Differences in combinations and concentrations of drugs of abuse in fatal intoxication and driving under the influence cases

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Abstract

Background

In toxicology, international classification systems focus on single intoxicants as the cause of death. It is, however, well known that very few drug related deaths are caused by a single substance and that information concerning the drug concentrations as well as the combinations of drugs are essential in order to ascertain the cause of death. The aim of the study was to assess whether those prone to fatal intoxications differ significantly from chronic drug users - in terms of demographics and drug exposure patterns.

Material and Methods

Fatal psychoactive drug intoxications in Norway during 2012, where a forensic autopsy including toxicological analysis were performed, were included. Analytical findings in blood were compared with concentrations in blood from apprehended drivers under the influence of drugs and ethanol (DUID) during the same time period. The opioid and benzodiazepine concentrations were assessed as morphine and diazepam equivalents, respectively, in order to compare concentrations across the different groups.

Results

A total of 194 autopsy cases and 4,811 DUID cases were included. Opioids were detected in around 90% of the drug intoxication cases, but in only 16% of the DUID cases. The number of substances detected in fatal intoxications was 4.9 compared to 2.4 in the DUID cases. The total opioid concentrations were significantly higher in the fatal intoxication cases compared to DUID cases (229 ng/mL versus 56.9 ng/mL morphine equivalents, respectively). Benzodiazepines were detected in 90% of the fatal cases. Only one fatal opioid mono-intoxication was found; a case with a very high methadone concentration (1238 ng/mL).

Discussion

Mono-intoxication with heroin was not seen in any of the fatal intoxications in Norway, and single drug intoxications were rare (1.5%). Fatal intoxications were caused by a combination of drugs with significantly more substances as well as higher total drug concentrations among the fatal cases compared to the DUID cases. The combination of opioids and benzodiazepines seemed to represent an increased risk of death.

Conclusion

The total load of drugs influence the degree of intoxication and the total concentration level must be considered, including the total number of substances. Our findings imply that international statistics regarding an opioid being the main intoxicant should have a shift in focus towards combinations of drugs (especially opioids and benzodiazepines) as a major risk factor for fatal drug overdoses.

Keywords: Fatal intoxication; narcotic; death; drugs addict; drug combination; drug concentration; forensic toxicology

Introduction

Both national and international statistics indicate opioids to be the leading cause of fatal intoxications in Norway (1-3). Heroin is the most commonly used opioid in Norway, and it is estimated that approximately 85% of the heavy opioid users inject heroin (1). Injection of heroin is a drug administration route prone to cause fatal overdoses, and could partly explain the high overdose rate seen in Norway compared with many other European countries where injecting heroin is less common (2, 4).

In the Global Burden of Health calculations, misuse of illicit drugs is ranked as the 10th leading risk factor for a reduction of disability-adjusted life years (DALYs) in Norway in 2015 (5). More than 41 000 years of life lost (YLLs) are attributed to the use of alcohol and illicit drugs, and ranks as the 5th leading risk factor for early death in Norway in 2015; for the ages 15 to 49 years it is regarded as the leading contributor to early death. Fatal opioid-related intoxications among men are stated to be a strong driving force for the YLLs (5, 6).

Drug induced deaths are classified according to the presence of drugs in toxicological samples, and most countries use international classification systems, like the ICD (International Classification of Diseases) (7), for diagnostic purposes. A single substance is typically chosen as the main intoxicant, and positive findings of e.g. morphine/heroin or methadone, lead to the classification of a heroin or methadone related death, respectively, by hierarchal traditions. However, in the majority of the fatal intoxications, several drugs may contribute to death (8-11). There is consistent knowledge about the dose-response relationship for specific psychoactive substances and the risk of intoxication is highly related to the drug concentrations, still with individual variations (12). A considerable overlap between concentrations of drugs of abuse seen in living persons and in fatal overdose cases has been reported (12). Possible explanations include the administration route, drug combinations, variable tolerance and metabolism within and between individuals, and post mortem redistribution of drugs.

In order to prevent fatal drug intoxications and to develop appropriate preventive strategies, it is important to be aware of and further understand the interrelationships between risk factors for intoxication, and especially whether such increased risk might be related to drug combinations and concentrations.

The aim of the study was to assess whether those who died from intoxications differed significantly from a group considered as chronic drug users regarding demographical data, choice of drug(s), and blood concentrations.

Materials and Methods

Material

All instances of fatal intoxications in Norway subject to forensic autopsy during 2012 were assessed according to inclusion criteria described by Simonsen et al. (13). The cause of death was determined to be intoxication. Mono-intoxications with ethanol were excluded.

According to the Norwegian Criminal procedure Act, a forensic autopsy is only mandatory where death is suspected to have been caused by a punishable act, in cases where the deceased is unidentified or among deceased younger than 18 years. However, a forensic autopsy is also recommended in suicides, accidents and cases of sudden, unexpected death. Further, the doctor is obliged to report such cases to the police, also including cases of suspected drug related deaths (14). A forensic autopsy is thus not performed in all suspected intoxication deaths, but it is estimated that approximately 90% of the cases are subject to such an autopsy (15).

Whole blood samples collected during autopsies were, for 95% of the cases, analysed at the Department of Forensic Sciences, Oslo University Hospital (OUH). The remaining 5% were analysed at the Department of Clinical Pharmacology, St. Olavs Hospital – Trondheim University Hospital.

In fatal overdoses, several drugs are often detected in blood (16). We do not know whether the pattern of number of drugs and concentrations reflect regular drug use. Therefore, we wanted to compare findings among deceased with findings among a population of living drug users. The preferred comparable data would be findings from non-fatal intoxications, but such data are not available. The comparison with DUID cases was considered the second best option because drivers apprehended by the police often are chronic drug users, reflected in the fact that they frequently test positive for more than one psychoactive substance in high concentrations (17). In a study of apprehended drivers in Norway one or more drugs were detected in

concentrations above the limit for graded sanction corresponding to 0.12% blood alcohol concentration (BAC) in about 40% of the cases (18). Other studies have shown that a significant number of drivers killed in traffic accidents had been apprehended by the police due to impaired driving at previous occasions (19). The DUID cases in the present study thus consist mainly of persons with significant drug use, and represent, to a certain extent, individuals with characteristics similar to those of fatal drug deaths in terms of dangerous/problematic drug use.

Samples from drivers apprehended by the police nationwide due to suspected driving under the influence of drugs and ethanol (DUID) in 2012, were included for comparison of drugs involved, drug concentrations and demographic data. All DUID cases were analysed according to a standard protocol at OUH for ethanol and approximately 40 medicinal substances and illicit drugs.

Samples

From the autopsy cases, only cases with whole blood samples collected from the femoral vein were included in the study. The samples were collected into 20 mL Steriline® tubes (Bibby Sterilin, Staffordshire, UK), containing 0.3 ml 67 % (w/v) potassium fluoride (KF) solution as a preservative. Blood obtained from a peripheral vein from DUID subjects were collected into 5 mL Vacutainer® tubes, containing 20 mg NaF (a preservative) and 143 IU of heparin (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK).

Analyses

The samples were analysed shortly after arrival at the laboratories. Figure 1 illustrates the distribution and analytical principles of the sample handling.

The autopsy samples received at OUH were analysed for around 100 different psychoactive compounds in total. Ethanol screening was performed by an enzymatic method (20) and a positive finding was confirmed by gas chromatography (21). Amphetamines, cannabinoids, cocaine metabolites, and opiates were screened for by an immunological method (22). Screening for other drugs was performed using high-performance liquid chromatography with mass spectrometry detection (LC-MS) (23). Confirmatory analyses were done by gas chromatography with mass spectrometry (GC-MS) or LC-MS (23-26).

In the autopsy samples received at St. Olavs Hospital, whole blood was subjected to specific analyses for alcohols (ethanol, methanol, isopropanol, acetone) using a headspace GC–MS method, and specific analyses for benzodiazepines (diazepam, nordiazepam, oxazepam, nitrazepam, 7-aminonitrazepam, flunitrazepam, 7-aminoflunitrazepam, clonazepam, 7-aminoclonazepam, alprazolam, midazolam), opioids (morphine, codeine, ethylmorphine, oxycodone, fentanyl, buprenorphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), 6-MAM) and amphetamines (amphetamine, methamphetamine, MDMA and MDA) using LC–MS methods. In addition, blood specimens were screened against comprehensive drug libraries (National Institute of Standards and Technology Mass Spectral Library, Forensic Toxicology Retention Time Locking Database/Library and Pfleger/Maurer/Weber Drugs and Pesticides Library for Toxicology) with a GC–MS method. When available, urine was also screened for drugs of abuse using LC–MS and GC-MS methods. Positive screening results, as well as explicit information about drug use in the case histories, were confirmed by specific analyses in blood using LC–MS and GC–MS methods.

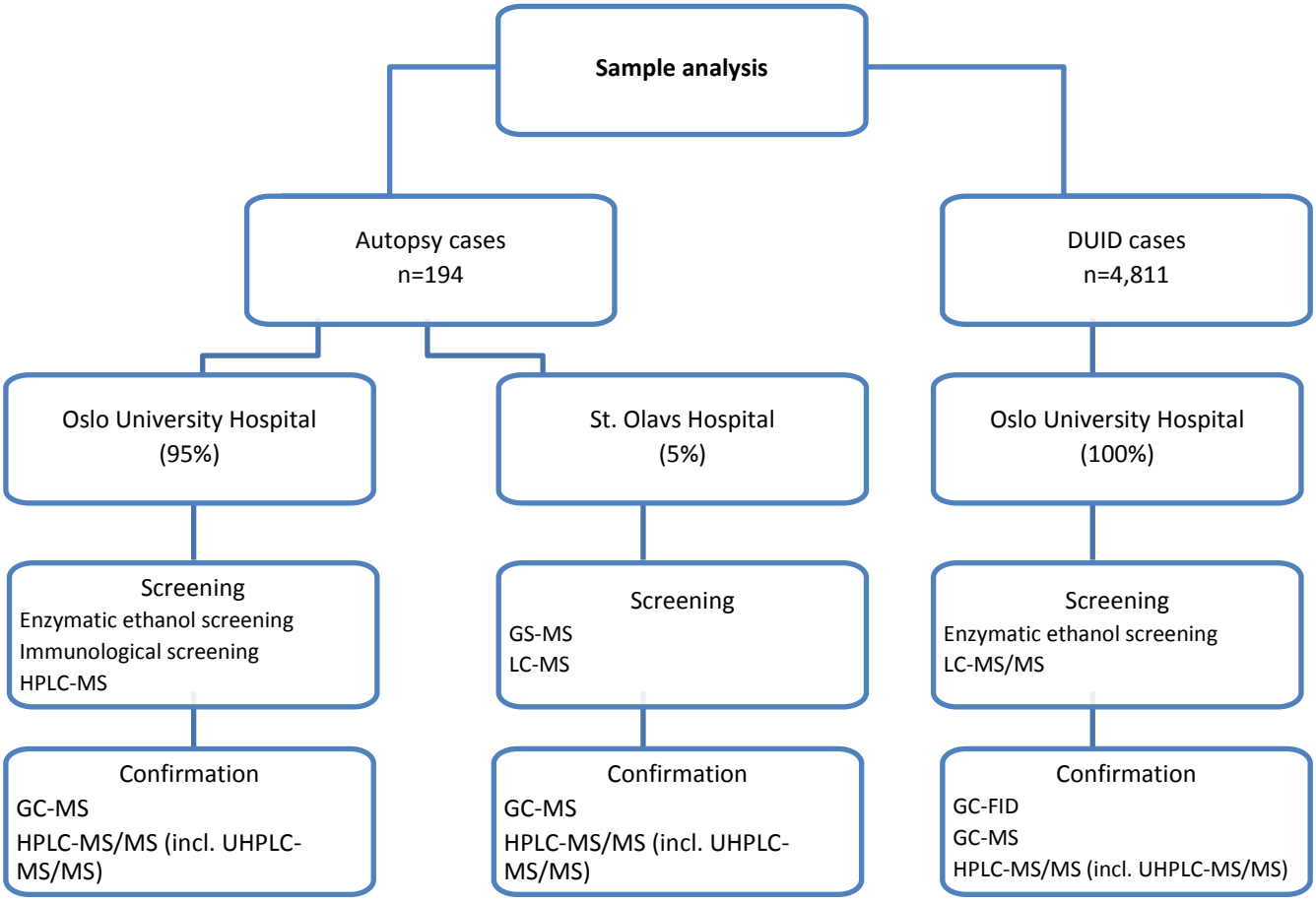

Figure 1: The distribution and analyses of the samples

DUID samples (all analysed at OUH) were screened for ethanol by an enzymatic method (20) and the ethanol concentration was quantified using headspace GC-FID (22). High-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used for analysing a selection of illicit drugs, sedatives, hypnotics and analgesics (27). The confirmation analyses of tetrahydrocannabinol (THC) were done by GC-MS (24), for amphetamine and methamphetamine by GC-MS (26), for benzodiazepines by LC-MS/MS (28), for heroin and its metabolites by LC-MS/MS (29), for other opiates by ultra-high liquid chromatography with tandem mass spectrometry (UHPLC-MS/MS) (30), for gamma-hydroxybutyrate (GHB) by UHPLC-MS/MS (31), for lysergic acid diethylamide (LSD) by UHPLC-MS/MS (32), and for z-hypnotics by UHPLC-MS/MS (33).

Drug groups

The drugs were classified in drug groups for comparison of drug findings- and concentrations. The definitions of the groups are presented below.

Opioids: Included opioids were heroin/morphine, methadone, buprenorphine, oxycodone, fentanyl, hydromorphone, codeine, tramadol and AH-7921.

Heroin is rapidly metabolised to 6-monoacetylmorphine (6-MAM) in blood and further into morphine after intake. Consequently, if 6-MAM is not detected, it is impossible to determine whether heroin or morphine was used. We have therefore defined cases with morphine in blood and/or 6-MAM in blood/urine without a high codeine concentration as heroin/morphine cases on the basis of the toxicological analysis.

Codeine was regarded as a codeine-case if there was no concomitant morphine or if a concomitant morphine concentration was <10% of the codeine concentration (34). If the concomitant morphine concentrations were >10%, the cases were not regarded as codeine cases. Codeine was regarded as a trace amount/pollution if concomitant 6-MAM in blood or urine was present.

Benzodiazepines: Included benzodiazepines were clonazepam, 7-aminoclonazepam, diazepam/nordiazepam, alprazolam, oxazepam, etizolam, phenazepam, flunitrazepam, lorazepam, and nitrazepam. The z-hypnotics zolpidem and zopiclone were added to benzodiazepines due to their similar sedating effects.

Amphetamine/methamphetamine: Methamphetamine is partly metabolised into amphetamine *in vivo* (35). It is not possible to differentiate between intake of pure methamphetamine and intake of a mixture of methamphetamine and amphetamine. These findings were therefore summarized, and denoted "amphetamine/methamphetamine".

Cannabis: Detection of THC in blood above the detection limit was defined as a positive THC-sample.

Ethanol: Ethanol was only included with concomitant findings of the metabolites ethyl glucuronide or ethyl sulphate in the autopsy cases.

Other substances: Substances not eligible to any of the above mentioned groups were called "other substances". This group consists of a variety of substances with a broad spectrum of effects, but the number of cases where these drugs were found was low compared to the other groups. Further analysis of these findings were thus considered unwarranted. Substances in this group were: 2-phenylethylamine, cocaine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), para-methoxyamphetamine (PMA), para-methoxymethamphetamine (PMMA), methylphenidate, methoxetamin, alimemazine, promethazine, amitriptyline, nortriptyline, bupropion, citalopram, duloxetine, fluoxetine, mianserin, mirtazapine, paroxetine, sertraline, trimipramine, venlafaxine, phenytoin, carbamazepine, lamotrigine, pregabalin, valproic acid, hydroxyzine, ketamine, flupenthixol, chlorprothixene, clozapine, levomepromazine, olanzapine, perphenazine, quetiapine, risperidone and LSD.

All of the abovementioned drugs are counted as psychoactive substances in the "Results" section.

Compilation of drug concentrations

The opioid and benzodiazepine concentrations were assessed as morphine and diazepam equivalents, respectively, in order to compare concentrations across the different groups (Table 1). Clonazepam is metabolised into the inactive metabolite 7-aminoclonazepam post mortem (36), and clonazepam itself is rarely detected in autopsy cases. The concentration of 7-aminoclonazepam is therefore regularly used

as a proxy for interpretation of clonazepam concentrations in forensic toxicology cases.

Table 1: Conversion factors for morphine- and diazepam equivalents

Compound	Conversion factor
Morphine equivalents	
Methadone	0.375
Morphine	1.00
Morphine-6-glucuronide	1.00
Oxycodone	0.60
Diazepam equivalents	
Alprazolam	20.0
Nordiazepam	0.50
Diazepam	1.00
Fenazepam	33.0
Flunitrazepam	40.0
Clonazepam	48.0
7-aminoclonazepam	48.0
Lorazepam	6.70
Nitrazepam	3.30
Oxazepam	0.33
Zolpidem	2.00
Zopiclone	6.70

For the DUID cases, only clonazepam is measured and used in evaluation of impairment, since 7-aminoclonazepam is inactive and not relevant for evaluation of impairment.

Diazepam equivalents (37-39) were used to calculate the total benzodiazepine concentration for comparison of concentrations from the fatal intoxication cases with the DUID cases (40). For the autopsy cases, clonazepam was not included in the calculation, only 7-aminoclonazepam, and for the DUID cases the metabolite was not measured, hence only clonazepam-levels were available for consideration and the

concentration was multiplied with 48 to mimic the clonazepam-concentration. For nitrazepam and flunitrazepam, only the parent compounds were included in the calculation in both groups.

Measured levels of methadone, oxycodone and morphine-6-glucuronide (M6G), were expressed as morphine equivalents (40-44). Morphine and M6G have similar effects, but somewhat different potency, and M6G has lower depressant effects on the respiration centre (45). In the present study M6G is regarded as a product of heroin/morphine intake and the concentrations of M6G and morphine considered as equipotent. A number of studies show that M6G is psychoactive (45); therefore it is included in order to evaluate the effects of opioid concentrations.

Statistical methods

Differences in the number of psychoactive substances and concentrations were assessed using Wilcoxon Rank Sum Test in SPSS Statistics Version 22 and 23 (IBM Corporation, Armonk, NY).

Ethics

Approval has been achieved from the Regional Ethics Committee, 2013/786 REK sør-øst B, and from the Public Prosecutor at the Office of the Director of Public Prosecutions, 2013/01346-002 AGJ/ggr 639.2. Only anonymised data is presented in tables and figures.

Results

A total of 194 fatal intoxication cases and 4,811 DUID cases were included. Mean age, age and gender distribution and mean number of drugs detected are presented in Table 2. The age distribution is somewhat lower among the DUID cases, with 57% of the cases being younger than 35 years versus 42% of the autopsy cases. Men were overrepresented in both groups, and the prevalence of men was highest among the DUID cases.

Table 2: Demographic data for both groups

Group	N	Mean age	Age range	Men (%)	Mean number of drugs*	Range, number of drugs
Autopsy	194	37.8	18-66	79	4.9	1-12
DUID	4,811	34.1	14-79	86	2.6	1-10

*incl. ethanol

Toxicological findings in autopsy cases

Among the autopsy cases, only three (1.5%) mono-intoxications were found (Figure 2).

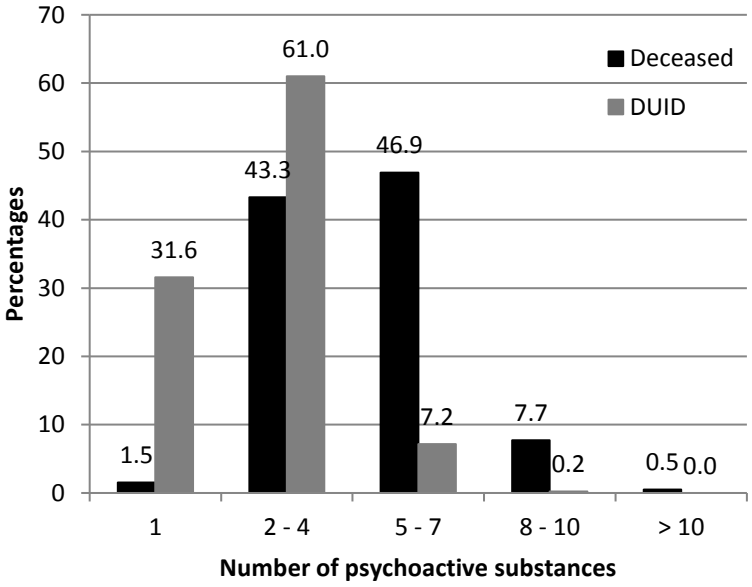

Figure 2: Number of psychoactive substances detected in the autopsy and the DUID group.

Opioids were found in 179 (92%) of the cases, and benzodiazepines in 175 (90%) cases. Amphetamine/methamphetamine was found in 85 (44%) cases and THC in 77 (40%) cases. Ethanol was detected in 28 (14%) cases. “Other substances” were detected in 101 (52%) cases (Figure 3).

Figure 3 shows in more detail the ten most frequently detected substances in the autopsy group, with heroin/morphine (as indicated by findings of 6-MAM and/or morphine; 54%) and clonazepam/7-aminoclonazepam (40% and 54% of cases,

respectively; total of 54%) being the most frequent substances found. Other frequently found substances were diazepam/nordiazepam (44% and 47% of the cases, respectively; total of 50%), amphetamine and/or methamphetamine (44 % of cases), THC (40 % of cases) and methadone (34 %).

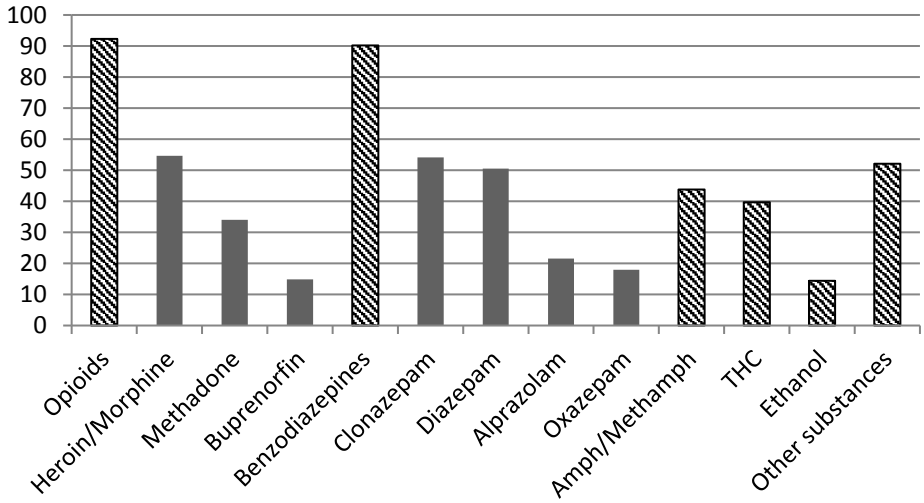

Figure 3: The most frequently found substances in fatal intoxications in 2012 (grey bars), along with total percentage of the positive cases for the different drug groups (shaded bars).

Of the three mono-intoxication cases, relatively high concentrations of amphetamine/methamphetamine (446 ng/mL and 343 ng/mL) were found in two cases; the third case had a methadone concentration of 1238 ng/mL. In the sixteen cases with two different substances opioids were detected in 13 cases, benzodiazepines in 9, THC in 3, ethanol in 2, amphetamine/methamphetamine in 2 cases, and single cases with perphenazine, sertraline, and valproic acid. All of the remaining autopsy cases were poly drug cases with substances from at least two different drug groups.

Toxicological findings in all cases

The autopsy cases were positive for more psychoactive substances than the DUID cases ($p<0.001$; Figure 2).

Higher concentrations of benzodiazepines and opioids were found in the autopsy cases ($p<0.001$), whereas higher concentrations of THC ($p=0.005$) and ethanol ($p=0.04$) were found in the DUID cases. There was no significant difference in the

concentrations of amphetamine/methamphetamine between the two groups (Table 3). The mean diazepam concentration in the DUID cases was nearly three times higher than in the autopsy cases, whereas the nordiazepam concentration was twice as high. The median concentrations of amphetamine/methamphetamine were high in both groups; however, amphetamine/methamphetamine is rarely associated with fatal mono-intoxication (46-48).

Table 3: Median, minimum and maximum concentrations (ng/mL); autopsy and DUID cases

	Autopsy cases (n=194)					**DUID (n=4,811)**					**Wilcoxon Test**
	Valid N	**%**	**Median**	**Min**	**Max**	**Valid N**	**%**	**Median**	**Min**	**Max**	**P=**
Benzodiazepines*	173	89.2	1.76	5.69	45.9	2,887	60.0	1.03	28.5	28.2	<0.001
Opioids**	159	82.0	211	2.85	3.91	403	8.4	40.0	6.56	2.60	<0.001
Amphetamine/ methamphetamine	85	43.8	385	104	5.15	1,997	41.5	343	27.0	5.68	0.386
THC	77	39.7	2.30	0.31	157	1,823	37.9	2.96	0.63	72.3	0.005
Ethanol (‰)	28	14.4	0.85	0.10	4.1	1,698	35.3	1.4	0.04	4.3	0.040

* Diazepam equivalents of alprazolam, nordiazepam, diazepam, fenazepam, flunitrazepam, clonazepam, 7-aminoclonazepam, lorazepam, nitrazepam, oxazepam, zolpidem, and zopiclone. The autopsy cases excluded clonazepam, whereas the DUID cases were not analysed for 7-aminoclonazepam
** Morphine equivalents of morphine, M6G, methadone, oxycodone

Heroin/morphine cases

Heroin/morphine and one or more benzodiazepines was the most frequent drug combination found among the autopsy cases. In total, benzodiazepines were detected in 94 (89%) of the 106 heroin/morphine positive cases, with 7-aminoclonazepam and/or diazepam/nordiazepam being the most frequently found benzodiazepines present in 79 of the heroin/morphine positive autopsy cases. Stimulants were detected in 48 cases (45%), whereas THC was found in 35 cases (33%). Only 14 (13%) of the 106 heroin/morphine positive cases were positive for ethanol. Other substances were detected in 42% of cases. Between two and 12 different substances were found in each heroin/morphine-positive case, with a mean number of 4.9 substances per case.

Heroin/morphine was found in less than 5% of the DUID cases. Among these, the same pattern of combinations was seen, with almost 80% of heroin/morphine positive cases testing positive for benzodiazepines (especially clonazepam and diazepam,

but also alprazolam). The heroin/morphine positive DUID cases were to a lesser degree associated with stimulants (34%) and other substances (9%) than the heroin/morphine positive autopsy cases. In the heroin/morphine-positive DUID cases the total number of different substances varied between one and nine, with a mean number of 3.6 substances per case.

As presented in Table 4, when only taking into consideration heroin/morphine-positive cases, there were still significant differences between autopsy and DUID cases when considering concentrations of benzodiazepines (p=0.036) and opioids (p<0.001), with autopsy cases having the highest concentrations. For THC, there were higher concentrations among the DUID heroin/morphine-positive cases than among the autopsy cases. There were no significant differences in amphetamine/methamphetamine and ethanol concentrations.

Table 4: Median, minimum and maximum concentrations (ng/mL) in heroin/morphine-positive cases; autopsy and DUID cases.

	Autopsy cases (n=194)					**DUID (n=4,811)**					**Wilcoxon Test**
Heroin/morphine cases	106					230					
	Valid N	**%**	**Median**	**Min**	**Max**	**Valid N**	**%**	**Median**	**Min**	**Max**	**p=**
Benzodiazepines*	92	86.8	2.13	5.69	43.6	182	79.1	1.64	71.2	15.5	0.036
Opioids**	106	100	225	2.85	3.91	218	94.8	27.8	7.99	2.60	<0.001
Amphetamine/ methamphetamine	47	44.3	303	10.4	3.20	76	33.0	172	31.1	2.18	0.131
THC	35	33.0	1.79	0.35	15.4	74	32.2	2.69	0.79	18.2	0.049
Ethanol (‰)	14	13.2	1.0	0.10	2.2	24	10.4	1.0	0.04	2.2	0.586

* Diazepam equivalents of alprazolam, nordiazepam, diazepam, fenazepam, flunitrazepam, clonazepam, 7-aminoclonazepam, lorazepam, nitrazepam, oxazepam, zolpidem, and zopiclone. The autopsy cases excluded the concentrations of clonazepam, whereas the DUID cases were not analysed for 7-aminoclonazepam.
** Morphine equivalents of morphine, M6G, methadone, oxycodone.

Discussion

Our study shows that in approximately 90% of the fatal intoxications, opioids were detected, but as a single intoxicant in only one case (0.5%). The median concentration of morphine equivalents was 5 times higher in the fatal intoxications cases than in the DUID cases (Table 3). Benzodiazepines were detected in approximately 90% of the opioid positive fatal cases, indicating that opioids rarely were the sole causative agents in these deaths. Benzodiazepines alone did not

cause fatalities in any cases. The median diazepam equivalent concentration was higher in the fatal intoxication cases than in DUID cases, even though the mean concentrations of diazepam and nordiazepam were highest among the DUID cases. The estimated equivalence concentrations for the benzodiazepines in the autopsy cases were thus based mainly on clonazepam intake prior to death.

Drug combinations

A combination of more than one drug was frequently found in both DUID and autopsy cases. The mean number of drugs per case was almost twice as high among the fatal intoxication cases, thus the number of ingested drugs seems to increase the death risk. A previously published study by Sun et al., and an accompanying editorial in the BMJ, support our findings, and emphasise the increased risk of death when opioids and benzodiazepines are used concomitantly (49, 50). Not surprisingly, the number of opioid intoxications was high in the present study, but the fact that benzodiazepines were concomitantly detected in as many as 90% of these cases, is an important finding. The most frequently found drugs in both autopsy and DUID cases were opioids, benzodiazepines, THC and amphetamine/methamphetamine in different combinations.

Concentrations

Interpretation of concentrations of clonazepam/7-aminoclonazepam is difficult in the autopsy cases, due to post mortem degradation of clonazepam and the formation of 7-aminoclonazepam (36). The 7-aminoclonazepam concentrations found in the autopsy cases were more than twice as high as the clonazepam concentrations in DUID cases, indicating a more widespread exposure for clonazepam among the autopsy cases.

Limitations

There are several limitations when using routine cases for research purposes in order to throw light on drug intoxication deaths. However, these available data are important in order to achieve more knowledge about the lethal drug use patterns in order to prevent drug overdoses.

The estimated equivalence concentrations of opioids did not include all of the analysed opioids, which might underestimate the total load of opioids. However, the most frequently detected opioids (morphine and methadone) were included in the

calculations. The other opioids were detected in less than 15% of the cases and always in low concentrations.

The equivalence concentrations of benzodiazepines were limited by the fact that the nitro benzodiazepines are unstable post mortem (51). Despite that, the equivalence concentrations were significantly higher among the fatal intoxication cases.

Furthermore, post mortem redistribution and formation/degradation make post mortem findings more challenging to interpret than the DUID findings. The concentrations might not be representative for the the ante mortem concentrations (52). The time from drug administration until death will affect the degree of metabolism and excretion prior to death (36, 51, 53). The time period between death and autopsy may vary greatly, and within this period, changes in drug concentrations in the blood samples are likely to take place. Changes in drug concentrations can also be seen in vitro after sample collection (34).

Our study included blood concentrations, but information regarding drug intake is missing. The data can therefore not be used to assess the dosage that lead to intoxication.

Conclusions

Our study has confirmed that fatal intoxications by single substances are rare in Norway (1.5%) and mono-intoxication with heroin was not seen in any of the fatal intoxications that underwent forensic autopsy in 2012. Fatal intoxications were caused by a combination of drugs, with significantly more substances as well as higher total drug concentrations among the autopsy cases. Heroin/morphine are the most frequently detected drugs in fatal intoxications, often combined with benzodiazepines. The combination of opioids and benzodiazepines seemed to represent a particular increased risk of death.

It is important to consider the concentrations of all different psychoactive substances when these cases are categorised for determining the cause of death, since it is very rare that one intoxicant alone causes death. Furthermore, interpretation of the concentrations must be done with caution in poly-intoxications since reference concentrations often are based on mono-intoxications.

These results imply that international statistics regarding an opioid being the main intoxicant should have a shift in focus towards combinations of drugs (especially opioids and benzodiazepines) as a major risk factor for fatal drug overdoses.

Conflict of interest

None

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Table 3: Median, minimum and maximum concentrations (ng/mL); autopsy and DUID cases

	Autopsy cases (n=194)					DUID (n=4,811)					Wilcoxon Test
	Valid N	%	Median	Min	Max	Valid N	%	Median	Min	Max	P=
Benzodiazepines*	173	89.2	1765	5.69	45922	2,887	60.0	1025	28.5	28185	<0.001
Opioids**	159	82.0	211	2.85	3910	403	8.4	40.0	6.56	2597	<0.001
Amphetamine/ methamphetamine	85	43.8	386	9.46	5112	1,997	41.5	333	29.8	5678	0.386
THC	77	39.7	2.20	0.31	157	1,823	37.9	2.83	0.63	72.3	0.005
Ethanol (‰)	28	14.4	0.85	0.10	4.1	1,698	35.3	1.4	0.04	4.3	0.040

* Diazepam equivalents of alprazolam, nordiazepam, diazepam, fenazepam, flunitrazepam, clonazepam, 7-aminoclonazepam, lorazepam, nitrazepam, oxazepam, zolpidem, and zopiclone. The autopsy cases excluded clonazepam, whereas the DUID cases were not analysed for 7-aminoclonazepam
** Morphine equivalents of morphine, M6G, methadone, oxycodone

Table 4: Median, minimum and maximum concentrations (ng/mL) in heroin/morphine-positive cases; autopsy and DUID cases.

	Autopsy cases (n=194)					DUID (n=4,811)					Wilcoxon Test
Heroin/morphine cases	106					230					
	Valid N	%	Median	Min	Max	Valid N	%	Median	Min	Max	p=
Benzodiazepines*	92	86.8	2078	5.69	40997	182	79.1	1651	71.2	15459	0.036
Opioids**	106	100	225	2.85	3910	230	100	28.0	7.99	2597	<0.001
Amphetamine/ methamphetamine	47	44.3	304	9.46	3200	76	33.0	164	31.1	2183	0.131
THC	35	33.0	1.89	0.31	15.7	74	32.2	2.83	0.63	18.9	0.049
Ethanol (‰)	14	13.2	1.0	0.10	2.2	24	10.4	1.0	0.04	2.2	0.586

* Diazepam equivalents of alprazolam, nordiazepam, diazepam, fenazepam, flunitrazepam, clonazepam, 7-aminoclonazepam, lorazepam, nitrazepam, oxazepam, zolpidem, and zopiclone. The autopsy cases excluded the concentrations of clonazepam, whereas the DUID cases were not analysed for 7-aminoclonazepam.
** Morphine equivalents of morphine, M6G, methadone, oxycodone.