



Full length article

## Toxicological oral fluid results among Spanish drivers testing positive on on-site drug controls from 2013 to 2015

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### ABSTRACT

**Background:** Driving under the influence of drugs (DUID) increases the risk of serious injury or death in traffic accidents. The aim of this study was to provide information about DUID in Spanish drivers.

**Methods:** 10,064 oral fluid samples were collected from Spanish drivers that tested positive on the roadside using the Dräger DrugTest 5000 (DDT5000) between 2013 and 2015. Samples were collected using Quantisal™ and analysed by LC–MS/MS at the Toxicology Laboratory of the Institute of Forensic Science of the University of Santiago de Compostela.

**Results:** Drivers were mainly young men (85.1% male,  $29.7 \pm 8.1$  years old). In 98.5% of cases, LC–MS/MS results confirmed at least one of the positive results detected on the roadside. Cannabis (82.4%) and cocaine (42.1%) were the most commonly detected drugs. Poly-drug use was observed in 42.7% of drivers, mostly for all illicit drugs (> 80%) except for cannabis (42.6%). Illicit drug and single-drug use was more frequent among drivers under 35 years old, and medicines and poly-drug use more common among drivers older than 35 years old. The on-site device performance was calculated using both the DDT5000 cut-offs and the LC–MS/MS method LOQs. Sensitivity (> 73% vs > 58%), specificity [ $> 94\%$  for all the compounds regardless the cut-offs used, except for cannabis (71%)] and accuracy (> 87.5% with both cut-offs) fulfilled the DRUID Project requirements in all cases.

**Conclusion:** LC–MS/MS confirmation result was negative in only 1.5% of the cases. The DUID driver profile was a young man, consuming cannabis or a combination of cannabis and cocaine.

### 1. Introduction

The use of illicit psychoactive substances shows a general prevalence about 5% of the adult population worldwide aged 15–64 years (United Nations Office of Drugs and Crime (UNODC, 2017). Cannabis is the most common illicit drug (2.7%–4.9%, depending on the country), followed by amphetamines (0.3%–1.24%), opioids (0.6%–0.9%), opiates (0.27%–0.49%), “ecstasy” (0.19%–0.71%) and cocaine (0.27%–0.46%). Consumption of illicit drugs in Europe is even higher, and Spain is one of the European countries with the highest prevalence of illicit drug use, especially for cannabis (9.5%) and cocaine (2%) (Observatorio Español de la Droga y las Adicciones (OEDA, 2017).

Driving under the influence of drugs (DUID) impairs essential cognitive and psychomotor skills (perception, attention, coordination, reaction time, information processing or visual function), and is associated with behavioural changes (aggressiveness, impatience, competitiveness, excessive self-confidence, recklessness). DUID

increases the risk of serious injury or death in traffic accidents, being a leading cause of global injury mortality and the second cause of preventable traffic death, after speeding (World Health Organization (WHO, 2015).

DRUID (DRiving Under the Influence of Drugs, alcohol and medicines) Project was the most important research project related to drugs and driving in the EU to date. DRUID Project results showed that 7.4% of European drivers tested positive for any psychoactive substance, 3.5% for alcohol, 1.9% for illicit drugs and 1.4% for medicines. These figures in Spanish drivers were 17%, 6.6%, 10.9% and 2%, respectively (Gómez-Talegón et al., 2012). Spain introduced mandatory on-site oral fluid (OF) drug controls in 2010, with a zero-tolerance law. If the on-site screening test is positive or the driver has signs of drug impairment, a second OF sample must be collected and analysed using GC–MS or LC–MS/MS. The Laboratory of Toxicology of the Institute of Forensic Sciences of the University of Santiago de Compostela (USC) was responsible for the confirmation analysis until 2015, so valuable

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epidemiological information about drug use on Spanish roads is currently available.

The main aim of this study was to provide recent information about DUID among Spanish drivers by analysing 10,064 OF samples that previously tested positive on-site using the Dräger DrugTest 5000 (DDT5000) (Dräger Safety AG and Co. KGaA, Lübeck, Germany), in order to: a) know demographic characteristics of the Spanish drivers who tested positive on the on-site OF drug test; b) analyse the prevalence of the different psychoactive drugs detected and the pattern of drug use; and c) assess the performance of the on-site drug test device.

## 2. Material and methods

### 2.1. Participants

Between December 2013 and February 2015, Spanish traffic police officers performed roadside OF drug tests to drivers suspected of DUID, using the DDT5000. Drivers with a positive on-site result donated a second OF specimen, which was collected with the Quantisal™ device (Inmunalysis, Pomona, CA, EE.UU). OF specimens were sent to the Laboratory of Toxicology of the Institute of Forensic Sciences of the USC under cold conditions and keeping the chain of custody.

### 2.2. LC–MS/MS method

A previously published method, with minor modifications, was used for confirmation purposes (Concheiro et al., 2008). The method allows the identification of the main illicit drugs and common psychoactive medicines that cause driving impairment, including morphine, codeine, 6-monoacetylmorphine (6-AM), amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxy-N-ethylamphetamine (MDEA), benzoylcegonine (BE), cocaine, delta-9-tetrahydrocannabinol (THC), ketamine, methadone, zolpidem, zopiclone, alprazolam, clonazepam, oxazepam, nordiazepam, lorazepam, flunitrazepam, diazepam. Briefly, solid phase extraction (SPE) was performed with Strata X cartridges (Phenomenex, Torrance, CA, USA). After loading the sample, two consecutive washes with water:methanol (95:5, v/v) and water:methanol:NH<sub>4</sub>OH (70:29.5:0.5, v/v) were applied. Elution was performed with dichloromethane:2-propanol (75:25, v/v), and dried extracts were reconstituted in a mixture of 0.1% formic acid:acetonitrile (90:10, v/v). Chromatographic separation was performed using an Atlantis® T3 (2.1 mm x 50 mm, 3 µm) column and a gradient with acetonitrile and 0.1% formic acid in water. Detection was conducted using a Quattro Micro™ API ESCI tandem mass spectrometer (Waters Corporation, Milford, MA, USA), operating in electrospray in positive mode (ESI+), and two MRM transitions were monitored for each compound. The method was fully validated, and a limit of quantification (LOQ) of 1 ng/mL was applied for all the analytes.

### 2.3. Comparison of on-site and LC–MS/MS confirmation results

On-site screening results (when available) were compared with the laboratory confirmation results in order to evaluate the DDT5000 performance. Calculated parameters included True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN), Sensitivity, Specificity, and Accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV), when possible (Blencowe et al., 2010). To consider a positive OF sample, both DDT5000 cut-offs (Table 1) and LC–MS/MS LOQs (1 ng/mL) were used. Analytes identified with the LC–MS/MS method and not included on the on-site screening device panel were designated as additional findings (AF).

### 2.4. Statistical analysis

An excel database was created with the information available,

**Table 1**  
Analyte cut-offs (ng/mL) for the Dräger DrugTest 5000 (DDT5000).

Analyte group	DDT5000 cut-off (ng/mL)	Confirmed analyte
Cannabis	25	THC
Cocaine	20	Cocaine BE
Amphetamine	50	Amphetamine
Methamphetamine	35	Methamphetamine MDMA MDA MDEA
Opioids	20	6-AM Morphine Codeine

THC: delta-9-tetrahydrocannabinol; BE: benzoylcegonine; MDMA: 3,4-methylenedioxyamphetamine; MDA: 3,4-methylenedioxyamphetamine, MDEA: 3,4-methylenedioxy-N-ethylamphetamine; 6-AM: 6-acetylmorphine.

including the demographic data (sex, age), sampling date, day of the week, working day or holiday according to the Spanish working schedule, and on-site screening result (positive/negative) and LC–MS/MS (concentration) confirmation results. IBM SPSS Statistics 20.0 software (IBM Inc., IBM Corporation, Armonk, NY, USA) was used to carry out the statistical analysis. For the analysis of quantitative variables (age and analyte concentrations), mean and median values were used as central measures, and standard deviation (SD), maximum and minimum values as measures of dispersion. Qualitative variables were expressed as number of events and frequency (%). In the bivariate analysis, Chi-Square test ( $\chi^2$ , for qualitative variables), Student's *t*-test (for quantitative variables with normal distribution), and Mann-Whitney test (for quantitative variables with no normal distribution) were used. Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to check the fit to a normal distribution. The level of significance was set at  $p < 0.05$ .

## 3. Results

### 3.1. Participants

The laboratory analysed 10,064 OF specimens during the 15-month period of study. On-site screening results were available in 98% of the cases ( $n = 9868$ ). Men accounted for 85.1% ( $n = 8561$ ) of drivers and women for 3.5% ( $n = 351$ ); sex was unknown in 11.4% of the cases ( $n = 1152$ ). Drivers mean age was  $29.7 \pm 8.1$  years old (median = 28; range = 15–83), with 64.2% of the drivers between 15–34 years old (26.9%  $\leq 24$  years old; 37.3% between 25–34 years old; 18.4% between 35–49%; and 2%  $\geq 50$  years old). Age was unknown in 15.1% of the cases. Age was similar between men ( $29.7 \pm 8.1$  years) and women ( $30.2 \pm 8.3$  years) ( $p = 0.197$ ).

### 3.2. Analytical results

#### 3.2.1. LC–MS/MS results

Confirmation of at least one of the on-site positive results detected was possible in 98.5% ( $n = 9912$ ) of the 10,064 OF specimens analysed. Among these drivers, 91.9% used only illicit drugs ( $n = 9106$ ), 0.35% ( $n = 35$ ) only psychoactive medicines, and 7.8% ( $n = 771$ ) both illicit drugs and medicines.

Among the total number of drivers ( $n = 10,064$ ), the most prevalent drug was cannabis (82.4%,  $n = 8294$ ), followed by cocaine (42.1%,  $n = 4237$ ), amphetamines (14.2%,  $n = 1431$ ), heroin (confirmed by the presence of 6-AM) (7.9%,  $n = 796$ ) and ketamine (2.1%,  $n = 215$ ). For cocaine positive specimens, the presence of cocaine and its metabolite benzoylcegonine (BE) were confirmed in nearly all cases, while cocaine was the only analyte detected in two specimens and BE in one specimen. For amphetamine and derivatives, MDMA (9.9%,  $n = 993$ ),

**Table 2**

Mean, median, maximum and minimum concentrations (ng/mL), and standard deviation (SD) observed in the oral fluid specimens analysed by the LC–MS/MS confirmation method.

Drug	N	Mean	SD	Median	Maximum	Minimum
THC	8,294	346.5	1418.2	121.0	107886.1	1.0
BE	4,235	766.6	2981.7	107.6	100096.7	1.0
Cocaine	4,236	2567.6	8022.8	195.6	131456.9	1.7
Amphetamine	857	3049.8	10107.5	604.4	213511.2	1.5
Methamphetamine	64	1074.3	2273.6	125.0	11226.4	1.5
MDA	646	92.8	325.8	23.7	5795.8	1.0
MDMA	993	2128.5	5905.8	286.2	94324.7	1.0
MDEA	11	315.7	940.0	15.8	3147.5	1.3
6-AM	796	6411.7	50968.9	255.0	1323921.0	1.0
Morphine	816	2488.1	10212.0	293.4	216145.8	1.1
Codeine	703	213.2	1344.7	34.4	32166.2	1.0
Ketamine	215	516.1	1316.6	50.4	10073.4	1.0
Methadone	493	456.7	1735.1	127.3	26542.0	1.0
Clonazepam	9	161.3	304.3	4.4	931.2	1.9
Flunitrazepam	4	3.7	1.0	3.3	5.0	3.1
Alprazolam	169	362.3	3343.5	7.2	42865.8	1.0
Oxazepam	32	6.4	6.9	2.9	25.1	1.0
Lorazepam	43	123.3	481.4	7.0	2655.8	1.2
Nordiazepam	210	30.6	139.0	7.5	1828.3	1.1
Diazepam	61	239.2	1463.6	4.1	10891.9	1.0
Zolpidem	10	41.6	59.2	17.0	181.2	2.7

THC: delta-9-tetrahydrocannabinol; BE: benzoylecgonine; MDMA: 3,4-methylenedioxyamphetamine; MDA: 3,4-methylenedioxyamphetamine, MDEA: 3,4-methylenedioxy-N-ethylamphetamine; 6-AM: 6-monoacetylmorphine; N: number of positive cases for each drug.

amphetamine (8.5%, n = 857) and MDA (6.4%, n = 646) were the most frequent analytes, and to a lesser extent methamphetamine (0.6%, n = 64) and MDEA (0.1%, n = 11). Regarding opiates other than heroin, 55 cases tested positive for codeine, nine for morphine and 12 for both codeine and morphine (three cases due to codeine use as morphine/codeine ratio was < 0.1, four to morphine use and five of unknown origin as similar concentrations for morphine and codeine were measured) (Gasche et al., 2004; Jones et al., 2008). AF to other psychoactive medicines not included in the DDT5000 drug panel were detected in 7.5% of drivers (n = 757), methadone being the most frequent analyte detected (4.9%, n = 493), followed by benzodiazepines (3.8%, n = 387) and zolpidem (0.1%, n = 10). Among benzodiazepines, the most prevalent were nordiazepam (2.1%, n = 210) and alprazolam (1.7%, n = 169) and, with a frequency below 1%, diazepam, lorazepam, oxazepam, clonazepam and flunitrazepam. Zopiclone was not detected in any specimen.

Table 2 shows OF concentrations for the analytes identified by LC–MS/MS. Median concentrations ranged between 100–650 ng/mL for most illicit drugs, except for MDA, MDEA and ketamine, which were in the range of 15–50 ng/mL. Minimum concentrations usually corresponded with the method LOQ (1 ng/mL).

**3.2.2. Performance of DDT5000 screening device**

DDT5000 performance was evaluated considering only the OF specimens with on-site screening results available (n = 9868; 98% of the total). To evaluate PPV and NPV, prevalence of substance use among the tested drivers was estimated by multiplying prevalence of

each drug among the confirmed cases by 0.8. Tables 3 and 4 show the parameters for the evaluation of the on-site screening device using the DDT5000 cut-offs and the LC–MS/MS method LOQs, respectively. The lack of agreement between the number of known on-site results (n = 9868) and those shown in the Tables 3 and 4 was due to the presence of a variable number of on-site “invalid” results (0.3%–2.1% of the known on-site results, depending on the drug).

Using the DDT5000 cut-offs, good sensitivity was obtained for all drug groups (81%–95.3%) except for methamphetamine and derivatives (73.5%). Specificity was high for all drugs (≥ 94%), except for cannabis (71%), and accuracy ranged from 87.5% for cannabis to 97.7% for opiates. Using the LC–MS/MS LOQs, sensitivity decreased (ranging from 58% for methamphetamine to 88.7% for cannabis and opiates), and specificity increased for all drugs, especially for cannabis (95.4%).

Positive predictive value (PPV) using the DDT5000 cut-offs ranged between 77.3% (opiates) to 87.7% (cocaine) for all drugs except for amphetamine (65%), while higher values were observed using the LC–MS/MS LOQs, especially for the most prevalent drugs (cannabis = 97.4%, and cocaine = 91.0%). Negative predictive values (NPV) ranged from 88.6% (cannabis) to 99.4% (opiates) using the DDT5000 cut-offs, while lower values (ranging from 81.3% for cannabis to 99.2% for opiates) were achieved using the LC–MS/MS LOQs.

With the DDT5000 cut-offs, the highest % false positive results (% FP) were for cannabis (9.3%) and the lowest for methamphetamine (1.4%), while the highest %false negative results (%FN) were for cocaine (6.1%) and the lowest for opiates (0.7%). Using the LC–MS/MS

**Table 3**

Assessment of the Dräger DrugTest 5000 (DDT5000) performance using the DDT5000 cut-offs.

Drug Group	n*	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Accuracy	PPV (%)	NPV (%)
CAN	9842	6371	916	316	2239	95.3	71.0	87.5	86.4	88.6
COC	9660	3209	352	595	5504	84.4	94.0	90.2	87.7	92.2
AMP	9749	567	283	133	8766	81.0	96.9	95.7	65.0	98.6
MAMP	9721	547	133	197	8844	73.5	98.5	96.6	80.5	97.7
OPI	9659	682	160	64	8753	91.4	98.2	97.7	77.3	99.4

CAN: cannabis; COC: cocaine; OPI: opioids; AMP: amphetamine and derivatives; MAMP: methamphetamine and derivatives; TP: true positive; FP: false positive; FN: false negative; TN: true negative; PPV: positive predictive value; NPV: negative predictive value. PPV and NPV were calculated estimating 80% prevalence of positive on-site results. \*For each analyte, invalid DDT5000 results were observed in 9868-n cases.

**Table 4**  
Assessment of the DDT5000 performance using the LC–MS/MS LOQs (1 ng/mL).

Drug Group	n*	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Accuracy	PPV (%)	NPV (%)
CAN	9842	7208	79	917	1638	88.7	95.4	89.9	97.4	81.3
COC	9660	3332	229	766	5333	81.3	95.9	89.7	91.0	91.0
AMP	9749	587	263	251	8648	70.0	97.0	94.7	67.9	97.3
MAMP	9721	570	110	413	8628	58.0	98.7	94.6	79.1	96.5
OPI	9659	753	89	96	8721	88.7	99.0	98.1	85.6	99.2

CAN: cannabis; COC: cocaine; OPI: opioids; AMP: amphetamine and derivatives; MAMP: methamphetamine and derivatives; TP: true positive; FP: false positive; FN: false negative; TN: true negative; PPV: positive predictive value; NPV: negative predictive value. PPV and NPV were calculated estimating 80% prevalence of positive on-site results. \*For each analyte, invalid DDT5000 results were observed in 9868-n cases.

LOQs, the %FP decreased for all drugs (ranging from 2.7% for amphetamine to 0.8% for cannabis) while, inversely, the %FN increased (ranging from 9.3% for cannabis to 1% for opiates).

### 3.3. Patterns of drug consumption

#### 3.3.1. Single-drug use vs poly-drug use

Detection of single-drug use was frequent (57.3%, n = 5679) in those OF specimens with a positive LC–MS/MS result (n = 9912). Cannabis was the most common drug in single-drug users (83.7%; n = 4754), followed by cocaine (12.8%; n = 727), amphetamine and derivatives (2.5%; n = 140), heroin (0.4%; n = 22), codeine (0.4%; n = 24), benzodiazepines (0.14%; n = 8), ketamine (0.05%; n = 3) and methadone (0.02; n = 1).

Poly-drug use was observed in 42.7% (n = 4233) of the positive cases. Association of two (28.8%; n = 2853) or three (10.4%; n = 1031) drugs was the common trend. Nevertheless, combinations of four (2.9%, n = 286), 5 (0.6%, n = 61) or even 6 (0.02%, n = 2) drugs were also observed. Except for cannabis (42.6%) and codeine (56.9%), poly-drug use clearly predominated for all the substances (≥ 82% of the positive cases) (Table 5).

Table 6 shows the frequency of different drug combinations in poly-drug users. The majority of the drugs were consumed in association with cannabis and/or cocaine. Nevertheless, methadone was usually associated with heroin and cocaine, and ketamine was frequently associated with amphetamines.

Finally, the most popular trends in this population were consumption of cannabis alone (48%, n = 4754), cannabis and cocaine association (19.1%, n = 1889), and cocaine alone (7.3%, n = 727). Other common associations were cannabis, cocaine and amphetamine (4.6%, n = 459), and cannabis and amphetamines (4.6%, n = 456).

#### 3.3.2. Working days vs holidays

On-site drug tests were performed on national holidays in 35.3% (n = 3548) of the cases. No significant differences were found on the

**Table 5**  
Single vs poly-drug users (%) and frequency of combinations (%) for each drug group.

Drug Group	Single-drug use (%)	Poly-drug use (%)	2 substances (%)	≥ 3 substances (%)
Cannabis	57.4	42.6	29.8	12.8
COC	17.2	82.8	52.6	30.2
AMP	9.8	90.2	43.7	46.5
Heroin	2.7	97.3	22	75.3
Ketamine	1.4	98.6	8.4	90.2
Methadone	0.2	99.8	11	88.8
BZD	2.1	97.9	27.1	70.8
Zolpidem	–	100	20	80
Codeine	43.1	56.9	39.7	17.2

COC: cocaine; AMP: amphetamine and derivatives; BZD: benzodiazepines; Heroin: cases with 6-monoacetylmorphine detection.

illicit drugs pattern detected on working days and holidays. However, benzodiazepines and methadone were more frequently detected on working days than on holidays (71.3% vs 28.4%, p = 0.016; and 79.1% vs 20.9%, p < 0.001, respectively).

#### 3.3.3. Men vs women

Illicit drug use was similar in men and women (98.2% vs 97.7%, p = 0.837). On the contrary, benzodiazepines and methadone use was more common in women than in men (5.7% vs 3.9%, p = 0.032; and 8.8% vs 5.0%, p < 0.001, respectively). Poly-drug use was also more common among women (51.2% vs 43.2%), but no statistically significant differences were observed. No statistically significant differences between men and women were neither observed in the number of associated drugs (30% men and 29% women consumed two drugs; and 21.1% men and 14.2% women combined 3 or more drugs).

Fig. 1 shows psychoactive substances frequency within men and women. Cannabis was the most frequent drug in both sexes, followed by cocaine, amphetamines and heroin. However, statistically significant differences on the pattern of drug use between men and women were observed for amphetamine and derivatives (14.3% men vs 28% women, p < 0.001), and for heroin (8.4% men vs 12.8% women, p < 0.001). For the remaining substances, the lower number of positive results did not allow to evaluate the significance of the results. Finally, combination of illicit drugs and psychoactive medicines were detected more frequently among women (12.2% women vs 8% men, p < 0.001).

#### 3.3.4. Young vs old drivers

Drivers under 35 years old represented 64.5% of the positive cases, while only 2% of the drivers were > 50 years old. Fig. 2 shows the prevalence of drug use among the different age groups. Illicit drug use was higher in young drivers (64.5% drivers < 35 years old vs 20.4% drivers aged ≥ 35 years old) while the contrary was observed for psychoactive medicines (26% drivers < 35 years old vs 62% drivers aged ≥ 35 years old). Cannabis and cocaine were the most prevalent drugs regardless the age group. However, among the youngest drivers (≤ 24 years old) cannabis was identified in 92% of the positive cases, followed by cocaine (31.9%) and amphetamine and derivatives (17.5%), while in the oldest drivers (> 50 years old) cocaine and cannabis prevalence was similar (63.1% and 55.6%, respectively), followed by heroin (43.4%). The use of cannabis and amphetamine and derivatives declined with age, while the use of cocaine, heroin and medicines increased. Moreover, single-drug use predominated in drivers < 35 years old, while poly-drug use was observed in 65% of the drivers > 50 years old (Fig. 3).

## 4. Discussion

The present study provides data on the illegal drugs and medicines detected in on-site OF drug controls performed to Spanish drivers between 2013 and 2015, and confirmed in the laboratory. Since drug controls were only performed to drivers suspicious of DUID, this cannot be considered a nationwide representative sample of the general

**Table 6**

Frequency of drug associations in poly-drug users for each drug group (%). Data were calculated related to the total number of positive cases for each drug group.

	Associated with (%)								
	Cannabis	COC	AMP	Heroin	Ketamine	MTD	BZD	Zolpidem	Codeine
Cannabis (n = 8,294)	–	34.6	13.1	4.3	2.1	2.6	2.9	0.1	0.3
COC (n = 4,237)	67.7	–	18.2	16.2	3.8	9.6	6.3	0.2	0.3
AMP (n = 1,431)	75.8	53.9	–	1.5	11.8	1.0	2.4	0.1	0.3
Heroin (n = 796)	44.6	86.2	2.8	–	1.0	51	21.9	0.1	None
Ketamine (n = 215)	79.5	74.9	78.6	3.7	–	None	4.2	None	None
MTD (n = 493)	43.8	82.8	2.8	82.4	None	–	26.2	0.4	None
BZD (n = 387)	62.8	69.5	8.3	45.0	2.3	33.3	–	1.0	1.6
Zolpidem (n = 10)	50.0	90.0	20.0	10.0	None	20.0	40.0	–	None
Codeine (n = 58)	41.4	20.7	6.9	None	None	None	10.3	None	–

COC: cocaine; AMP: amphetamine and derivatives; MTD: Methadone; BZD: benzodiazepines; Heroin: cases with 6-monoacetylmorphine detection; n = number of positive cases for each drug.

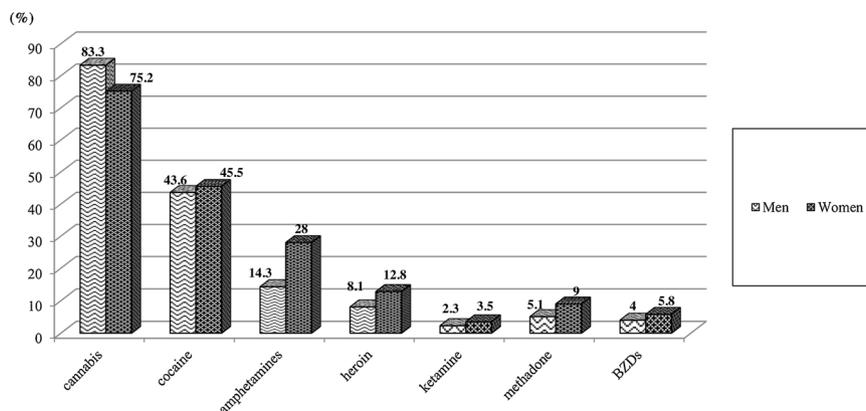
population of drivers. Therefore, these results do not intend to draw the epidemiological profile of drug use among Spanish drivers or to be a prevalence study, but offer important information regarding patterns and trends of psychoactive substances use among them.

Approximately 1/3 of our samples were collected on national holidays. Although we do not know the number of on-site tests performed on holidays compared to workdays, this was probably due to a higher proportion of positive on-site test detected on holidays (as people are more prone to consume recreational substances), and also to the intensification of drug controls performed on these dates. This last reason could represent a bias in the selection of the sample in a prevalence study; however, as mentioned above, this was not the intention of the present work. Sex distribution of the sample (85.1% males and 3.5% females) does not follow the gender distribution in the Spanish general population (49.1% men vs 50.9% women) (Instituto Nacional de Estadística (INE, 2015) nor in the Spanish driving population (57.7% men vs 42.3% women) (Government of Spain, 2018). Although consumption of illicit drugs in Spain is higher in men than in women (2–8 times higher, depending on the drug) (Observatorio Español de la Droga y las Adicciones (OEDA, 2017), it does not justify the large difference between men and women with a positive on-site drug result. However, other Spanish studies showed similar figures. Alcañiz et al. (2018) found a much higher proportion of positive OF tests among men than women (96.3% vs 3.7%) in drug controls where drivers were randomly selected. Arroyo et al. (2008), in a sample of suspected DUID drivers, also reported a similar distribution between sexes (86.6% vs 4.5%). Therefore, although a bias in the criteria for stopping drivers on roadside drug controls cannot be excluded, one plausible explanation for this disproportionally higher prevalence of positive results among male drivers could be a higher tendency of DUID among men. Mean drivers age was 29.7 years old, but near 65% of the cases were < 35 years old, which is in accordance with previous studies (Arroyo et al.,

2008).

Confirmation of at least one of the on-site positive results was possible in 98.5% (n = 9912) of the specimens using the 1 ng/mL cut-off, which is the same percentage than that referred by Arroyo et al. (2008) (83% on-site positive OF tests, and 82% confirmed in the laboratory). Even though on-site results were unknown for 1.9% of the specimens, we globally considered a test as TP when the on-site positive result was confirmed at least for one substance in the laboratory.

In the present study, cannabis was the most common detected drug, followed by cocaine (82.4% vs 42.1%, respectively). Our data are in agreement with the Spanish results of the DRUID Project and subsequent similar studies conducted in 2013 and 2015 in Spain where drivers were randomly selected (Gómez-Talegón et al., 2012; Fierro et al., 2015; Domingo-Salvany et al., 2017). On the contrary, cocaine was the most prevalent drug (49.3% cocaine and 48.4% cannabis) in another Spanish study carried out in DUID drivers (Arroyo et al., 2008), while Alcañiz et al. (2018) found methamphetamine as the second most frequent drug (3.4%) after cannabis (12.4%) in a study performed in 2014 to investigate drug prevalence among Catalanian drivers. The pattern of illicit drug use found in our study is also observed in the Spanish general population, where cannabis and cocaine are the most common illicit drugs (Observatorio Español de la Droga y las Adicciones (OEDA, 2017). Studies carried out in other countries showed very variable results. For example, cannabis was also the most common illicit substance detected in studies performed in Denmark (Simonsen et al., 2012), Belgium and the Netherlands (Houwing et al., 2012) and Hungary (Institoris et al., 2013), where oral fluid specimens from randomly selected drivers were analyzed. In Norway, some authors (Gjerde et al., 2008, 2013; Jamt et al., 2017) found cannabis as the most prevalent drug in randomly selected drivers, while Vindenes et al. (2012) reported methamphetamine and amphetamine as the most common drugs in drivers suspected of DUID. In Italy, cocaine was the



**Fig. 1.** Prevalence (%) of drug consumption by sex (N<sub>men</sub> = 8434; N<sub>women</sub> = 344). [BZDs: benzodiazepines].

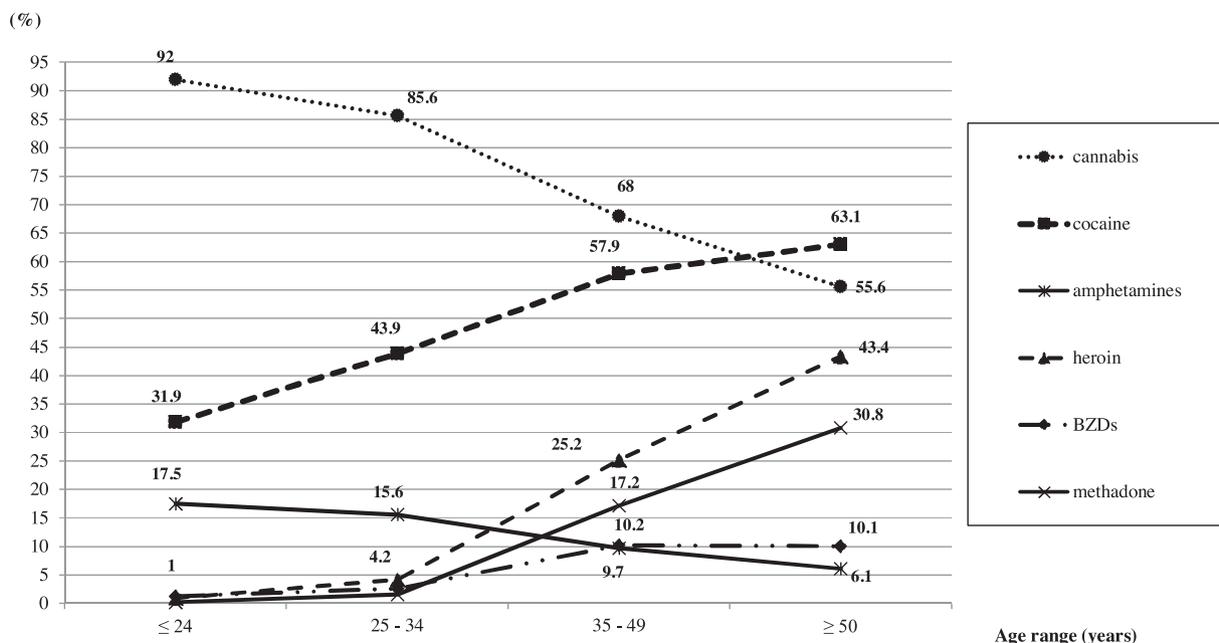


Fig. 2. Trends in drug use (%) by age group. Percentages were calculated referring the number of positive cases for each substance to the total of positive cases within each age group. [BDZs: benzodiazepines].

main detected drug, although followed closely by cannabis (Strano-Rossi et al., 2012). Finally, methamphetamine was the most prevalent drug in Australian drivers (Drummer et al., 2007; Chu et al., 2012; Davey et al., 2014), although in these studies only methamphetamine, MDMA and THC were analysed. These data reflect the high variety of trends in drug use among the different countries.

We only detected benzodiazepines in 3.8% of the cases, nordiazepam being the most prevalent (2.1%), followed by alprazolam (1.7%) and diazepam (0.6%). Benzodiazepines were not included in the DDT5000 panel used by the Spanish traffic police, so they were only detected as AF in cases with a positive on-site result to an illicit drug. For this reason, the calculated prevalence cannot be considered representative of its use in the Spanish drivers' population. In spite of this, benzodiazepines prevalence in our study was higher than that observed

in the DRUID project (Gómez-Talegón et al., 2012), where drivers were randomly selected to perform the on-site drug screening test, and all the specimens (positive and negative) were sent to the laboratory for the determination of drugs of abuse and benzodiazepines.

Regarding drug levels detected in OF, there was a wide concentration range for all the drugs. For each analyte minimum concentrations usually corresponded with the method LOQ (1 ng/mL). The lowest mean concentrations were observed for medicines, mainly for benzodiazepines (2.9–7.5 ng/mL), due to the neutral character of these compounds, which hinders drug transference from blood to OF. However, for most of the analytes maximum concentrations were extremely high (> 10,000 ng/mL), probably due to contamination of the oral cavity in relation to the recent consumption of the drug.

According to the DRUID Project report, on-site screening devices

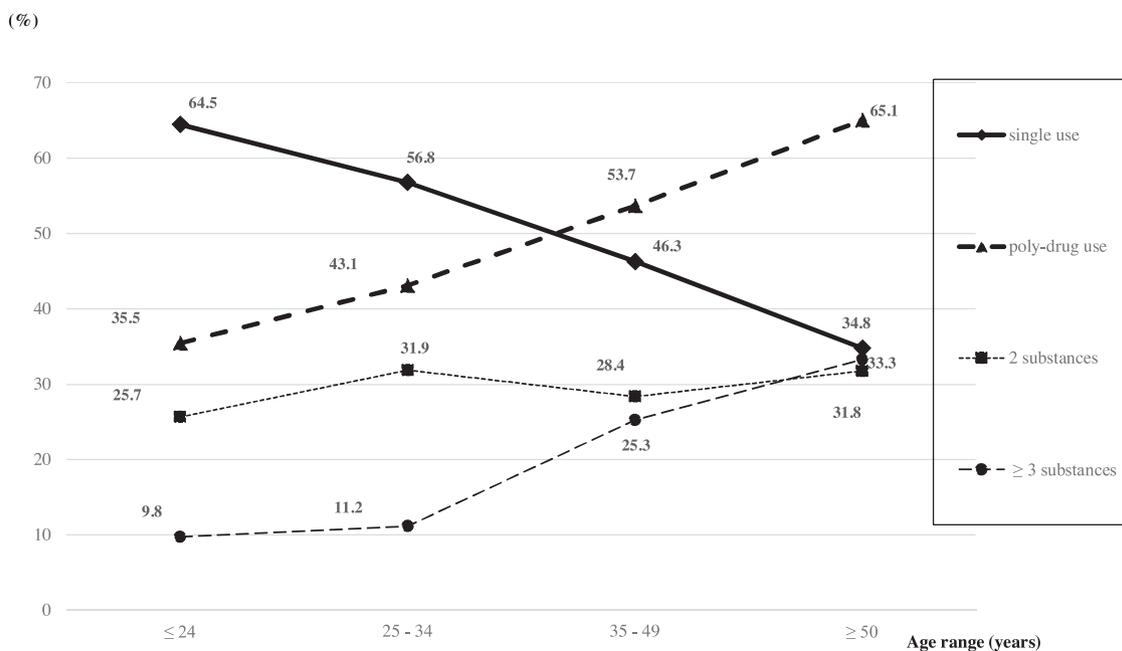


Fig. 3. Distribution (%) of single and poly-drug use by age group.

should provide sensitivity, specificity and accuracy > 80% (Blencowe et al., 2010). Although this criterion could be very lax if drug prevalence is low, in the present study OF specimens were collected from drivers suspected of DUID and, therefore, a high prevalence of positive on-site results is expected. In order to evaluate the performance of the DDT5000, two different confirmation cut-offs were applied, the DDT5000 cut-offs (Table 1) and the LC–MS/MS LOQs (1 ng/mL). Although the DDT5000 cut-offs could seem to be high according to the zero-tolerance legislation in Spain, they actually assure the detection of recent drug use in DUID drivers, while avoiding a high ratio of positive results in drivers who consumed the drug time ago and are not under the influence at the moment of the test.

Globally, the best results were obtained for opiates and cocaine, for which all the evaluated parameters fulfilled the DRUID Project requirements, regardless of the cut-off employed. Regarding PPV and NPV, both depend on the prevalence of substance use among the tested population, and this information was unknown in our study. Nevertheless, Arroyo et al. (2008), in a similar study where drug controls were also performed to Spanish drivers suspected of DUID, reported an 83% of positive on-site tests and a 98.8% rate of confirmation among them (similar to our 98.5% confirmation rate). Therefore, due to the similarity of Arroyo et al. data and our study, we assumed a prevalence of positive on-site tests of 80% (0.8). So, we estimated the prevalence for each drug by multiplying its prevalence among the confirmed cases by 0.8. As expected, when using the on-site DDT5000 cut-offs, better results were achieved in terms of sensitivity and NPV, and, on the other hand, specificity and PPV values increased for all the analytes using the LC–MS/MS LOQs. High PPV figures are crucial as they limit the possibility of erroneously classifying a driver's on-site result as a FP. However, for amphetamine and derivatives PPV values < 70% were observed, regardless the cut-off used. For these compounds the FP results were probably due to the presence of other substances causing the positive on-site result, and not to the lower concentrations found in the OF sent for confirmation. It should also be taken into account that the OF sample analysed in the laboratory was a second sample obtained after the positive on-site result. Therefore, drug concentrations in this sample could be lower than those observed in the first sample analysed on-site. For this reason, in a real setting, cut-offs for lab confirmation should be lower than those used on the on-site drug controls.

To compare our results for the DDT5000 performance with those described in other studies we must bear in mind that some of them used blood for confirmation (Biermann et al., 2004; Wille et al., 2010; Musshoff et al., 2014), which is not directly comparable to results achieved in OF. It is well known that there is no correlation between concentrations found in OF and in blood for several reasons, including oral contamination or the different factors affecting blood/OF analytes diffusion, such as the OF/plasma pH ratio (Wille et al., 2009). Nevertheless, Gjerde et al. (Gjerde et al., 2018), who compared on-site results obtained with the DDT5000 and confirmation results in blood and in OF, reported that in most cases where on-site results could not be confirmed, traces of drugs were found in OF samples. Other factors to take into consideration are the very variable confirmation cut-offs used by different authors (which dramatically affects sensitivity), the prevalence of drug use in the population or the number of samples analysed, as a low number of positive results will increase the specificity. Two research groups used OF as confirmation matrix, and they used the DRUID Project cut-offs to evaluate the performance of different screening devices for the detection of cocaine, cannabis, opiates, amphetamine and methamphetamine (Blencowe et al., 2011; Strano-Rossi et al., 2012). For the DDT5000, Blencowe et al. (2011) tested 223 OF samples, and obtained better specificity (> 89% for all the analytes) than sensitivity (50%–89%). Strano-Rossi et al., analysing around 500 specimens, also reported a higher specificity (> 96.7%) than sensitivity [> 92% for all the analytes, except for methamphetamine (86.4%)]. In our study sensitivity and specificity were similar to the one found by

Strano-Rossi et al. and, as expected, we had less %FP (0.8–2.7% vs 0.25–6%). Nevertheless, as our LC–MS/MS cut-off (1 ng/mL) was lower than the DRUID Project cut-offs, we had more %FN (1.0–9.30% vs 0.25–2.9 %). In our study the DDT5000 met DRUID Project requirements (sensitivity, specificity and accuracy > 80%) in all cases, except for methamphetamine and cannabis when using the DDT5000 cut-offs (sensitivity 73.5% and specificity 71%, respectively), or amphetamine and derivatives (sensitivity 70% and 58%, respectively) using the LC–MS/MS LOQs.

Concerning the pattern of consumption, single drug use predominated over poly-drug use (57.3% vs 42.7%), which agrees with results from a similar study conducted in Spanish drivers (Arroyo et al., 2008). In contrast, in studies describing results from randomly selected drivers, poly-drug use among drivers was lower than 25% (Alcañiz et al., 2018; Wylie et al., 2005; Gjerde et al., 2008; Davey et al., 2009; Houwing et al., 2011, 2012; Simonsen et al., 2012; Insti toris et al., 2013). In our study, all the drugs were usually consumed in combination, except for cannabis. Illicit drug use was more frequent among young male drivers (< 35 years old), while psychoactive medicines, and especially benzodiazepines, were more common among older female drivers ( $\geq 35$  years old), which agrees with the pattern of illicit drugs and medicines consumption in the general population (Observatorio Espa ol de la Droga y las Adicciones (OEDA), 2017) and among Spanish drivers (G mez-Taleg n et al., 2012). Male drivers predominated also among the positive cases found in the DRUID Project and a similar study conducted in 2015 (EDAP'15) (Domingo-Salvany et al., 2017). In addition, the pattern of drug consumption changed with drivers' age, decreasing the use of cannabis and amphetamines, and increasing the use of cocaine, benzodiazepines, heroin and methadone. This tendency also agrees with results from the DRUID Project and EDAP'15 study, except for cocaine.

#### 4.1. Limitations and strengths

A major limitation of this study is the lack of important information for a more comprehensive analysis of drug use among drivers. For example, knowing the total number of tests performed on roadside controls (including also the negative ones) and results of alcohol tests would give a more accurate picture of the problem. In addition, the more appropriate way to assess the performance of the on-site device would be the inclusion of the tests that were negative for all the drugs. Unfortunately, these data were not available, so we evaluate the DDT5000 performance for each drug group with those specimens that were negative for this specific drug (although positive for at least other drug). However, on-site drug controls in Spain are mainly performed on drivers suspected of DUID and, as shown in a similar study (Arroyo et al., 2008), the expected proportion of negative test to all drugs is low. Therefore, in our opinion, the exclusion of these tests may have just slightly influenced our results.

The comparability of our results with those observed in previous studies was difficult due to multiple reasons, including differences in study designs [drivers selection (random, impaired, injured or killed), drugs included, sampling devices, analytical confirmatory methods, screening and confirmatory cut-offs, biological matrices...] or in legislation between countries.

On the other hand, a great strength of this study is the high number of positive samples, with a confirmation positivity rate of 98.5%, being the largest study of these characteristics carried out in Spain covering the national territory. Another strength is the absence of non-response bias (which prevented the loss of positive results), as in Spain it is mandatory for drivers to undergo the roadside OF test.

## 5. Conclusion

The present study evaluates LC–MS/MS confirmation results for more than 10,000 positive on-site drug screening tests performed by the

Spanish traffic police between end of 2013 and beginning of 2015, using the DDT5000 on-site screening device.

In 98.5% of cases, LC–MS/MS results confirmed at least one of the positive results detected on the roadside. DDT5000 satisfied DRUID Project performance requirements regardless the cut-off used, except for methamphetamine and cannabis when using the on-site device cut-off, and for amphetamine/methamphetamine when using the LC–MS/MS cut-off. The DRUID driver profile was a young man (< 35 years old), consuming cannabis or a combination of cannabis and cocaine.

## Contributors

José Ángel Lema Atán elaborated the database including all the information available related to the real specimens (date/time of collection, donor, results, etc) and wrote the draft of the manuscript. Ana de Castro Ríos performed the analysis of the real specimens, and assisted in the interpretation of the results and manuscript writing. Elena Lendoiro performed the analysis of the real specimens, and assisted in the interpretation of the results and manuscript writing. Manuel López-Rivadulla: assisted in the interpretation of the results and revised the draft manuscript. Angelines Cruz performed the statistical analysis and assisted in the interpretation of the results and manuscript writing. All authors have approved of the final manuscript for submission.

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## Conflict of interest

No conflict declared.

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