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Alcohol and drug use in drug-related deaths in Campania (Italy): a snapshot study over the years 2008-2018

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ABSTRACT

The aim of the study is the evaluation of incidence of mortality, directly or indirectly linked to drug abuse in one of the most populated Italian region (Campania). Trends on psychotropic substances intake and prevalence of drug-related deaths (DRDs) are assessed over an eleven-year observation period from 2008 to 2018. Data from toxicological investigations applied, for forensic purpose, on post-mortem blood sampled from 640 suspected DRDs (267 in the years 2008–2012 and 373 in the years 2013–2018) has been revised. A Systematic Toxicology Analysis (STA) by validated GC/MS or LC-MS/MS methods for licit drugs (benzodiazepines, antidepressants/antipsychotics, hypnotics) and illicit drugs (amphetamine and analogous, cocaine, opiate, methadone, barbiturate, buprenorphine, cannabis and new psychoactive substances) was applied. A conventional methodology (GC/HS-FID) was used to test the blood alcohol concentration (BAC). Toxicological results were positive in 403 cases out of 640 autopsies totally performed: 202 DRDs out of 267 deaths were identified during the years 2008-12 and 201 DRDs out of 373 during the 2013-2018 period. Among the 403 DRDs, more than 90% of cases were males aged between 41-50 years. A remarkable increase in the number of alcohol related deaths (42 cases) was observed in the years from 2013 to 2018 compared with the previous one. Most of these cases showed a BAC in the range 1.5 – 4 g/L, compared to the only 3 cases occurred in 2008-2012 years. During the eleven-year observation period, the poly-drug use has been recognized as responsible for 258 deaths (64%) out of 403 cases in total. The association of cocaine and morphine was predominant in the years 2008-2012 while in the years 2013-2018 pharmaceuticals (benzodiazepines, antidepressants etc.), alcohol and illicit drugs (cocaine and morphine), alone or in combination, were the substances mainly detected. Methadone was detected more frequently in associations with other drugs (mainly pharmaceuticals) or ethyl alcohol but it was also found alone in 3 DRDs only. Surprisingly in few DRDs cannabis metabolites were found neither a single fatal poisoning by amphetamines and new psychoactive substances (NPS) was recorded. During the eleven-year observation period, an increase in DRDs involving ethyl alcohol intake has been observed. A relevant variability in the prevalence among the licit/illicit drug use has been also found, mainly represented by the poly-drug intake respect to the abuse of a single drug. Data collected demonstrate that it is crucial a continuous updating about the territorial trends of the drug abuse in order to develop a Community Data Bank, for planning strategies of prevention.

Keywords: *Drug-related deaths; GC-LC/MS analysis; alcohol/drugs abuse; blood alcohol concentration; poly-drug abusers; pharmaceuticals abuse.*

1. Introduction

Drug-related mortality is a complex phenomenon, which accounts for a considerable percentage of deaths in many Countries. Odds of dying of drug abusers have been estimated to be from three to seven times more likely than those of the general population [1]. According to the system

for categorizing mortality data involving drug abuse deaths developed by the Drug Abuse Warning Network (DAWN), drug-related deaths (DRDs) are “deaths where there is an evidence of voluntary and recent use of drugs under circumstances that reveal a causal relationship between these and do not suggest other causes of death”. There are several types of DRDs: a) deaths caused by overdose both

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intentional or accidental events (including body packers); b) diseases directly caused by the drug use or chronic abuse, as infections due to subsequent non-sterile needles use (HIV-AIDS, hepatitis), myocarditis, and respiratory deficit; c) drugs abuse related suicides and homicides, and d) other violent deaths attributed to traumatic injuries due to the behavior's alterations under drug use (traffic accidents for drivers under the influence, work-related accident, etc.) [2].

The pattern of drug abuse usually differs among Countries and even territories of the same Country. It changes also over the time. Aim of the study is the evaluation of incidence and prevalence of mortality due to DRDs in one of the most populated Italian region (Campania). It is the third-most-populous region of Italy with a population of around 5.800.000 people located on the Southern west coast. In Campania the "Forensic Toxicological Unit" of the University of Campania "L. Vanvitelli" is the "Forensic Reference Laboratory" (FRL) for the entire territory. The FRL performs toxicological analyses for medico-legal purpose on biological samples collected from people alive but also on post-mortem specimens.

Goal of the forensic approach to DRDs is to support the diagnosis of fatal poisoning through the analytical detection of xenobiotic substances (alcohol, illicit drugs, pharmaceuticals or other poisons) in traditional body fluids and tissues (blood, urine, bile and samples of internal organs) or alternatives matrices (humor vitreous, hairs and saliva) according to the information available from the medical history and the circumstances of the fatal event. In this retrospective study, only toxicological results obtained in post mortem blood samples were reviewed in order:

- a) to assess the trends of alcohol and drugs abuse among DRDs during the years from 2013 to 2018;
- b) to compare the results observed during the years 2013 to 2018 with those collected during the previous years from 2008 to 2012 already assessed and published in a previous study [3];
- c) to provide data useful for the development of preventive strategies with regional relevance.

2. Material and Methods

During the eleven-year observation period (from 2008 to 2018), post-mortem toxicological analyses have been performed by FRL on 640 suspected DRDs. The distribution was the following: 267 autopsies during the years 2008– 2012 and 373 fatalities in total during the years 2013 – 2018. The analytical procedures on post-mortem blood include an immunoassay screening techniques, addressed to the most common drugs of abuse such as amphetamines, barbiturates, cannabis, cocaine, methadone, opiates, 6-AM (6-acetylmorphine, heroin metabolite) and buprenorphine. A qualitative Systematic Toxicology Analysis (STA) [4] was also applied using a mass spectrometry methodology coupled with gas or liquid chromatography (GC/MS or LC-MS/MS) for licit drugs (benzodiazepines, antidepressants/

antipsychotics, hypnotics) and illicit drugs (amphetamine and analogous, cocaine, opiate, methadone, barbiturate, buprenorphine, cannabis) and the new psychoactive substances (NPS). Each positive results obtained from the STA was confirmed by quantitative methods, validated in accordance with both National and International Guidelines and Recommendations [5,6], using specific analytical cut-offs established in National Guidelines. A conventional GC/HS-FID methodology was used to test the blood alcohol concentration (BAC). Finally, the interpretation of toxicological data was achieved in accordance with circumstantial information and medical history.

3. Results and Discussion

During the observation period from 2013 to 2018, toxicological investigations were requested in 373 judicial autopsies in which drug toxicity was suspected to be involved. Positive toxicological results were achieved only in 202 cases (54%) finally assessed as DRDs. No great differences in the incidence of DRDs were observed between the two considered period. Although in the recent observation period from 2013 to 2018 there were more medico-legal autopsies (373 in total) than the previous observation period 2008-2012 (267 only), the total amount of positive toxicological analyses performed on postmortem samples was quite the same: 201 in the year 2008-2012 vs 202 in the years 2013-2018.

3.1 Age and gender distribution among DRDs

During the years 2013-2018 the 202 DRDs involved mostly males in 191 fatalities (94.5%). Females were in only 11 cases (5.5%). Victims aged between 41 and 50 years occurred in the majority of cases (29%). The mortality rate among younger people (less than 25 years of age) was significantly low (6.4%) Age and gender distribution among DRDs occurred during the years from 2013 to 2018 is shown in Table 1.

These results were consistent with data observed in the years 2008-2012 [3]. In fact, a very low mortality rate was also found among young males (< 25 years old) accounted in

Table 1 | Age and gender distribution among the 202 drug-related deaths (DRDs) occurred in Campania (Italy) during the years 2013-2018.

Age group (years)	Number M (male) / F	Frequency
< 25	12 M / 1 F	6.4 %
25-30	21 M / 2 F	11.4 %
31-40	37 M / 2 F	19.3 %
41-50	56 M / 2 F	28.7 %
> 50	35 M / 4 F	19.3 %
N.D.	30 M / 0 F	14.9 %

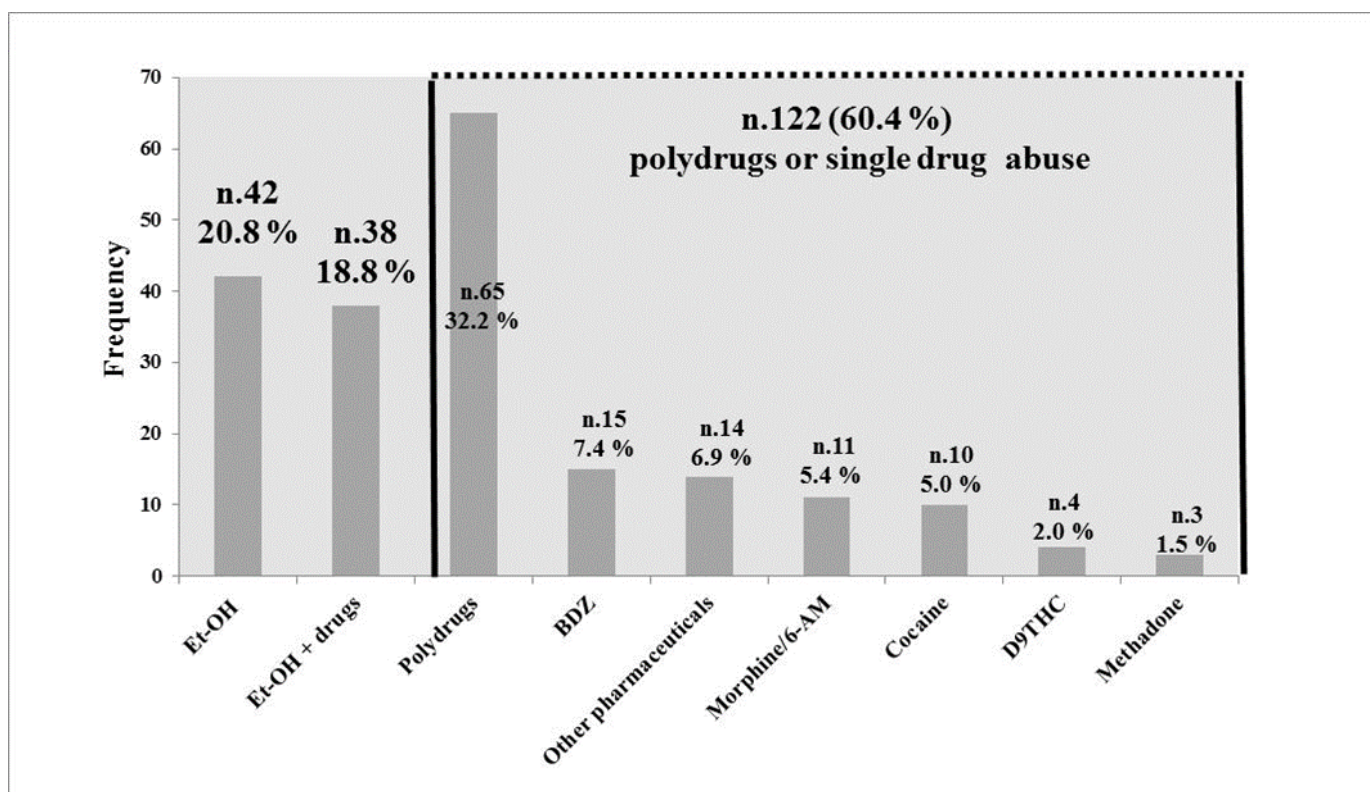


Figure 1 | Distribution of ethyl alcohol, licit and illicit drugs among 202 drug-related deaths (DRDs) occurred in Campania (Italy) during the years 2013-2018.

the years 2008-2012. During the overall eleven year observation period more than 90 % of the 403 victims were males, mostly with an age range of 41-50 years. It is quite interesting that in DRDs the mean age of victims seems to vary greatly between Countries. The lowest values have been reported in Slovenia (20-24 years old) [7] and Eastern Germany (20-24 years old) [8] followed soon after by Finland (29 years old) [9], Romania (31 years old) [10], Norway (34 years old), Sweden (36 years old) and Denmark (38 years old) [9]. In all these Countries, so far the mean age victims by DRDs is lower than that observed in our Southern Italian territory.

3.2 Typology of drug involved in DRDs

The distribution of alcohol and drugs among the 202 DRDs accounted during the observation period from 2013 to 2018 is shown in Figure 1. The overall toxicological results demonstrate that the highest mortality rate (60.4%) is related to the intake of psychoactive substances (illicit and licit drugs) and that the multiple drug abuse is a critical issue (32.2%). Among these 202 cases, the ethyl alcohol alone was the most frequently detected xenobiotic substance in 80 fatalities (39.6%) out of 202 totally. Among these fatalities, ethyl alcohol was the only poison detected in 42 cases (20.8%) while it was in association with one or more drugs in 38 DRDs (18.8%). The intake of illicit drugs and pharmaceuticals, as single or in combination with multiple drugs was detected in 122 DRDs (60.4%), more than half of

the total fatalities occurred during the observation period.

In DRDs involving ethanol, a BAC greater than 1.5 and up to 4 g/L was observed in most of the cases, 28 fatalities (66.6%) out of the 42 in total where ethyl alcohol was detected. A BAC between 0.8 -1.5 g/L and a BAC less than 0.8 g/L were detected in 9 (21%) and in 5 (12%) deaths involving ethanol, respectively.

The distribution of blood alcohol levels found in combination with one single drug or with a poly-drug intake among 38 DRDs is summarized in Table 2.

In 18 out of 38 DRDs involving ethanol in association with a single drug, cocaine or therapeutic agents were the xenobiotic substances more represented. Among these 18 cases involving ethanol in combination with a single drug, in 9 DRDs BAC level was > 1.5 g / L. In 20 out of 38 DRDs involving ethanol in association with poly-drugs, the intake of cocaine/morphine and pharmaceuticals/cocaine was well represented in all four BAC concentration ranges (Table 2).

Among the 202 DRDs, 57 fatalities were positive to a single substance (Figure 1) mostly represented by pharmaceuticals: benzodiazepines (BDZ) occurred in 15 cases and antidepressants in 14 cases. Among the illicit drugs, morphine was detected only in 11 DRDs (5.4%) and cocaine in 10 cases (5%). Surprisingly the metabolites of cannabis and methadone have been identified alone respectively in 4 and 3 cases out of 202 DRDs in total. None case was positive only to amphetamines or to NPS.

Over the years 2013-2018, deaths due to poly-drug abuse have been assessed in 65 cases out of 202 DRDs in total

Table 2 | Distribution of single/multiple drug intake versus the blood alcohol concentration (BAC) levels among 38 drug-related deaths (DRDs) occurred in Campania (Italy) during the years 2013-2018.

Range of BAC (g/	Single Drug (18)	Polydrugs (20)
< 0.5	Δ^9 THC (1)	Cocaine + Morphine/6-AM (1)
		Cocaine + Morphine/6-AM (2)
0.5 – 0.8		Cocaine + Δ^9 THC (1)
		Cocaine + Methadone + Pharmaceuticals (1)
		Cocaine + Morphine/6-AM + Methadone (1)
		Cocaine + Morphine/6-AM (3)
		Cocaine + Pharmaceuticals (2)
0.8 – 1.5	Cocaine (1)	Morphine/6-AM + Pharmaceuticals (1)
	Δ^9 THC (1)	Morphine/6-AM + Methadone (1)
	Methadone (1)	Methadone + Pharmaceuticals (1)
	Δ^9 THC (1)	Cocaine + Δ^9 THC (1)
	Cocaine (3)	Cocaine + Morphine/6-AM (2)
> 1.5	Pharmaceuticals (6)	Cocaine + Pharmaceuticals (1)
	Morphine/6-AM (1)	Δ^9 THC + Pharmaceuticals (1)
	Methadone (1)	Cocaine + Morphine/6-AM + Methadone (1)

(Table 3). Among these, in 44 DRDs, pharmaceuticals were found in 11 different associations with other substances. Cocaine was detected in 12 different associations in 32 cases totally. Methadone and morphine in combination with other substances, were detected each in 29 cases. Metabolites of cannabis were found to a lesser extent in only 13 DRDs but in seven different associations. It is worth mentioning that methadone was the only one drug abused in 3 cases while it

Table 3 | Distribution of poly-drug abuse among the 65 drug-related deaths (DRDs) occurred in Campania (Italy) during the years 2013-2018.

Poly-drugs	Total number of DRDs 65
Pharmaceuticals (BDZ + other medicinal drugs)	10
Pharmaceuticals + Methadone	8
Pharmaceuticals + Morphine	6
Pharmaceuticals + Cocaine + Methadone	5
Pharmaceuticals + Morphine + Methadone	4
Pharmaceuticals + Cocaine + Morphine	4
Pharmaceuticals + Cocaine + Morphine + Methadone	2
Pharmaceuticals + Cocaine	2
Pharmaceuticals + Cocaine + Morphine + THC + Methadone	1
Pharmaceuticals + Morphine + Methadone + THC	1
Pharmaceuticals + THC	1
Cocaine + THC	5
Cocaine + Morphine	4
Cocaine + Methadone	3
Cocaine + THC + Morphine	2
Cocaine + Morphine + Methadone	2
Cocaine + THC + Morphine + Methadone	1
Cocaine + Morphine + Cocaethilene	1
Methadone + THC	2
Methadone + Morphine	1

was more frequently detected in combination with other drugs (mainly pharmaceuticals) or ethyl alcohol.

Finally, toxicological results reviewed during the eleven-year observation period from 2008 to 2018 have been sub-grouped in two different data sets: the first data set goes from 2008 to 2012 with details already discussed in a previous article [3], the second data set goes from 2013 to 2018 as illustrated above. A comparison of the two sub-groups is shown in Table 4.

Table 4 | Distribution of single/multiple drug intake versus the blood alcohol concentration (BAC) levels among 38 drug-related deaths (DRDs) occurred in Campania (Italy) during the years 2013-2018.

Substances	years 2008-2012 (201 DRDs / 267 autopsies)	years 2013-2018 (202 DRDs / 373 autopsies)
	n. cases (frequency)	n. cases (frequency)
Et-OH	3 (1.5%)	42 (20.8 %)
Et-OH + Drugs	33 (16.4%)	38 (18.8 %)
Drugs or pharmaceuticals (single drug / polydrug)	165 (82.1%) (43 / 122)	122 (60.4 %) (57 / 65)

The comparison of data sets show a significant increase in DRDs due to the intake of ethyl alcohol occurred in the years 2013-2018 with 80 cases in total versus only 36 in the years 2008-2012. The 42 DRDs involving ethanol alone in the years 2013-2018 are fourteen times more than the 3 only cases observed during the years 2008-2012. During the years 2008-2012, the multiple drug abuse was recognized as responsible for most of the DRDs with 122 cases out of 201 (60.6%). In the recent observation period 2013-2018, this result was not confirmed with only 65 cases out of 202 (32%) probably due to a descending trend of heroin or cocaine intake in the general population.

In fact, although the association of heroin (morphine and/or 6-AM) and cocaine was the combination of drugs more frequently observed with 60 cases out of 122 DRDs during the years 2008-2012 [3], in the more recent observation period 2013-2018, the xenobiotic substances detected mostly were the pharmaceuticals (mainly BDZ, such as clonazepam, diazepam, lorazepam) and alcohol, alone or in combination with cocaine and morphine.

BDZ are commonly prescribed psychoactive drugs because considered safe and effective against anxiety disorders and panic attacks [11-14]. The large use of BDZ around the world is consistent with the high detection rate of BDZ among the DRDs occurred in the recent observation period 2013-2018. It seems that in Campania region also, a relevant shift to pharmaceuticals abuse in association with traditional illicit drugs, is taking place. Such trend in the behavior of drug abusers has been already reported in many European countries. In fact, BDZ, barbiturates, antipsychotics and anti-epileptics, were also identified as the most common agents in 35% DRDs in Romania [10]. Half of the reported DRDs in 2017 in Scotland (UK) involved new BDZ such as etizolam [15]. A combination of BDZ (mainly diazepam) and methadone has been recorded in 12% of DRDs in the Republic of Macedonia, with a clear increase since 2011 [16]. Finally, during the eleven-year observation period, the poly-drug use has been recognized as responsible for 258 deaths (64%) out of 403 cases in total.

4. Concluding Remarks

Despite several recommendations and always more deterrent laws suggest caution in the use of drugs and alcohol, in Campania region (Italy), toxicological data on DRDs demonstrate a constant number of fatalities but characterized by a great variability in the prevalence of licit/illicit substances.

During the eleven-years observation period from 2008 to 2018, there was an increasing trend of the ethanol intake, alone or in combination with other agents. Moreover, over the time, a shift to pharmaceuticals abuse in association with traditional illicit drugs was highlighted. The fast growing of the poly-drug intake, compared to single drug abuse and a descending trend of overdose rate due to heroin or cocaine abuse were also recorded. Data revised demonstrate that it is

crucial the continuous updating of the local trends of the drug abuse. Providing this information to the Italian Department for the Antidrug Policies and to the European Monitoring Center for Drugs and Drug Addictions is the main goal of forensic toxicologists in order to develop a Community Data Bank, for planning strategies and preventing the consumption of all substances harmful to the population.

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