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Polysubstances in Drug-Induced Deaths: A Case Report

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Abstract

Objectives: *We present a recent case of lethal polysubstance intoxication that had been almost unreported due to the lack of interest in further investigation by the competent authorities. Results from post-mortem examination are discussed in terms of their relevance on drug-mortality surveillance system.*

Methods: *The autopsy of 40-year-old man was performed upon the coroner's request. Biological samples were collected and analysed histologically and by toxicological procedures involving immunoassays and gas chromatography–mass spectrometry (GC–MS). Ind addition, the samples of medications found next to the dead body were toxicologically analysed and compared with the result of tested biological samples.*

Results: *Severe cerebral and pulmonary oedema, as well as general congestion were detected, in the absence of any other pathological changes. Toxicological analysis of blood and urine revealed the presence of opioids (Buprenorphine, Methadone, Tramadol), antipsychotics (Clozapine), benzodiazepines (Diazepam), antidepressants (Mirtazapine), and Pregabaline (antiepileptic, analgesic, anxiolytic).*

Conclusion: *The cause of death was attributed to an acute mixed intoxication by various substances. This case represents a continuation of the trend observed in the last few years in the Split-Dalmatian County and once again calls for improvements of the present monitoring and communication system in Croatia, which currently provides inadequate measurement of drug trends and lacks a timely response to drug-related dangers.*

Keywords: Drug Related Deaths, Epidemiology, Forensic Autopsy, Polysubstance Use, Toxicology.

Key Points

- This case presents an example of lethal polysubstance misuse involving psychotropic medications such as benzodiazepines, antidepressants, and opioids.
- The combined use of several CNS depressants led to fatal respiratory depression. This highlights the need for comprehensive toxicological analysis in all suspected deaths caused by the misuse of medications or addictive substances.
- The case reveals weaknesses in the national drug-mortality surveillance system and underscores the need for improved intersectoral communication in Croatia.

Introduction

Deaths due to drug consumption represent an important indicator of the burden that psychoactive substances impose on public health systems. Despite long-standing prevention programs and expanded treatment options, the number and complexity of fatal outcomes resulting from intoxications continue to rise, primarily due to changes in consumption patterns, the increasing availability of potent synthetic substances, and the persistent co-use of multiple substances [1]. Therefore, systematic monitoring of drug and medication related deaths is essential for identification of epidemiological trends, resource allocation optimization, and effective interventions implementation.

European data indicate that opioids are the leading substances involved in fatal overdoses in a large proportion of cases [2]. These cases often include multiple substances, particularly benzodiazepines, antidepressants, antipsychotics, gabapentinoids, and alcohol, which, when consumed together, create a potent synergistic effect on the respiratory system, leading to respiratory depression, loss of consciousness, suppression of protective reflexes, and death [2-4]. The concurrent use of multiple substances and resulting fatal outcomes complicate the interpretation of toxicological findings due to the unpredictability of pharmacodynamic and pharmacokinetic interactions among central nervous system depressants [4]. Pregabalin and related gabapentinoids have recently emerged as substances with a high potential for misuse, especially among opioid-dependent individuals, significantly increase the risk of fatal overdose [5, 6].

These trends underscore the need for comprehensive and timely monitoring. Despite this, significant inconsistencies persist in documenting drug-related deaths across different jurisdictions in Croatia. Also, the World Health Organization has highlighted that many fatal intoxications remain misclassified or unreported due to incomplete post-mortem examinations, insufficient toxicological analyses, and discrepancies in death certification [7]. Similar challenges have been observed in several regions of Southeast Europe, where limited laboratory capacity, administrative delays, and insufficient inter-agency communication hinder surveillance and contribute to underestimation of drug-induced mortality [8]. Similar issues have been reported in Croatia. National analyses indicate that the country lacks an integrated system combining forensic medicine, public health, clinical toxicology, and psychiatry into a coordinated surveillance framework [9]. Previous studies have highlighted substantial discrepancies between toxicology-positive cases and officially recorded drug-related deaths, suggesting that a considerable proportion of cases remains misclassified [10].

We report the fatal case of polysubstance intoxication that once again points to the systemic weaknesses in Croatia's monitoring and reporting drug-related mortality system.

Case History

A 40-year-old man, in psychiatric treatment for heroin addiction 5 years ago, now on substitution therapy with heptanone, which he takes irregularly, was found dead in his bedroom. According to his wife, he would occasionally consume alcohol. Two months before his death, he was found unconscious in a park, hospitalized and treated under a diagnosis of acute alcohol and methadone poisoning. The wife stated that he suddenly died during the night, presenting no symptoms previously. She denied any possible consumptions of drugs, although several vials and packages of medication were found beside him.

Figure 1A: Paper unmarked container with contents found at the scene,
Figure 1B: Three vials with contents.

The case was at risk of being overlooked due to limited initial institutional interest in deeper investigation. The coroner asked for the autopsy and further post mortem analyses were performed, including toxicological analysis of medication recovered at the death scene.

Material and Methods

The autopsy was performed 2 days after death and incorporated a complete postmortem examination as well as collection of tissues and biological fluids' samples (femoral vein blood, cardiac blood and urine) for histopathological and toxicological analyses, respectively. All biological samples were refrigerated at 4 °C until laboratory processing. Non-biological samples (classified as scene samples) were stored at room temperature in sealed forensic evidence bags and later analyzed qualitatively to identify the substances and correspond them with biological samples.

A two-step analytical workflow was applied, beginning with immunoassay screening methods followed by confirmatory instrumental analysis using a liquid–liquid extraction (LLE) and gas chromatography–mass spectrometry (GC–MS) operating in full-scan mode. The analyses were conducted on a Shimadzu GC/MS QP-2030 Nexis system (Kyoto, Japan), equipped with an autosampler and an electron-impact (EI) ionization source. Blood alcohol concentration (BAC) and urine alcohol concentration (UAC) were measured using the Shimadzu GC 2030 with headspace and flame ionisation detector (FID). (Note: as it was not requested quantification of the detected substances, their presence was determined only.)

Results

The autopsy was performed on middle age man, properly developed and nourished, who showed no signs of external trauma or

injection marks. Only severe cerebral and pulmonary oedema, together with congestion of parenchymal organs, were observed. This was confirmed by histological examination, and no additional pathological findings were found.

The results of the examination of medications found at the death scene and their toxicological identification are shown in Table 1 and Figure 2.

Table 1: Medications/drugs found in bottles labeled Lumidol (tramadol)

Tablet/capsule	Description	Substance (trade name)	Activity	No. of bottles	Pieces
caps. PGN 300 VTRS	burgundy/white, oval	pregabalin (Lyrica)	analgesic, anxiolytic, antiepileptic	1	9
caps. without tag	pink, oval	tramadol (Tramadol)	analgesic (opioid)	3	20
tbl. C7PN	yellowish-white, round	clozapine (Klozapin, Leponex)	antipsychotic	1 2	4 whole, 14 halves, 11 quarters 6 whole, 2 halves
tbl. without tag	blue, round	diazepam (Diazepam, Apaurin)	anxiolytic	1	27
tbl. Q200	ocher-yellow, oval	quetiapine (Q-PIN)	antipsychotic	1 2	2 2
tbl. without tag	pink, oval	mirtazapine (Calixta, Mirzaten)	antidepressant	1 2	12 35
tbl. P&U59	white, round	alprazolam (Xanax)	anxiolytic	2	9
tbl. without tag	ocher, oval	acetaminophen (Acetaminofen, Paracetamol)	analgesic, antipyretic	1 2	4 3

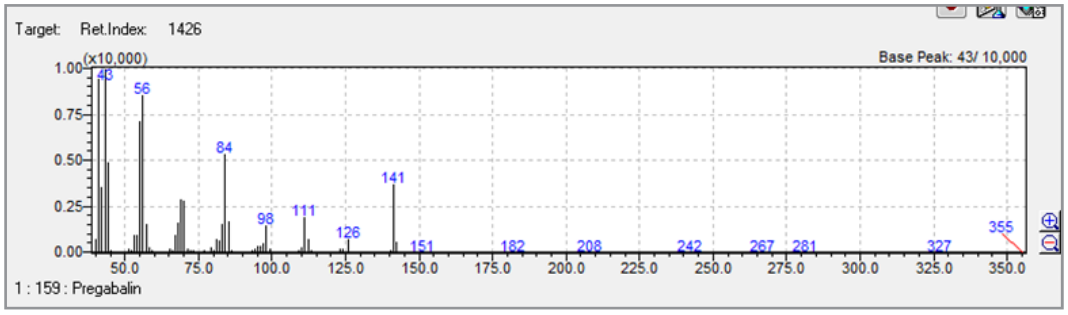

Figure 2: Mass spectrum of pregabalin, obtained using the Shimadzu Nexis GC-2030 GC–MS system, with the characteristic fragment ions.

Toxicological analysis of biological samples revealed the presence of a complex combination of opioids (buprenorphine, methadone, tramadol), benzodiazepines (diazepam), antipsychotics (clozapine), antidepressants (mirtazapine) and pregabalin (Fig. 3). Alcohol in blood and urine samples was not detected.

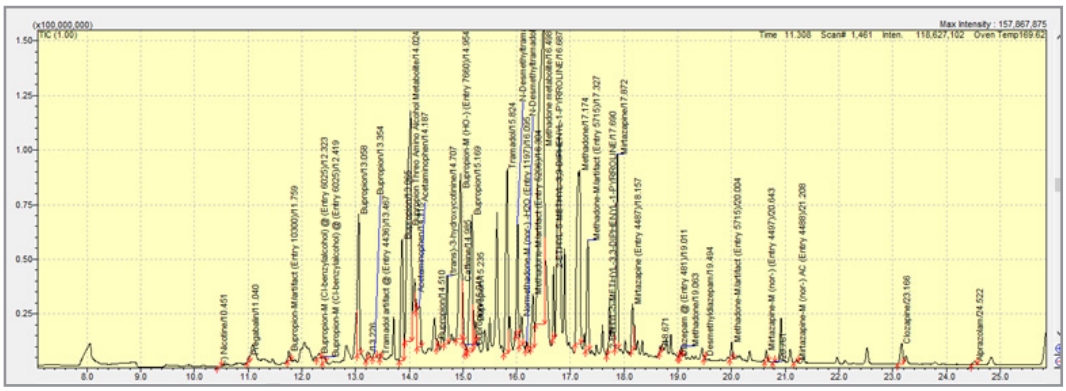

Figure 3: Total ion chromatogram (TIC) of the urine sample, acquired in scan mode using a Shimadzu Nexis GC-2030 GC–MS system, with the identified analytes annotated.

Comparing the results of toxicological analysis of samples from the scene and biological samples, it is evident that methadone and buprenorphine were found in the biological samples but not in the scene samples. At the same time quetiapine, alprazolam and acetaminophen, which were identified in the scene samples were not found in the biological samples.

The autopsy findings were interpreted in conjunction with the toxicological results. Consideration was given to drug detection, polypharmacy effects, and the combined pharmacodynamic interactions of the detected substances, particularly opioids, benzodiazepines, antipsychotics, antidepressants, and pregabalin as shown in Table 2. Pharmacological classification and toxicological effects were summarized from standard toxicology sources, including Goodman & Gilman's Pharmacological Basis of Therapeutics (14th edition), Katzung'Basic and Clinical Pharmacology (16th edition), Baselt's Disposition of Toxic Drugs and Chemicals in Man (8th edition), Clarke's Analysis of Drugs and Poisons (4th edition).

Table 2: Detected substances, pharmacological classes, and toxicological significance

Substance	Drug class	Toxicological significance
Methadone	Opioid (long-acting)	Potent respiratory depressant; high synergistic poten-tial with benzodi-azepines and gabapentinoids
Buprenor-phine	Partial opioid recep-tors agonist	Respiratory depression possible especially in combi-nation; additional sedative effect
Tramadol	Atypical opioid	CNS depression; serotonergic component; increases overall sedative burden
Diazepam	Benzodiazepine	Sedation and muscle relaxation; markedly enhances opioid-induced respiratory depression
Pregabalin	Gabapentinoid	Strong sedation; loss of protective reflexes; well-documented synergy with opioids
Clozapine	Antipsychotic	CNS depression; potential cardiac arrhythmias; in-creases sedative burden
Mirtazapine	Antidepressant	Sedative effect; contributes to overall CNS depression

Based on the integrated evaluation of autopsy and toxicological data, the cause of death was determined to be mixed-drug intoxication.

Discussion

The presented case of fatal outcome due to combined intoxication with multiple psychoactive substances highlights several important forensic, toxicological, clinical, and public-health aspects related to the growing prevalence of polysubstance drug use. In accordance with European data, opioids continue to occupy a central position in fatal cases caused by drug intoxication, especially when taken together with other central nervous system depressants [1, 2].

In the presented case, the simultaneous presence of buprenorphine, methadone, and tramadol illustrates a typical pattern of misuse among individuals dependent on opioids. This is particularly evident in patients who undergo irregular psychiatric treatment or substitution therapy. Such combinations greatly increase the risk of respiratory depression and loss of consciousness, which has been documented in previous researches on opioid-related mortality [3, 4].

The combination of multiple opioids (methadone, buprenorphine, tramadol) in the presence of benzodiazepine (diazepam) and pregabalin produces a well-documented synergistic respiratory depression. Each of these substances can cause sedation on its own, but together they markedly reduce ventilatory drive, protective reflexes, and the ability to compensate for hypercapnia. Pregabalin further enhances sedation and the loss of oropharyngeal reflexes, increasing the risk of hypoventilation and fatal respiratory failure. This synergistic effect is clinically and forensically more relevant than the pharmacological impact of any individual substances.

The toxicological findings additionally confirmed the presence of antipsychotic clozapine, and antidepressant mirtazapine, contributing to a pronounced cumulative depressant effect on respiratory and cardiovascular function. Polypharmacy involving opioids, benzodiazepines, and sedative psychotropic medications in this case represented a high-risk factor for a fatal outcome due to polysubstance use, which has also been highlighted in other studies [2-4]. Interactions between the consumed drugs are difficult to predict because of individual differences in tolerance, metabolism, and patterns of use, particularly in populations with chronic dependence or psychiatric comorbidities [11].

A particularly significant finding was the presence of pregabalin, a gabapentinoid that has become increasingly relevant in substance misuse and fatal intoxications in recent years. Pregabalin is frequently misused due to its euphoric and sedative properties, especially when combined with opioids [5, 6, 12]. Among European countries, Finland has reported a sharp rise in pregabalin-related deaths, with the number of such cases significantly increasing between 2020 and 2021 [13]. Pregabalin contributes to respiratory depression, and its combination with the aforementioned psychotropic drugs is especially dangerous [6]. Among opioid-dependent individuals, pregabalin is often obtained without a prescription or through illegal channels, indicating a high potential for misuse and insufficient prescribing control [5, 6, 14, 15].

The autopsy finding of severe cerebral and pulmonary oedema, together with general congestion, is consistent with mixed-drug

intoxication and is commonly observed in fatal cases involving opioids and polysubstance use [4, 16]. Although autopsy findings alone rarely allow for identification of the specific toxic agent, they are essential for interpreting toxicological results and confirming the shared physiological effects of multiple CNS depressants [17].

This case also points to systemic weaknesses in Croatia's monitoring and reporting of drug-related mortality. According to national reports, the surveillance system still lacks strong integration among forensic medicine, public health, clinical toxicology, and psychiatry [9]. Such inconsistency and the lack of multidisciplinary communication contribute to the underestimation of the true number of drug-related deaths and delay recognition of emerging trends. Previous studies have shown substantial discrepancies between toxicology-positive cases and administratively recorded deaths, revealing difficulties in classification and documentation [10]. Similar issues have been documented in the Split-Dalmatia County, where opioids have dominated fatal outcomes for many years, and polysubstance use has often been underestimated [18, 19]. Subsequent studies have continued to report similar toxicological findings, emphasizing that many cases involve multiple psychoactive substances and require comprehensive laboratory analysis for identification of the full toxicological profile. Research on detecting drugs even in necrophagous insects has further underscored the importance of detailed toxicological approaches, particularly in cases with advanced post-mortem changes or limited biological material. More recent evaluations suggest that the prevalence of deaths associated with polysubstance use continues to rise in the region. An overview of drug-related deaths in Split-Dalmatia County for the period 2015–2024 highlighted an increasing involvement of various prescription medications, including gabapentinoids, benzodiazepines, and atypical antipsychotics, in combination with opioids [19]. These findings are consistent with broader European trends and further reinforce concerns regarding insufficient early-warning mechanisms and limited inter-agency communication [20].

The fact that this case was almost left uninvestigated due to insufficient initial institutional interest indicates a real risk that many intoxications remain misclassified as a result of incomplete autopsies, inadequate toxicological analyses, and inconsistent death certification [7, 8]. Increasingly complex patterns of drug consumption, including prescription medications, opioids, benzodiazepines, gabapentinoids, and antipsychotics, clearly require a comprehensive toxicological approach and improved communication among responsible institutions to ensure accurate classification [21]. A particularly vulnerable group includes patients undergoing psychiatric treatment or substitution therapy. Several studies have shown that individuals with co-occurring psychiatric disorders and substance dependence are at significantly higher risk for uncontrolled medication use and fatal intoxication [16, 22]. This case reflects such a pattern: the availability of multiple medications and their unsupervised use considerably increased the likelihood of overdose. Also, this case report contributes to a better understanding of mortality related to polysubstance use and emphasizes the urgent need to strengthen early warning systems, improved surveillance, and inter-institutional communication in Croatia. Detailed analyses of individual cases represent a valuable tool for identifying emerging trends, developing preventive strategies, standardizing toxicological procedures, refining clinical guidelines and improving the national response to public-health risks [23]. They also highlight the need for more responsible prescribing of CNS depressants, closer therapeutic monitoring, and better patient education regarding the risks associated with combined drug use.

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