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Review Article

A review of drug abuse in recently reported cases of driving under the influence of drugs (DUID) in Asia, USA, and Europe

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ABSTRACT

Driving Under the Influence of Drugs (DUID) is considered a serious issue related to the abuse of illegal drugs. DUID cases, including deaths, are being continuously reported in Asia, USA, and Europe. This literature review focuses on illegal drug abuse in recent DUID cases reported in Asia, USA, and Europe. To determine illegal drug abuse in DUID suspects, previous studies collected and analyzed biological samples, such as blood, urine, oral fluids, and hair. In addition, there were forensic autopsies and surveys for investigation of illegal drugs in DUID cases and drivers. In previous studies, ketamine, morphine, methamphetamine (MA), and khat were mainly reported in Asia, whereas amphetamine, benzodiazepines (BZDs), and cannabinoids were mainly reported in USA, and synthetic cannabinoids (SCs), opiates, and cocaine were mainly reported in Europe. Since DUID suspects related to illegal drugs have been frequently reported in Asia, USA, and Europe, there is a need to plan for national monitoring for drivers or motor vehicles to regulate and prevent drug abuse and relevant DUID cases.

Contents

1. Introduction

Traffic accidents associated with driving under the influence (DUI) of alcohol are considered a serious problem worldwide, and these concerns have resulted in the establishment of regulations to monitor

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and prohibit DUI of alcohol. However, driving under the influence of drugs (DUID) is also a serious problem, and one that is being steadily reported. According to recent studies, cocaine, amphetamine, tetrahydrocannabinol (THC), opiates, and methadone are frequently detected in oral fluid samples in the USA [1], Brazil [2–4], Norway [3], Spain [5], Italy [6–7], and Hungary [8], and these studies concluded that amphetamine, cannabinoids, cocaine, and opiates were highly abused and globally associated with DUID. However, ketamine was highly detected among samples of impaired drivers in Hong Kong in 2016 [9], and chlorpheniramine and benzodiazepines (BZDs) were highly detected in alcohol-positive blood samples obtained from Korean drivers in 2016 [10], which suggests that the drugs most frequently detected in samples related to DUID differ in Asia, USA, and Europe. Although fewer DUID cases are reported in Asia than USA and Europe, DUID is a serious problem in Asia, and thus, there is a need to investigate the prevalence of DUID and drug abuse in Asia.

This review focuses on the prevalence of DUID cases in Asia, USA, and Europe and compares illegal drugs related to DUID cases in these three geographical regions. In this review, illegal drugs associated with DUID were described in order of biological samples, autopsies and surveys.

2. Methods

A comprehensive literature search was conducted to determine the current prevalence of DUID in Asia, USA, and Europe. Investigations of DUID cases in Asia, USA, and Europe were conducted using combinations of keywords such as “Asia”, “USA”, “Europe”, and “DUID” in PubMed. To identify papers that addressed the detection of drugs related to DUID using biological samples, keywords, such as, “drug”, “driving”, “detection”, “blood”, “oral fluids”, “urine”, “oral”, “hair” or “biological sample” were included. In addition, this review investigated recent papers described illegal drugs related to DUID identified in autopsies and surveys using keywords including “postmortem” or “autopsy” or “survey”. The legislations on DUID established in each region were also investigated to compare the difference in illegal drugs reported in DUID cases. To investigate recent DUID cases, papers published from 2013 to 2018 were included. To investigate the trend of drug abuse related to DUID, this study excluded papers for only DUI of alcohol without illegal drugs. In addition, this study excluded papers that only focused on the development of analytical methods for determination of illegal drugs without application of analytical method for actual biological samples.

3. Results and discussion

We excluded duplicates and confirmed the relevance with this review to select references. In particular, we focused on; 1) recent DUID cases and 2) drugs frequently reported to be involved in DUID cases in Asia, USA, and Europe. As a result, a total of 61 papers were included. In this literature review, DUID cases and relevant illegal drugs reported between 2013 and 2018 in Asia, USA, and Europe were described in order of the biological samples and other cases including autopsies and surveys. In addition, this review described illegal drugs and psychoactive substances in three regions and we did not discuss the concentrations of illegal drugs detected in biological samples because the legal limits for concentrations would vary from region to region.

3.1. Recent DUID cases reported in biological samples

3.1.1. Blood

Among diverse biological samples, blood analysis studies related to DUID cases have been conducted steadily. In Asia, blood analysis studies related to DUID cases were reported in Hong Kong, Turkey, Jordan, and South Korea. Ketamine was frequently detected followed by MA and cocaine/benzoylecgonine in Hong Kong [9] and barbiturates, BZDs, cannabinoids, and cocaine were detected in blood samples collected from DUID suspects in Turkey [11]. Barbiturates and BZDs were detected in blood samples from car accident victims in Jordan though other drugs, such as, cocaine, amphetamine, and cannabinoids, were not detected in any sample [12]. One study targeted blood samples positive for alcohol to investigate DUID in South Korea. In the blood analysis, BZDs (diazepam, nordiazepam and temazepam) were detected [10], suggesting that there was a need to carry out national monitoring project to investigate DUID in random drivers. These results showed that BZDs were frequently detected followed by cannabinoids, barbiturates, and cocaine in blood samples collected from Asian drivers.

In USA, cannabinoids and stimulants were frequently identified drugs in blood samples collected from DUID suspects and victims of car accidents including death cases [13]. THC [14] and cannabinoids [15,16] were also detected in blood samples from DUID drivers. Among blood samples positive for cannabinoids, cocaine/benzoylecgonine and MA/amphetamine were also identified [15]. Alpha-pyrrolidinovalerophenone (α-PVP, a sympathomimetic drug) was detected in blood samples collected from DUID suspects [16]. In other studies, BZDs, MAs, opiates [17], carisoprodol/meprobamate, and zolpidem [18], carfentanil, fentanyl/norfentanyl [19] were detected in the blood samples of DUID cases. In addition, MA/amphetamine, cannabinoids, cocaine, and opiates, cocaine were also detected in blood samples collected from drivers related to motor vehicle accidents [20]. These results showed that there were a variety of drugs related to DUID, including cannabinoids, THC, cocaine, MAs, α-PVP, opiates, and BZDs in USA.

As for the Europe, the most commonly detected SCs were AM-2201 and JWH-018 in blood samples from DUID cases followed by JWH-122, JWH-250, JWH-081, and RCS-4 in Norway. Other drugs, such as, amphetamines, LSD, ketamine, and THC were also detected [21]. In addition, MA/amphetamine, THC [22,23], and methiopropamine [23] were commonly detected in arrested drivers’ samples. SCs were commonly detected and there were positive results for the combination of SCs with cannabinoids and other substances, such as amphetamine, cocaine, diazepam, and morphine in Germany [24]. Frequently detected drugs were amphetamine [25,26] and MA [26] in Sweden. In addition, positive blood results for amphetamine were found to have increased since 2001 among DUID cases [26]. Midazolam and zolpidem were commonly detected and combinations of sedative agents with stimulants, such as amphetamine, and designer drugs including 3,4-methylenedioxypyrovalerone (MDPV) and 2-DPMP, and SCs were also detected in Finland [27]. In addition, the most frequently detected drugs were amphetamines followed by BZDs, cannabinoids, MDPV, and opiate in DUID cases in Finland [28]. Blood samples related to DUI were re-analyzed and positive results were obtained for cannabinoids, cocaine, MDMA, and morphine in Switzerland [29]. Positive results were obtained for cathinone, phenethylamines, and SCs [30] and 3-methylmethcathinone (3-MMC) and other NPSs, such as α-PVP, and conventional drugs, such as, BZDs (diazepam/nordiazepam, midazolam, alprazolam, clonazepam/7-aminoclonazepam) and MA were detected in blood samples related to DUID and car accidents in Poland [31]. Cannabinoids was most frequently detected followed by amphetamine, BZDs, cocaine, MDMA/methyl-amphetamine, opiates in DUID cases in the UK [32]. Cocaine was the most commonly detected drug followed by cannabinoids, opiates, methadone, and amphetamine [33] and blood samples collected from Padova province showed positive results for amphetamines, barbiturates, BZDs, cannabinoids, cocaine, ketamine, and opiates in Italy [34]. In addition, buprenorphine, cannabinoids [35], barbiturates, BZDs [36], opiates [35,36], amphetamine, cocaine, methadone [35,36] were also detected. In another study, various drugs including amphetamine, cocaine, clonazepam, methadone, morphine, THC were in Denmark [37] Though there was a difference among

countries, a lot of illegal substances including SCs, THC, MA/amphetamine, cocaine, MDPV, cannabinoids, MDMA, cathinone, 3-MMC, and α-PVP were identified in blood samples collected from DUID cases in Europe.

Blood samples were commonly analyzed in Asia, USA, and Europe. In the analytical results, there was a difference in the kinds of drugs detected in blood samples among regions. BZDs, cannabinoids, and cocaine were commonly detected in blood samples in all regions. Only a few drugs were identified in blood samples in Asia while a variety of NPSs, such as, α-PVP, MDPV, MDMA, and 3-MMC, were identified in Europe.

These results indicated that 1) less DUID cases occurred in Asia than USA and Europe and 2) the number of drugs abused in Europe was higher than in Asia and USA. However, there is a need to national investigation for DUID cases related to drug abuse because the abuse of drugs has been commonly reported in Asia and USA.

3.1.2. Oral fluids

In case of oral fluids, MA and morphine were detected in China [38] while more various drugs including amphetamine, BZDs, cannabis, cocaine, MA, opiates, and THC were detected in USA [39–41]. In Europe, 6-acetylmorphine, codeine, methadone, morphine, opiates [42], cannabis, and cocaine were detected in oral fluids in Spain [43]. In addition, a single drug was frequently detected in young Spanish drivers (<35 years) and poly drugs in older Spanish drivers (>35 years) [43]. Amphetamines, BZDs, and THC were frequently detected drugs in Norway [22,44,45]. Three kinds of on-site oral fluid devices for DUID were evaluated with random samples and THC [46,47], amphetamine, BZDs, cocaine, MA, and opiates [46] were detected in Germany.

The number of previous studies for oral fluids was less than blood analysis and there was no big difference for illegal drugs related to DUID between regions. Morphine and MA were commonly detected in all regions while opiates, cannabinoids, cocaine, THC, BZDs, and amphetamine were also detected in oral fluids in USA and Europe, which indicated that oral fluids tests enabled to detect various drugs. However, previous studies evaluated oral test tool for determination of illegal drugs and concluded that oral fluid was not the best biological matrix due to its poor validation results, such as, low sensitivity and specificity [46] and a potential risk for not detecting drugs in oral fluids [41]. In addition, previous study described that oral fluid was more acidic than blood, which caused high concentration of basic drugs, such as, cocaine and amphetamines in oral fluids [48]. Therefore, there was a need to consider a potential uncertainty of oral fluids for determination of illegal drugs related to DUID cases.

3.1.3. Urine

Urine analysis for DUID suspects was performed between 2013 and 2018 in Asia, USA, Europe. Cocaine/benzoylecgonine, ketamine, MA, and morphine were detected in Hong Kong [9]. On the other hand, 12 SCs' metabolites including UR-144N-pentanoic acid, JWH-073 butanoic acid, JWH-018 petanoic acid were detected in urine samples in USA [49].

Cannabinoids were the most commonly detected drugs in urine samples followed by amphetamine, buprenorphine, cocaine, methadone, and opiates in Italy [33]. In addition, urine samples were collected from subjects in license regranting program and BZDs, cocaine, ketamine, and THC were detected in Northeast Italy [50].

In case of urine analysis, a previous study pointed out the low accuracy of urine sample in identification of low drug concentrations compared with blood though amphetamine, cocaine, MA, and THC were detected in urine samples collected from drivers in Belgium, Finland, Italy, and Norway [51] This result suggested that there is a need to consider the accuracy of urine analysis. By comparing the drugs related to DUID cases between regions, all drugs detected in urine were different from region to region. In urine samples, MA and ketamine were detected in Asia and SCs and its metabolites were detected in USA whereas cocaine, opiates, amphetamine, ecstasy, cocaine, BZDs were detected in Europe.

Table 1
Summary of DUID cases reported between 2013 and 2018 in Asia.

Biological sample	Country	Subjects (N)	Subjects' characteristics	Related illegal drugs	Published year	References
Blood	Hong Kong	Drivers (223)	Most male (95%)	Cocaine/ benzoylecgonine Ketamine MA	2016	[9]
	Turkey	Suspects for DUI (91)	Most male (85.7%) Age range: 14–64 Mean age: 32.9 ± 11.7	Barbiturates BZDs Cannabinoids Cocaine	2013	[11]
	Jordan	Car accident victims (311)	Most male (82.6%) Age range: <18–60>	Barbiturates BZDs	2016	[12]
	South Korea	Drivers (275)	Positive results for alcohol test	BZDs	2016	[10]
Oral fluids	China	Drivers arrested due to DUID	–	MA Morphine	2016	[38]
Urine	Hong Kong	Drivers (223)	Most male (95%)	Cocaine/ benzoylecgonine Ketamine MA Morphine	2016	[9]
Forensic autopsy	Iran	Dead drivers from car accidents (106)	Most male (98.1%) Age range : 11 – >50	Amphetamine BZDs Morphine	2013	[53]
Survey	Iran	Motorcyclists (414)	Male Age range: 14–64 Mean age: 27.0 ± 9.3	Cannabis Opiates	2016	[55]
	Iran	Car drivers motorcyclists related to road traffic accidents (n = 441)	Most male Age range: 14–68	Cannabis MA Opiates	2017	[56]
	Saudi Arabia	Drivers collected randomly (215)	Age range: 22–89 Mean age: 47.8 ± 11.9	Khat	2017	[57]

3.1.4. Hair

Hair analysis was conducted to investigate drug use history during license regranting program of drivers disqualified for driving due to DUID. However, because hair analysis results could not be directly associated with DUID case, hair samples would not be generally used to detect DUID. In a previous study, cocaine was the most frequently detected drug followed by morphine and THC in Italy. Positive results were obtained for multiple drugs, such as, the combination of cocaine with morphine or THC [52]. In addition, amphetamines-like drugs, cocaine, ketamine, THC, and the combination of THC and cocaine were detected in hair samples collected from subjects in license regranting program [50]. These results indicated that hair analysis enabled to investigate illegal drugs abused in long-term and to suggest the need for stricter regulations for license regranting of drivers related to DUID cases in Europe.

3.2. Recent DUID cases reported in other cases

3.2.1. Autopsies

Forensic autopsies for the identification of DUID cases were conducted in Asia, USA, and Europe. Many of death cases related to car accidents were negative for toxicological tests, but amphetamine, BZDs, and morphine were detected in blood and tissue samples in Iran [53]. Among the deaths associated with DUID cases, cannabinoids [15], carfentanil, 3-methylfentanyl, 2-furanyl fentanyl, acetyl fentanyl, and fentanyl/norfentanyl were detected in blood and vitreous humor samples collected from postmortem cases in USA [19]. Forensic autopsy cases showed positive results for BZDs, heroin/morphine, MA/amphetamine, opiates, and THC in whole blood samples from femoral vein in Norway [54]. Morphine, BZDs, and amphetamine were detected in both Asia and Europe,

Table 2
Summary of reported DUID cases between 2013 and 2018 in the USA.

Biological sample	Subjects (N)	Subjects' characteristics	Related illegal drugs (Detected rate)	Published year	References
Blood	Dead drivers from car accidents (16,942)	Most male (78%) Age range: 16–34	Cannabinoids Stimulants	2013	[13]
	Drivers related to DUID (12,082)	Most male (87%) Age range: 14–77 Median age: 24	THC	2014	[14]
	DUID drivers	Most male Age range: 14–68 Mean age: 30.8	Cannabinoids Cocaine/benzoylecgonine MA/amphetamine	2015	[15]
	Suspects (21)	Most male Age range: 22–59	α-PVP Cannabinoids	2016	[16]
	DUID drivers (170)	–	BZDs MA Opiates	2016	[17]
	Suspects for car accidents (11,621)	Most male (74%) Age range: ≤ 20 – > 61	Carisoprodol/meprobamate Zolpidem	2017	[18]
	DUID with heroin use history (1) without heroin use history (25)	–	2-furanyl fentanyl 3-methylfentanyl Acetyl fentanyl Carfentanil Fentanyl Norfentanyl	2017	[19]
	Drivers related to motor vehicle crashes (174)	Most male (83%) Age range: more than 15 years	Amphetamine/MA Cannabis Cocaine Opiates	2018	[20]
Oral fluids	Subjects arrested for operating while intoxicated	Most male (79%) Age range: 18–72	Amphetamine BZDs Cannabis Cocaine Opiates	2017	[39]
	DUID suspects (88)	Age range: 18–65	Amphetamine BZDs Cocaine Methamphetamine Opiates THC	2017	[40]
	DUID suspects	–	Amphetamine BZDs Cocaine Methamphetamine THC	2018	[41]
Urine	Suspects for car accidents (526)	In 19 SC-positive cases Most male (79%) Age range: 22–53 Mean age: 33.3	SC metabolites UR-144 N-pentanoic acid JWH-073 butanoic acid JWH-018 petanoic acid	2016	[49]
Forensic autopsy	Dead drivers from car accidents	Most male Age range: 14–68 Mean age: 30.8	Cannabinoids	2015	[15]
	Postmortem with heroin use history (4) without heroin use history (94)	–	2-furanyl fentanyl 3-methylfentanyl Acetyl fentanyl Carfentanil Fentanyl Norfentanyl	2017	[19]

Table 3
Summary of DUID cases reported between 2013 and 2018 in Europe.

Biological sample	Country	Subjects (N)	Subjects' characteristics	Related illegal drugs (Detected rate)	Published year	References
Blood	Norway	DUID cases (726)	Most male	SCs (2.2%) AM-2201 (0.7%) JWH-018 (0.7%) JWH-122 (0.4%) JWH-250 (0/1%) JWH-081 (0.1%) RCS-4 (0.1%) Amphetamines LSD Ketamine THC	2014	[21]
		Arrested drivers (2738)	Most male Age range: $\leq$ 25 – > 64	Amphetamine/MA THC	2014	[22]
		DUID suspects (1231)	All Male Age range: 20 – > 50 Mean age: 31	Amphetamine/MA Methiopropamine THC	2016	[23]
	Germany	Criminal and traffic offences (2201)	In 12 SCs positive cases All male Age range: 18–38 Median age: 22	Amphetamine Cocaine Diazepam Morphine	2014	[24]
	Sweden	Dead drivers from car accidents (2696)	Most male (95%) Age range: 16–67 Mean age: 37 $\pm$ 11.4	Amphetamine MA	2015	[25]
		Amphetamine users (69,001)	Most male (87%) Average age: 33–39	Amphetamine	2013	[26]
	Finland	DUID cases (13,248)	In positive cases Most male (84.8%) Age range: 14–88 Mean age: 33.5	2-DPMP Amphetamine MDPV Midazolam Zolpidem	2015	[27]
		MDPV-positive DUID cases (486)	In positive cases Most male (86%)	Amphetamines BZDs Cannabinoids MDPV Opiates	2015	[28]
	Swiss	Drivers related to DUI (500)	–	Cannabinoids Cocaine MDMA Morphine	2016	[29]
	Poland	NPS cases including DUID (1058)	Most male Age range: 16–50 Mean age: 25.4 Median age: 24.5	Cathinone Phenethylamines SCs	2016	[30]
		Investigated blood samples (5200)	In 3-MMC users Most male (93.7%) Age range: 17–50 Average age: 25.9 Median age: 26.0	3-MMC α-PVP BZDs MA	2016	[31]
	UK	Car drivers and motorcyclists (118)	Most male (88%) Age range: 17–86	Amphetamine BZDs Cannabinoids Cocaine MDMA/methyl-amphetamine Opiates	2017	[32]
	Italy	Drivers related to traffic accidents (1730)	Most male Age range: 16 – > 50	Amphetamine Cannabinoids Cocaine Methadone Opiates	2017	[33]
		Drivers related to road accidents in Padova province (4443)	–	Amphetamines Barbiturates BZDs Cannabinoids Cocaine Ketamine Opiates	2018	[34]
		Drivers related to road traffic crashes (1258)	Most male (85%) Age range: 13–89	Amphetamine Buprenorphine Cannabinoids Cocaine Methadone Opiates	2018	[35]
		Injured drivers related to road accident (1797) during 8 years (2009–2016)	–	Amphetamine Barbiturates	2018	[36]

Table 3 (*Continued*)

Biological sample	Country	Subjects (N)	Subjects' characteristics	Related illegal drugs (Detected rate)	Published year	References
				BZDs Cocaine Methadone Opiates		
	Denmark	DUID suspects (11,493)	–	Amphetamine Clonazepam Cocaine Methadone Morphine THC	2018	[37]
Oral fluids	Spain	Spanish drivers (179,645)	In positive results for drug tests (65,244) Most male (94%) Age range: 18–64	6-acetylmorphine Codeine Methadone Morphine Opiates	2018	[42]
		Spanish drivers (10,064)	Most male (85.1%) Age range: 15–83 Median age : 28	Cannabis Cocaine	2018	[43]
	Norway	Drivers (5034)	–	Amphetamines BZDs THC	2018	[44]
		Controls (9375)	–	Amphetamines BZDs THC	2014	[22]
		Car drivers and motorcyclists (3228)	Most male Age range : ≤ 25 – > 65	Amphetamines BZDs THC	2017	[45]
	Germany	Drivers (1212)	–	Amphetamine BZDs Cocaine MA Opiates THC	2014	[46]
		On-site screening sample (70)	–	THC	2014	[47]
Urine	Italy	Drivers related to traffic accidents (1730)	Most male Age range : 16 – > 50	Amphetamine Buprenorphine Cannabinoids Cocaine Methadone Opiates	2017	[33]
		Drunk-drivers (2160)	–	BZDs Cocaine Ketamine THC	2018	[50]
	Belgium Finland Italy Norway	Drivers in Belgium, Italy, Finland, and Norway	–	Amphetamine Cocaine MA THC	2015	[51]
Hair	Italy	DUID suspects	Most male (94%) Age range: 18–60	Cocaine Morphine THC	2014	[52]
		Drunk-drivers (2160)	–	Amphetamine-like drugs Cocaine Ketamine THC	2018	[50]
Forensic autopsy	Norway	Autopsy cases (194)	Most male (79%) Age range 18–66 Mean age: 37.8	BZDs Heroin/morphine MA/amphetamine Opiates THC	2017	[54]

which indicated that these drugs were commonly abused. In addition, forensic autopsies enabled to determine various drugs including emerging drugs, such as carfentanil.

3.2.2. Survey

A survey using questionnaire was conducted for motorcyclists and there was a high prevalence for cannabis and opiates in Iran [55]. In addition, opiates were reported as the most commonly used drug in drivers followed by cannabis and MA [56] while khat was reported as the most frequently used drug in drivers including motorcycle and heavy trucks in Saudi Arabia [57].

3.3. Illegal substances reported in recent DUID cases

A variety of illegal substances related to DUID cases were reported in Asia, USA, and Europe. This review summarized recent DUID cases reported in Asia (Table 1), USA (Table 2), and Europe (Table 3) and described illegal substances reported only in each region (Table 4) and frequently reported in all regions (Table 5).

Table 4
Illegal drugs identified only in each region.

Region	Illegal drugs (Detected rate)	Biological samples	Country	Subjects' characteristics	References
Asia	Khat	Interview survey	Saudi Arabia	Drivers collected randomly (n = 215) Age range: 22–89 Mean age: 47.8 ± 11.9	[12]
USA	α-PVP (85.7%)	Blood	–	Suspects (n = 21) Most male Age range: 22–59	[22]
	Fentanyl (58.9%) Norfentanyl (51.6%) Carfentanil (0.2%) 2-furanyl fentanyl (0.1%) Acetyl fentanyl (0.1%) 3-methylfentanyl (0.1%)			[With use history of heroin] DUID & postmortem (n = 5) [Without use history of heroin] DUID & postmortem (n = 119)	[25]
Europe	MDMA (2.4%)		Norway	Arrested drivers (n = 2738) Most male Age range: ≤ 25 – > 64	[30]
	Methiopropamine (0.8%)			DUID suspects (n = 1231) All Male Age range: 20 – > 50 Mean age: 31	[32]
	Sedative agents with designer drugs (eg. MDPC, 2-DPMP, SCs)		Finland	DUID cases (n = 13,248) In positive cases Most male (84.8%) Age range: 14–88 Mean age: 33.5	[47]
	MDPV			MDPV-positive DUID cases (n = 486) In positive cases Most male (86%)	[48]
	MDMA (0.01%)		Swiss	Drivers related to DUI (n = 500)	[44]
	Cathinone (88%) Phenethylamines (3%) Piperazine & Piperidine (3%) Arylalkylamines (1%)		Poland	NPS cases including DUID (n = 1058) Most male Age range: 16–50 Mean age: 25.4 Median age: 24.5	[45]
	3-MMC (1.8%)			Blood samples (n = 5200) In 3-MMC users Most male (93.7%) Age range: 17–50 Average age: 25.9 Median age: 26.0	[46]
	MDMA (0.01%)	Urine	Norway	Controls (n = 9375)	[30]

Khat was only reported in Asia [12] whereas α-PVP and fentanyl were only reported in USA [22,25], and MDMA, MDPV, cathinone, and 3-MMC were only reported in Europe [30,32,44–48]. On the other hand, illegal substances frequently reported in three regions as followed: amphetamine [11,15,20–28,32–37,39–41,44–46,50,51,54], BZDs [10–12,17,22,28,32,34,36,39–41,44,46,50,53,54], cannabinoids [11,13,15,20,24,25,29,32–35,39–41,43,47,55,56], cocaine and benzoylecgonine [9,11,15,20,22,24,29,32–37,39–41,43,46,50–52], MA [9,10,15,17,20,22,23,25,38–41,45,46,51,55,56], opiates [12,17,20,28,33–36,39–41,42,46,55,56], SCs including metabolites [21,24,30,49], and THC [14,21–23,36,37,39–41,44–47,50–52,54] as described in Table 5. In addition, Fig. 1, summarizes llegal drugs reported in DUID cases between 2013 and 2018 in Asia, USA, and Europe.

3.4. Legislations related to DUID in Asia, USA, and Europe

According to the increase of DUID cases, legislations for DUID have been established and reported in USA and Europe. In Asia, legal regulations for DUID have been enacted in Hong Kong [9], Turkey [11], China [38] and the legislation for DUID was not established in Korea [10]. However, DUID cases have been reported continuously, which indicated that there was a need to establish stricter legislations for DUID in Asia. In USA, previous study suggested that DUID could not be controlled with law for alcohol-impaired driving [13], which resulted in the establishment of law for DUID and evaluation of law enforcement. In Europe, since 2012, legislative limits for DUID have been established for 20 drugs [58,59] in Norway, but this legislation did not consider drivers who had prescriptions for medicinal drugs [58], which enabled to exclude the abuse of medicinal drugs purchased from illegal market. In Belgium, there was a comparison between previous and new legislation on DUID and new legal approach published in 2009 showed fewer false positive results for drugs [60]. In Italy, DUID has been banned based on the law published in 1992 and updated in 2016 though DUID cases have been reported steadily [36]. These results indicated that there was a need to a continuous analysis of biological samples including blood, oral fluids, and urine to regulate DUID and evaluate law enforcement.

Many previous studies suggested the determination of drugs in biological samples could (1) propose legal limits for drugs in DUID cases, (2) evaluate law enforcement for DUID, and (3) improve legislation on DUID [14,28,36,39,40,61].

3.5. Limitations

There were some limitations in this review. First, the number of DUID cases including drug abuse reported in Asia was smaller than in USA and Europe, which resulted in incorrect results in comparisons of illegal drugs related to DUID cases between regions. Second, a majority of drivers targeted in previous studies were male, which showed illegal drugs related to DUID cases

b-
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e-
d
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o-

Table 5
Illegal drugs commonly detected in all regions.

Illegal drugs	Region	Country	References
Amphetamine	Asia	Turkey	[11]
	USA		[15,20,39–41]
	Europe	Belgium, Italy, Finland, Norway	[51]
		Denmark	[37]
		Finland	[27,28]
		Germany	[24,46]
		Italy	[33–36]
		Norway	[21–23,44,45,54]
		Sweden	[25,26]
		UK	[32]
BZDs	Asia	Iran	[53]
		Jordan	[12]
		South Korea	[10]
		Turkey	[11]
	USA		[17,39–41]
	Europe	Finland	[28]
		Germany	[46]
		Italy	[34,36,50]
		Norway	[22,44,54]]
		UK	[32]
Cannabis	Asia	Iran	[55,56]
		Turkey	[11]
	USA		[13,15,20,39–41]
	Europe	Germany	[24,47]
		Italy	[33–35]
		Spain	[43]
		Sweden	[25]
		Swiss	[29]
		UK	[32]
Cocaine/benzoylecgonine	Asia	Hong Kong	[9]
		Turkey	[11]
	USA		[15,20,39–41]
	Europe	Belgium, Italy, Finland, Norway	[51]
		Denmark	[37]
		Germany	[24,46]
		Italy	[33–36,50,52]
		Norway	[22]
		Spain	[43]
		Swiss	[29]
		UK	[32]
MA	Asia	China	[38]
		Hong Kong	[9]
		Iran	[56]
		South Korea	[10]
	USA		[15,17,20,39–41]
	Europe	Belgium, Italy, Finland, Norway	[51]
		Germany	[46]
		Norway	[22,23,45,54]
		Sweden	[25]
Opiates	Asia	Iran	[55,56]
		Jordan	[12]
	USA		[17,20,39–41]
	Europe	Finland	[28]
		Germany	[46]
		Italy	[33–36]
		Norway	[54]
		Spain	[42]
		UK	[32]
SCs(including metabolites)	USA		[49]
	Europe	Germany	[24]
		Norway	[21]
		Poland	[30]
THC	USA		[14,39–41]
	Europe	Belgium, Italy, Finland, Norway	[51]
		Denmark	[37]
		Germany	[46,47]
		Italy	[36,50,52]
		Norway	[21–23,44,45,54]

Reported illegal drugs related to DUID in Asia, USA, and Europe (2013-2018)

Asia	<year> Illegal drugs [ref]
China	<'16> MA, Morphine and/or MA [38]
Hong Kong	<'16> Cocaine/Benzoylecgonine, Ketamine, MA [9]
Iran	<'13> Amphetamine, BZDs, Morphine [53]
	<'16> Cannabis, Opiates [55]
	<'17> Cannabis, MA, Opiates [56]
Jordan	<'16> Barbiturates, BZDs [12]
Saudi Arabia	<'17> Khat [57]
South Korea	<'16> BZDs [10]
Turkey	<'13> Barbiturates, BZDs, Cannabinoids, Cocaine [11]

USA <year>	Illegal drugs [ref]
<'13>	Cannabinols, Stimulants [13]
<'14>	THC [14]
<'15>	Cannabinoid. Cocaine/benzoylecgonine, MA/amphetamine [15]
<'16>	α-PVP, BZDs, Cannabinoids, MA, Opiates, SC metabolites [16, 17, 49]
<'17>	2-furanyl fentanyl, 3-methylfentanyl, Acetyl fentanyl, Amphetamine, BZDs, Cannabis, Cannabinoids, Carfentanil, Carisoprodol/meprobamate, Cocaine, Fentanyl, Methamphetamine, Norfentanyl, Opiates, THC Zolpidem [18, 19, 39, 40]
<'18>	Amphetamine/MA, BZDs, Cannabis, Cocaine, Opiates, THC [20, 41]

Europe	<year> Illegal drugs [ref]
Belgium, Italy, Finland, Norway	<'15> Amphetamine, Cocaine, MA, THC [51]
Denmark	<'18> Amphetamine, Clonazepam, Cocaine, Methadone, Morphine, THC [37]
Finland	<'15> 2-DPMP, Amphetamine, BZDs, Cannabinoids, MDPV, Midazolam, Opiates, Zolpidem [27, 28]
Germany	<'14> Amphetamine, BZDs, Cocaine, Diazepam, MA, Morphine, Opiates, THC [24, 46, 47]
Italy	<'14> Cocaine, Morphine, THC [52]
	<'17> Amphetamine, Buprenorphine, Cannabinoids, Cocaine, Methadone, Opiates [33]
	<'18> Amphetamine, Amphetamine-like drugs, Barbiturates, BZDs, Buprenorphine, Cannabinoids, Cocaine, Ketamine, Methadone, Opiates, THC [34-36, 50]
UK	<'17> Amphetamine, BZDs, Cannabinoids, Cocaine, MDMA/methyl-amphetamine, Opiates [32]

Europe	<year> Illegal drugs [ref]
Norway	<'14> Amphetamine/MA, BZDs, Ketamine, LSD, Methiopropamien, SCs, SC metabolites, THC [21,22]
	<'16> Methiopropamine, Amphetamine, THC, MA [23]
	<'17> Amphetamine/MA, BZDs, Heroin/morphine, Opiates, THC [45, 54]
	<'18> Amphetamine, BZDs, THC [44]
Poland	<'16> 3-MMC, α-PVP, BZDs, Cathinone, MA, Phenethylamines, SCs [30, 31]
Spain	<'18> 6-acethylmorphine, Cannabis, Cocaine, Codeine, Methadone, Morphine, Opiates [42, 43]
Sweden	<'13> Amphetamine [26]
	<'15> Amphetamine, MA [25]
Swiss	<'16> Cannabinoids, Cocaine, MDMA, Morphine [29]

Fig. 1. Reported illegal drugs related to DUID in Asia, USA, and Europe (2013–2018).

ward male. Third, some papers investigated DUID cases in the number of subjects less than 100, which indicated that these results could not represent overall trend of drug abuse related to DUID in the region. Fourth, there were difficulties in comparing illegal drugs related to DUID because the laws and legal limits on DUID and illegal drugs were different between regions. Lastly, some studies focused on specific drugs to investigate the abuse trend in target drugs and evaluate the effectiveness of analytical methods developed in those studies, which could not investigate overall trend of drug abuse in each region.

4. Conclusions

This review describes the abuse statuses of illegal drugs detected in DUID cases included in studies performed from 2013 to 2018 in Asia, USA, and Europe. Many studies analyzed biological samples including blood, oral fluids, urine, hair, and even autopsies and conducted surveys to investigate DUID cases and the trend of drug abuse related to DUID in Asia, USA, and Europe. In the biological samples, various illegal drugs, such as, BZDs, cannabinoids, cocaine, THC, amphetamine, and MA were frequently detected. Khat was only identified in Asia, whereas α-PVP and fentanyl including its metabolites were only identified in USA and a variety of NPSs, such as, MDMA, methiopropamine, MDPV, and 3-MMC were only identified in Europe. DUID cases have been reported steadily in three regions though legislations for DUID have been established and enacted. Therefore, this review suggested that regular testing of drivers should be encouraged to gather more intelligence over role of drugs in traffic accidents. In addition, regulations should be improved to control and monitor DUID cases more strictly.

Conflict of interests

The authors declare no conflict of interests.

CRediT authorship contribution statement

Nam ji Kwon: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Eunyoung Han:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

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