

## SHORT COMMUNICATION

## THE CHANGING PATTERN OF POISONING WITH PSYCHOACTIVE DRUGS IN CROATIA

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The aim of this study was to analyse the frequency of poisoning with psychoactive drugs (benzodiazepines, antidepressants and neuroleptics) over the last 15 years in Croatia. The analysis was based on poisoning incidents reported over the phone (hot line) to the Zagreb Poison Control Center and included two periods: 1985–1991 (period I) and 1992–1999 (period II). The data were analysed separately for children and adults. Each phone call was counted as one poisoning incident. Child poisoning with neuroleptics was significantly higher in period II than in period I and so was the adult poisoning with antidepressants, amitriptyline, and combined psychoactive drugs. The frequency of total psychoactive drug poisoning was significantly higher in adults than in children in both periods. From 1992, the frequency of adult poisoning with antidepressants considerably increased as one of the many consequences of war-related stress. The results indicate a need for careful psychiatric evaluation and more critical use of antidepressants in affected individuals.

*Key words:*  
amitriptyline, antidepressants, benzodiazepines,  
neuroleptics, Poison Control Centre,  
posttraumatic stress syndrome

**D**rug overdose is the most common cause of acute poisoning according to data from Poison Control Centres throughout the world (1). In the USA, 25% of all routine hospital admissions and about 5% of all medical intensive care unit admissions involve some kind of drug-related adverse event (2). Poisoning is often referred to as the most frequent method of suicide or suicide attempt, and most cases involve drug poisoning, particularly with psychotropic drugs such as benzodiazepines, antidepressants, and neuroleptics (3–6).

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The most commonly prescribed of all drugs are benzodiazepines, sedative-hypnotic agents indicated in anxiety, depression, insomnia, musculoskeletal disorders, seizures, alcohol withdrawal, and initial anaesthesia. Benzodiazepine poisoning is common in combination with other drugs. Clinically, benzodiazepines cause central nervous system (CNS) depression, the degree of which depends on the ingested dose. Complications and the lethal outcome are rare (2, 5-7).

Antidepressants, particularly the tricyclic antidepressants (TCA), are common for drug overdosing that requires intensive care. Major toxic effects involve CNS and the cardiovascular system. Anticholinergic symptoms, sinus tachycardia, and hypotension are common. Impaired consciousness, acidosis, seizures, and cardiotoxicity (right axis deviation, prolonged QRS complex, and cardiac dysrhythmias) are associated with severe toxicity (2, 8, 9). Lethal outcome of TCA poisoning is still not rare and is usually related to cardiotoxic effects (10, 11). The mortality rate in patients treated in intensive care units is estimated to 2-3% (2).

Neuroleptics, also known as antipsychotic agents and major tranquilizers, are primarily used to treat schizophrenia, manic phase of bipolar disorders, and agitated behaviour. However, they are often used to treat nausea, vomiting, headache, and various neurological conditions (chorea, dystonia, spasms, tics, and torticollis). Beside accidental or intentional overdose, toxic effects often occur after ingestion of therapeutic doses. Toxic effects include anticholinergic and extrapyramidal syndromes as well as CNS and cardiovascular depression. Lethal outcomes are less frequent than in TCA poisoning because of the lower potential for CNS and cardiovascular complications (2, 12).

The aim of this study was to analyse the frequency of acute poisoning with psychoactive drugs in Croatia over a 15-year period (1985-1999). Data were collected from the national Poison Control Centre in Zagreb. It is a 24-hour telephone information service providing advice for treatment of ingestion or exposure to toxic materials to professionals and general public.

## SUBJECTS AND METHODS

This retrospective study was based on drug ingestions reported over the phone (hot line) to the Zagreb Poison Control Center from 1985 to 1999. The analysis was focused on three groups of psychoactive drugs: benzodiazepines, antidepressants, and neuroleptics. Among antidepressants, amitriptyline as the representative of the TCA group was separately analysed because of its potential to induce severe toxicity. Practically all psychoactive drug ingestions were symptomatic and were referred to as poisonings. Each phone call was counted as one poisoning incident, including multiple poisoning (ingestion of more than one drug at once) involving at least one psychoactive drug. In multiple poisonings with two or three groups of psychoactive drugs, the leading drug was determined according to the highest ingested dose and/or related clinical symptoms. Poisoning incidents were divided in two periods; period I stretched from 1985 to 1991 and period II from 1992 to 1999. The incidents were also grouped according to the age of poisoned subjects: children (<16 years), with a separate analysis of preschoolers (L 5 years), and adults (316 years). The analysis included methods of descriptive statistics and the *t*-test for differences in proportions. The *P*-value below 0.05 was considered significant.

## RESULTS

The frequency of poisoning with psychoactive drugs is shown here as the proportion of total recorded child or adult poisonings for each of the three groups of psychoactive drugs and multiple poisoning for periods I and II.

Table 1 shows the reported drug ingestion by children in both periods. The frequency of child poisoning with neuroleptics was significantly higher in period II than in period I, while it did not significantly change between the two periods with respect to benzodiazepines, antidepressants, and combined drugs. In period I, 55.2% of child poisonings with psychoactive drugs involved children under the age of five, while in period II that proportion grew to 65.4%. The frequency of child poisoning with amytriptyline was similar for both periods (1/341 or 0.3% in period I and 4/666 or 0.6% in period II).

Table 1 *Poisoning with psychoactive drugs in children*

Period	Poisoning with psychoactive drugs					
	Total drug ingestions N (%)	Neuroleptics N (%)	Benzodiazepine N (%)	Antidepressants N (%)	Total N (%)	Multiple poisoning N/total (%)
1985-1991	341 (100)	15 (4.4)	46 (13.5)	6 (1.8)	67 (19.4)	13/67 (19.4)
1992-1999	666 (100)	49 (7.4)*	66 (9.9)	12 (1.8)	127 (19.1)	26/127 (20.5)

Multiple poisoning in both periods was presented as proportion of total recorded poisonings with psychoactive drugs  
 \*P<0.05

Table 2 shows the reported drug ingestions by adults in both periods. The frequency of adult poisoning with antidepressants was significantly higher in period II than in period I, and so was the frequency of multiple poisoning. The frequency of adult poisoning with benzodiazepines and neuroleptics was similar in period I and II. Adult poisoning with amytriptyline was significantly more frequent in period II than in period I (3/102 or 2.9% v. 37/507 or 7.3%, respectively; P<0.05).

Table 2 *Poisoning with psychoactive drugs in adults*

Period	Poisoning with psychoactive drugs					
	Total drug ingestions N (%)	Neuroleptics N (%)	Benzodiazepine N (%)	Antidepressants N (%)	Total N (%)	Multiple poisoning N/total (%)
1985-1991	102 (100)	21 (20.6)	28 (27.5)	6 (5.9)	55 (53.9)	16/55 (29.1)
1992-1999	507 (100)	100 (19.7)	144 (28.4)	66 (13.0)*	311 (61.3)	141/311 (45.3)*

Multiple poisoning in both periods was presented as proportion of total recorded poisonings with psychoactive drugs  
 \*P<0.01

The frequency of total psychoactive drug poisoning was significantly higher in adults than in children in both periods (Table 3). In period I, the frequency of poisoning with neuroleptics and benzodiazepines was significantly higher in adults than in children. There was no significant difference in the frequency of poisoning with antidepressants or combined drugs between adults and children (Table 3). The frequency of poisoning with amitriptyline alone was similar in children and adults (1/341 or 0.3% v. 3/102 or 2.9%, respectively).

In period II, adults showed significantly higher poisoning frequencies than children for all three groups of psychoactive drugs as well as for the multiple poisoning (Table 3). The frequency of poisoning with amitriptyline alone was also significantly higher in adults than in children (37/507 or 7.3% v. 4/666 or 0.6%, respectively;  $P < 0.01$ ).

Table 3 Poisoning with psychoactive drugs in period I and II according to the age group.

Period	Age group	Poisoning with psychoactive drugs					
		Total drug ingestions	Neuroleptics	Benzodiazepine	Antidepressants	Total	Multiple poisoning
		N (%)	N (%)	N (%)	N (%)	N (%)	N/total (%)
1985-1991	Children	341 (100)	15 (4.4)	46 (13.5)	6 (1.8)	67 (19.4)	13/67 (19.4)
	Adults	102 (100)*	21 (20.6)*	28 (27.5)	6 (5.9)	55 (53.9)*	16/55 (29.1)
1992-1999	Children	666 (100)	49 (7.4)	66 (9.9)	12 (1.8)	127 (19.1)	26/127 (20.5)
	Adults	507 (100)*	100 (19.7)*	144 (28.4)*	66 (13.0)*	311 (61.3)*	141/311 (45.3)*

Multiple poisoning in both periods was presented as proportion of total recorded poisonings with psychoactive drugs  
\* $P < 0.01$

## DISCUSSION

Most authors agree that exact data about the frequency of acute drug poisoning are not available because no medical or other intervention is requested in many accidental or intentional poisonings (2, 13). It is therefore important to note that the actual frequency of acute poisonings in Croatia is likely to be significantly higher than registered by the national Poison Control Centre in Zagreb. However limited, the number of reported poisoning incidents is still able to give an insight into the pattern of poisoning in Croatia.

Changes in the frequency of poisonings with drugs in the developed countries are commonly associated with changes in prescriptions which are influenced by the introduction of new drugs on the market, changes in prices, and better knowledge of side-effects (14, 15). For example, the introduction of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression decreased the morbidity and mortality rates of TCA poisoning (7, 16).

Until 1992, pesticide poisoning or exposure accounted for the majority of incidents reported to the Poison Control Centre in Zagreb (>30%), which differed from similar reports in Europe and the USA (17). The results of this study show a considerable increase in the number of drug ingestions in Croatia since 1992, particularly in adults. Over 50% of all ingestions were related to psychoactive drugs in both periods. This agrees with the results of an earlier 5-year retrospective study which showed a high proportion of psychopharmaceuticals in self-poisoning in Zagreb from 1982 to 1986 (18). Although benzodiazepines were found the leading cause of poisoning in this study, high participation of neuroleptics (20.6% in period I and 19.7% in period II) calls for particular consideration. In the USA and other developed countries, poisoning with neuroleptics is rather low, only 1.2% of all drug poisonings (1). An important and disturbing fact is the high increase in adult poisoning with antidepressants (from 5.9% in period I to 13% in period II) and combined drugs (from 29.1% in period I to 45.3% in period II), including the significant proportion of TCA poisonings (from 2.9% to 7.3%) since 1992. TCA overdose is still the most common cause of severe toxic manifestations and lethal outcomes, even if treated in an intensive care unit. Many developed countries recommend a switch from TCA to SSRI treatment due to the significantly lower toxic potential of SSRIs (9, 19, 20). Multiple psychoactive drug overdose is also often associated with severe toxicity and needs complex treatment (1). The increase in adult poisoning with antidepressants and combined psychoactive drugs in this study may be the result of an increase in prescriptions of psychoactive drugs caused by altered population morbidity. War, migration, and related stress resulted in an increase in mental disorders, particularly the posttraumatic stress syndrome. The increase in TCA poisoning is probably due to a relatively low cost of TCA in comparison with other antidepressants (19, 20).

By contrast, the frequency of child poisoning remained similar throughout the 15-year period, except for the increase in poisoning with neuroleptics since 1992. Over 50% of poisonings were reported for children under the age of 5 and were accidental. Though the ingestion was the result of curiosity and accessibility drugs, the increase may be related to an increase in prescriptions of psychoactive drugs for adults (21).

## CONCLUSION

Since 1992, that is, the beginning of Serbian aggression in Croatia, the number of acute adults poisonings with antidepressants, particularly TCA, has been rapidly increasing in Croatia, reflecting an increased rate of prescriptions of these drugs. Fortunately, such increase has not been reported in children. The increasing rate of psychoactive drug poisoning as one of the many consequences of war-related stress underlines the need for careful psychiatric evaluation and treatment of affected individuals and more critical use of antidepressants. Future studies should be able to analyse and evaluate the practice of prescribing psychoactive drugs in Croatia.

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### Sažetak

## PROMJENE UČESTALOSTI TROVANJA PSIHOAKTIVNIM LIJEKOVIMA U HRVATSKOJ

Retrospektivno su analizirani telefonski pozivi vezani uz ingestije lijekova primljeni u nacionalnom Centru za kontrolu otrovanja u Zagrebu u posljednjih 15 godina. Tri skupine psihoaktivnih lijekova (benzodiazepini, neuroleptici, antidepresivi) bile su od posebnog značenja u ovom radu. Svi slučajevi ingestije lijekova analizirani su u dva vremenska intervala: period I (1985.-1991.) i period II (1992.-1999.) te u dvije skupine s obzirom na dob otrovanih: djeca (<16 godina) i odrasli (316 godina). Svaki telefonski poziv brojen je kao jedan slučaj trovanja, uključujući i višestruke ingestije lijekova (ingestije više od jedne vrste lijeka u isto vrijeme) koje su uključivale barem jedan psihoaktivni lijek.

Kod djece, učestalost akutnih otrovanja neurolepticima bila je značajno veća u periodu II nego u periodu I (7.4%:4.4%;  $P<0.05$ ). Učestalost otrovanja benzodiazepinima, antidepresivima i amitriptilinom kod djece nije se značajno razlikovala u periodu I i II (benzodiazepini - 13.5%:9.9%; antidepresivi - 1.8%:1.8%; amitriptilin - 0.3%:0.6%), kao ni učestalost višestrukih ingestija lijekova (19.4%:20.5%). Kod odraslih, učestalost otrovanja antidepresivima i amitriptilinom bila je značajno veća u periodu II nego u periodu I (antidepresivi - 13.0%:5.9%;  $P<0.01$ ; amitriptilin - 7.3%:2.9%;  $P<0.05$ ), kao i učestalost višestrukih ingestija lijekova (45.3%: 29.1%;  $P<0.01$ ). Učestalost otrovanja benzodiazepinima i neurolepticima kod odraslih nije se značajno razlikovala u periodu I i II (benzodiazepini - 27.5%: 28.4%; neuroleptici - 20.6%: 19.7%). U oba perioda učestalost otrovanja psihoaktivnim lijekovima bila je značajno veća u odraslih nego u djece (period I - 53.9%: 19.4%;  $P<0.01$ ; period II - 61.3%:19.1%;  $P<0.01$ ).

Od 1992. u Hrvatskoj se bilježi značajan porast broja akutnih otrovanja antidepresivima, osobito tricikličkim, u odraslih osoba, što je vezano vjerojatno uz učestalije propisivanje tih lijekova. Ovaj fenomen nije zabilježen u djece. Povećanje učestalosti akutnih otrovanja psihoaktivnim lijekovima, kao jedna od mnogih posljedica rata i posttraumatskoga stresnog poremećaja, upućuje na potrebu pažljive psihijatrijske procjene oboljelih, osobito pažljiviju uporabu antidepresiva. Rezultati ovog rada govore u prilog potrebe daljnjeg istraživanja učestalosti propisivanja psihoaktivnih lijekova u Hrvatskoj.

#### *Ključne riječi:*

amitriptilin, antidepresivi, benzodiazepini, Centar za kontrolu otrovanja, neuroleptici, posttraumatski stresni poremećaj

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