazodone intoxications. Clin. Pharm. 2021;25(1):57–62. Available from: http://cphj.nuph.edu.ua/article/view/223921.

**Перелік бібліографічних посилань**

1. Yajnik K., Thakar N., Chovatiya H., Desai S. Trazodone-Associated Extrapyramidal Syndrome: a Case Report and Review of Literature. *Ann. Indian Acad. Neurol.* 2024. Vol. 27, Iss. 1. P. 85–87. DOI: 10.4103/aian.aian_774_23
2. Yilbaş B. Restless Legs Syndrome Due to the Use of Trazodone: a Case Report. *Turk. Psikiyatri Derg.* 2022. Vol. 33, Iss. 1. P. 70–72. DOI: 10.5080/u25787
3. Khouzam H.R. A review of trazodone use in psychiatric and medical conditions. *Postgrad. Med.* 2017. Vol. 129, Iss. 1. P. 140–148. DOI: 10.1080/00325481.2017.1249265
4. Fagiolini A., Amodeo G., Goracci A., Blardi P. Trazodone Contramid® nella pratica clinica: strategie per la personalizzazione dell'intervento antidepressivo [Trazodone Contramid® in clinical practice: personalizing antidepressant intervention]. *Riv. Psichiatr.* 2016. Vol. 51, Iss. 4. P. 123–128. DOI: 10.3389/fpsyt.2021.704847
5. Pereira A.T., Mota D., Ribeiro L., Rodrigues J.D. Trazodone-induced delirium: case report. *Rev. Colomb. Psiquiatr.* (Engl Ed). 2020. Vol. 49, Iss. 3. P. 199–201. DOI: 10.1016/j.rcp.2018.10.006
6. Wichniak A., Wierzbicka A.E., Jarema M. Treatment of insomnia-effect of trazodone and hypnotics on sleep. *Psychiatr. Pol.* 2021. Vol. 55, Iss. 4. P. 743–755. DOI: 10.12740/PP/125650
7. Kanamori T., Kaneko Y., Yamada K., Suzuki M. Successful Combination Therapy of Trazodone and Fluvoxamine for Pica in Alzheimer's Disease: a Case Report. *Front. Psychiatry.* 2021. Vol. 12. P. 704847. DOI: 10.3389/fpsyt.2021.704847
8. He X., Lang Q., Pei Z.M., Yan H.Y. Successful treatment of auto-trilevel positive airway pressure plus trazodone for obstructive sleep apnea complicated by anxiety disorder: a case report. *J. Int. Med. Res.*

2023. Vol. 51, Iss. 8. P. 3000605231193924. DOI: 10.1177/03000605231193924
9. Case report: Personalizing the use of trazodone in real-world patients: a study of three cases of depression with comorbidities / G. Rosso, et al. *Front. Psychiatry.* 2024. Vol. 15. P. 1362221. DOI: 10.3389/fpsyt.2024.1362221
10. Khouzam H.R. A review of trazodone use in psychiatric and medical conditions. *Postgrad. Med.* 2017. Vol. 129, Iss. 1. P. 140–148. DOI: 10.1080/00325481.2017.1249265
11. Trazodone-induced parkinsonism in a middle-aged male: a case report / H.T. Ali, et al. *Afr. Health Sci*. 2024. Vol. 24, Iss. 1. P. 206–212. DOI: 10.4314/ahs.v24i1.25
12. Tardive Oromandibular Dystonia Induced by Trazodone: a Clinical Case and Management from the Perspective of the Dental Specialist / N.P. Skarmeta, et al. *Toxins (Basel)*. 2022. Vol. 14, Iss. 10. P. 680. DOI: 10.3390/toxins14100680
13. Fernandes N.F., Martin R.R., Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am. J. Gastroenterol*. 2000. Vol. 95, Iss. 2. P. 532–535. DOI: 10.1111/j.1572-0241.2000.t01-1-01780.x
14. Forensic Aspects of a Fatal Intoxication Involving Acetaminophen, Citalopram and Trazodone: a Case Report / G. Mannocchi, et al. *Toxics.* 2022. Vol. 10, Iss. 8. P. 486. DOI: 10.3390/toxics10080486
15. Warnant A., Gerard L., Haufroid V., Hantson P. Coma Reversal After Intravenous Lipid Emulsion Therapy in a Trazodone-Poisoned Patient. *Clin. Neuropharmacol.* 2020. Vol. 43, Iss. 1. P. 31–33. DOI: 10.1097/WNF.0000000000000376
16. Potměšil P., Kostýlková L., Kopeček M. Increased amisulpride serum concentration in a patient treated with concomitant pregabalin and trazodone: a case report. *Ther. Adv. Psychopharmacol.* 2022. Vol. 12. P. 20451253221136754. DOI: 10.1177/20451253221136754
17. Pharmacokinetics and selected pharmacodynamics of trazodone following intravenous and oral administration to horses undergoing fitness training / H.K. Knych, et al. *Am. J. Vet. Res.* 2017. Vol. 78, Iss. 10. P. 1182–1192. DOI: 10.2460/ajvr.78.10.1182
18. Investigations on dose proportionality and drug-drug interaction for a fixed-dose combination of trazodone and gabapentin / A. Ruggieri, et al. Int. *J. Clin. Pharmacol. Ther.* 2021. Vol. 59, Iss. 1. P. 71–86. DOI: 10.5414/CP203845
19. Development of a Novel Analytical Method for Determining Trazodone in Human Plasma by Liquid Chromatography Coupled with Mass Spectrometry Coupled with Automatic 2-Dimensional Liquid Chromatograph-Mass Spectrometer Coupler 9500 and Its Application to Therapeutic Drug Monitoring / J. Ding, et al. *Ther. Drug Monit.* 2022. Vol. 44, Iss. 3. P. 465–473. DOI: 10.1097/FTD.0000000000000921
20. Juvenile rat and pediatric trazodone studies: how to gain extra sensitivity to overcome bioanalytical challenges / S. Olivieri, et al. *Bioanalysis.* 2019. Vol. 11, Iss. 1. P. 21–22. DOI: 10.4155/bio-2018-0236
21. Ragab G.H, Bahgat E.A. Development of HPLC method coupled with fluorescence detection for simultaneous determination of donepezil HCl and trazodone HCl in spiked human plasma and tablets dosage forms. *Ann. Pharm. Fr.* 2019. Vol. 77. Iss. 4. P. 286–294. DOI: 10.1016/j.pharma.2019.02.003
22. Quantitative analysis of trazodone in human plasma by using HPLC-fluorescence detector coupled with strong cation exchange chromatographic column: application to a pharmacokinetic study in Chinese healthy volunteers / D. Li-Bo, et al. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 2014. Vol. 944. P. 43–48. DOI: 10.1016/j.jchromb.2013.11.013
23. Kashi F., Ebrahimzadeh H., Nejabati F. Development and characterization of a non-enzymatic electrochemical biosensor for rapid determination of sorbent-based extracted trazodone and doxepin in complicated samples. *Anal. Chim. Acta*. 2024. Vol. 1317. P. 342902. DOI: 10.1016/j.aca.2024.342902
24. Fast and easy extraction of antidepressants from whole blood using ionic liquids as extraction solvent / M. De Boeck, et al. *Talanta.* 2018. Vol. 180. P. 292–299. DOI: 10.1016/j.talanta.2017.12.044
25. ICH Harmonised Guideline. Validation of Analytical Procedures Q2(R2) [Electronic resource]. 2022. 39 p. URL: ich-guideline-q2r2-validation-analytical-procedures-step-2b_en.pdf.
26. Karpushyna S.A., Baiurka S.V., Merzlikin S.I. Laboratory toxicological diagnosis of trazodone intoxications. *Clinical pharmacy*. 2021. Vol. 25, Iss. 1. P. 57–62. URL: http://cphj.nuph.edu.ua/article/view/223921.

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