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Driving under the influence of drugs: Correlation between blood psychoactive drug concentrations and cognitive impairment. A narrative review taking into account forensic issues

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ABSTRACT

Driving under the influence of alcohol has been shown to increase the risk of involvement in road traffic collisions (RTCs) however, less is known about the effects of illicit drugs, and a clear correlation between drug concentrations and RTC risk is still debated. The goal of this narrative review is to assess the current literature regarding the most detected psychoactive drugs in RTC (ethanol, amphetamines, cannabis, opioids and cocaine), in relation to driving performance. Evidence on impaired driving due to psychoactive substances, forensic issues relating to the assessment of the impact of drugs, blood cut-off values proposed to date as well as scientific basis for proposed legislative limits are discussed. At present there is no unequivocal evidence demonstrating a clear dose/concentration dependent impairment in many substances. Per se and zero tolerance approaches seem to have negative effect on drugged driving fatalities. However, the weight of these approaches needs further investigation.

1. Introduction

According to the WHO, road traffic collisions (RTC) account for about 1.3 million deaths and 20–50 million non-fatal injuries worldwide [1] and all over the world driving under the influence of psychotropic substances has become a widespread phenomenon. Despite driving under the influence of alcohol (DUIA) has been shown to increase the risk of involvement in RTCs, with relative risk increasing with blood alcohol concentration [2], less is known about the effects of medicinal and illicit drugs [3], and a clear correlation between drug concentrations and RTC risk is still debated [3,4]. Actually, the association between such substances (especially alcohol, amphetamines, cannabis, opioids and cocaine), impaired driving and road accidents has been extensively investigated so far [3], with results stating a link to an increased risk of car crashes and serious injuries not only to the impaired driver but also to other people, constituting a threat for public safety [5]. Indeed, the assumption of these substances may impair the visual, cognitive, and/or motor abilities needed for safe driving [6]. A recent review published by Kwon and Han [7] showed that in Europe most of the studies on blood toxicological results are performed in northern countries, such as Norway [8,9], Germany [10], Sweden [11], Finland [12,13], Switzerland [14], Poland [15], UK [16], and Denmark [17], while fewer studies report blood results from southern European countries [6].

Over the years, countries have developed different strategies in order to face this relevant issue. For example, recently Norway and Sweden adopted a "zero tolerance approach" toward driving under the influence of psychoactive substances which has led to a reduction of positive cases [6], while other countries have introduced threshold limits. Alcohol is the only substance for which official international cut-off values have been clearly proposed, as well as standardized analytical methods. Indeed, for what concerns other substances, straightforward cut-off values are not available as a consequence of the heterogeneity of results in published studies and different involved approaches. In fact, even though blood is the gold standard matrix for drug confirmation and quantification analysis in DUID cases as the values found are considered to be closely related to current pharmacological effects on the central nervous system, a comparison between different proposed cut-off values evidenced great dissimilarity internationally [18].

Given the wide variability not only in the indicated cut-offs but also in the effects of the substances themselves, the authors present a

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summary of the results of studies on the subject, with emphasis on forensic aspects, to deepen the understanding of such a complex issue. The purpose of this narrative review is to evaluate current literature regarding the most detected psychoactive drugs in RTC, which are ethanol, amphetamines, cannabis, opioids and cocaine in relation to driving performance and traffic safety; benzodiazepines have not been included because of the wide differences between the various types. Limitations of current legal approaches in this area are considered. The scientific basis for the proposed legislative limits is presented and recent evidence on impaired driving due to psychoactive substances is reported, as well as blood cut-off values proposed to date.

2. Methods

Published articles from January 2010 to July 2021 were identified from PubMed, Embase, Scopus and Web of Science using the following keywords: "Alcohol", "cannabis", "marijuana", "opioids", "heroin", "cocaine", "amphetamines", "driving under the influence", "cognitive impairment", "neurocognitive correlates", "acute cognitive effects", "chronic cognitive effects", "toxicological analysis" and "*per se* drug limits". Keywords were searched individually and in association with each of the others. Only full text articles manuscripts in English have been included. Further search was performed through the reference-list of the retrieved articles for additional studies not found by the above search method.

2.1. Alcohol

Alcohol is the most commonly used psychoactive substance worldwide and is the most frequently identified in road-traffic driver victims [19,20]. A study analyzing Blood Alcohol Concentrations (BACs) from 2006 to 2008 using data from the Fatality Analysis Reporting System found that alcohol's contribution to crash risk was significantly higher compared to other drug use [21]. The significant association between alcohol level and crash risk has been stated several times also in the periodic reports by the U.S. Department of Transportation [22]. In general, most positive drivers are male: interestingly, while the percentage of positive female drivers has increased over the past years, the number of positive male drivers has remained almost constant. A general downward trend is evident with increasing age, when considering subjects older than 25 years of age, while a general increasing trend is prevalent during the night, especially at weekends, motivated by a consolidated increased alcohol use in social contexts [6].

Ethanol consumption causes substantial health loss, even if its overall association with health remains complex given the possible protective effects of moderate alcohol consumption on some medical conditions [23]. Chronic alcohol consumption may cause cancer, liver diseases, kidney diseases, cardiovascular disorders, respiratory diseases and mental impairment [24].

Even at low BAC levels (0.1 or 0.2 g/L), previous research showed that alcohol impairs oculomotor function and the ability to divide attention, essential for the driving task [25]. However, the actual level of impairment is also influenced by other different factors, such as the individual's tolerance, weight, and recent food consumption [26]. Recently, main clinical findings in different BAC groups among healthy volunteers have been reported. For up to 1 h, individually suitable alcohol beverage (beer, wine or spirits such as vodka, brandy, liqueur or whiskey) was consumed and the strength and amount consumed were noted in the protocol. Within 1 h after unspecified amount of alcohol administration, behavior and mood changes were usually observed. The most common finding is euphoria, associated with the absence of sweating or chills, even if interindividual differences exist [27]. Indeed, alcohol intoxication is a result of short-term effects on the central nervous system with symptoms that can vary drastically depending on the amount of alcohol consumption, bodily characteristics of the subject and time of the consumption. Symptoms of alcohol intoxication, such us mild cognitive and physical impairment, may become evident after just 1 or 2 drinks. The immediate effects of alcohol on the brain are due to its influence on the organ's communication and information-processing pathways. Several adverse mental effects may arise such us confusion, seizure, altered consciousness, impaired motor coordination and declined decision-making ability [28], as well as nystagmus and balance disturbance in Romberg's position [27] up to even drowsiness and eventually death [29]. Karlovsek and Balazic's study on the association of nystagmus with BAC found that nystagmus is a good test to assess alcohol intoxication when BAC is > 0.5 g/kg [27].

It is clear that such symptoms can drastically reduce driving ability: it has been demonstrated that alcohol mainly influences automated driving performance such as speed control and weaving (SDLP) [30] and may have negative effects also on reaction time, vision, tracking, concentration, comprehension, and coordination [31]. Driving ability is furtherly negatively affected by alcohol and drugs association.

Since alcohol is a legal substance in most countries and there is great variability in the effects on driving ability between different individuals, particular attention has been paid over time to what is the optimal BAC as a legal limit. Alcohol is the only one substance of abuse for which cut-off values have been clearly proposed intercontinentally. However, they vary among different countries, from zero tolerance, such as Sweden, to a maximum BAC limit of 1.2 in Sao Tome and Principe and 1.5 g/L in Liberia [1]. Moreover, some countries have more severe constraints for novice drivers, such as the "zero tolerance" legislation adopted in Italy [32]. To date, it is established that any amount of alcohol could impair driving ability and behaviour, with risks increasing exponentially when 0.5 g/L is exceeded for the general driving population [1]. In this respect, it has been suggested that reducing BAC from 1.0 to 0.5 g/L can help reduce traffic fatalities by 6–18% [33], and that BAC 0.5 g/L drivers are two-times more likely to be involved in crashes than sober drivers [22]. Therefore, the WHO on this subject suggests that the best at this time is to propose legal limits of 0.5 g/L in the general population and 0.2 g/L for novice drivers, motivated by a greater susceptibility to related impairment in the latter population: to such criteria more and more countries are adhering [1]. Similar considerations to those proposed for novice drivers have been proposed for commercial drivers with passengers, given the risks of crashes with more serious consequences due to the number of individuals they transport. However, not all countries in the world indicate BAC limits: WHO points out that of 174 states with laws on the subject, 136 countries identify BAC threshold limits [1]. Therefore, there is a wide heterogeneity in the preventive measures implemented from country to country.

2.2. Amphetamines

Amphetamine and amphetamine-type substances such as methamphetamine and 3,4-methylendioxymethamphetamine (MDMA, ecstasy) are most commonly abused due to their stimulant effect on the central nervous system [18]. Besides increased mood and energy boosting, such substances have also various adverse health effects. There is evidence regarding neurotoxicity (convulsions, loss of coordination, mood changes, stroke, etc) and cardiotoxicity (arrhythmias, heart attack, high blood pressure) long-term effects. Impairments in psychosocial functioning and mental health have been described, indeed such substances may induce psychotic symptoms, violent behavior and suicidal tendencies [34] as well as auditory and/or visual perceptions [18].

These effects may have a relevant impact on drivers' health and safety, increasing the risk of injuries and traffic accidents [18,35]. In fact, it has been demonstrated that both acute and chronic use of amphetamines is involved in higher dangerous driving. Amphetamine use in truck-drivers has been estimated to increase the risk of fatal accidents by 5-times [35]. Regarding the above, several studies performed in controlled clinical settings have suggested that low doses of amphetamines could improve psychomotor skills, such as driving ability, even in fatigued subjects [35,36]. On the other hand, amphetamines have

been shown to impair cognitive functions such as working memory and movement perception, while improving neuropsychological skills, such as tracking, impulse control, and reaction time [37–42]. The abuse of amphetamines has been described as causing hypersomnolence at the end-of-binge [43] and a negative impact on automated driving performances such as lateral and speed control [30]. It has been reported that amphetamines may provide a sense of adequate performance that is not in accordance with the actual performance, which can be considered as an additional risk factor when driving [30,37,44,45]. Further, studies using a driving simulator showed that amphetamine usage increases improper signaling, signal violations, slow reaction times, and acceptance of smaller gaps for vehicle maneuvers [40,46].

Several studies have combined brain imaging with neuropsychological evaluation, showing that, short-term, acute amphetamine improves cognitive performance of amphetamine abusers in some domains, for example, visuospatial perception, sustained attention, and response speed [37,45,47]. Similar findings have been reported also for amphetamine non-users. Memory impairments associated with methamphetamine use appears linked with temporal and parietal lobe dysfunction [48]. Interestingly, younger drivers were more often judged impaired by a police physician than older drivers at similar concentrations [43]. However, Jones et al. reported that driving simulator task after a dose (10–40 mg) of amphetamine in healthy volunteers was not much different from a placebo treatment [11].

The effects induced by contemporary alcohol consumption are a debated issue. Some authors stated that all the negative effects of amphetamines have been demonstrated to be worsened by the coexistent consumption of alcohol, hypothesizing synergistically diminished neurocognitive functioning [49].

It is important to emphasize that all the experimental studies are affected by some intrinsic limitations: because of medical and ethical constraints, doses of amphetamines tested on drivers are by far lower (ten-fold) than those registered taken in real life settings [18]. Despite this, in a meta-analysis performed by Elvik et al. [3], the odds ratio of fatal accident involvement with the use of amphetamine was 5.17 (95% CI 2.56–10.42), 6.19 (95% CI 03.46–11.06) for collisions with injuries and 8.67 (95% CI 3.23–23.32) for crashes resulting in property damage.

Over the years, some studies have tried to assess cut-off values for amphetamines. The criteria on which cut-offs have been proposed are predominantly clinical [18] or epidemiological [6,18,43,50–52]; expert opinions have also contributed [53,54]. An analytical criterion had also been proposed [55]. For studies with analytical criteria, the cut-off was proposed on the basis of the laboratory's limit of quantification. However, studies evaluating the issue on the basis of clinical reverberations have been published, mostly reviews, which refer to the study by Gustavsen et al. [18,43], who observed that in a sample of 878 cases impairment - measured on the basis of a clinical test for impairment (CTI) carried out by a police physician - occurred in the majority of individuals (73%) at a dose higher than 0.27–0.53 mg/l. In the study by Ferrari [50] the cut-offs reported were those proposed by the law of the land. Vindenes et al. [51], however, pointing to the absence of firm scientific evidence, assumed that impairment due to recreational use of alcohol with significant impairment could be considered with a BAC of 1 g/L - five times the legal limit in their country - and by analogy, proposed as a limit for amphetamines the value of one fifth of the blood concentrations corresponding to the "standard" concentrations of recreational drug dose as established from the literature. Regarding expert opinions [52–54], they are the result of the integration of a wide range of expertise in pharmacokinetics, pharmacology, psychopharmacology, forensic toxicology, clinical practice, mental health and transport safety. In summary, Walsh et al. [53] reported a value of 20 ng/ml, whereas Vindenes et al. [51] 41 ng/ml and Wolff et al. [52] 600 ng/ml. Other studies [52] have assessed the coexistence of amphetamine and alcohol (20 mg ethyl alcohol per 100 ml blood (0.02%): in such cases, the cut-off value was 300 ng/ml. Blood cut-off values for amphetamines have been therefore recently proposed, ranging from 20 to 600 ng/mL for amphetamine, from 20 to 200 ng/mL for methamphetamine, and from 20 to 300 ng/mL for MDMA [18,56]. Shortly following, other studies have assessed that such threshold values should be lowered since blood amphetamines concentration above 270–530 ng/mL has been associated with psychomotor impairment [35,43]. In conclusion, however, a cut-off of 20 ng/ml is usually considered acceptable for amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine, MDA; 3,4-methylenedioxy- N-ethylamphetamine MDEA, 3,4-methylenedioxy-N-methylamphetamine, MDMA [6,51–53] although in some States the legal cut-off is higher.

2.3. Cannabis

The main psychoactive substance of cannabis is tetrahydrocannabinol (THC), a highly lipophilic substance which is rapidly absorbed via smoking [57] and distributed in the body [56]. Other than alcohol, cannabis is the most commonly abused drug in the world [58]: its use has increased over the past 10 years particularly in the younger population [59], and it is available in different preparations, such as hashish and marijuana [57].

Despite the common use of cannabis for its euphoric and relaxing effects, the relationship between cannabis and psychomotor function and skills has not been clarified. Collaterally, it has been reported that cannabis may also increase the risk of cardiovascular toxicity [57], cognitive and psychomotor impairment, sedation [60,61], psychosis and increased risk for psychotic disorder [62]. However, cannabis lethal toxicity is rare, and there are very few studies that claim cannabis has contributed to death [57].

Memory problems are frequently associated with cannabis use, in both the short- and long-term. Recent studies have examined working memory and verbal episodic memory and cumulatively, the evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms in long-term or heavy cannabis users. These impairments are not dissimilar to those associated with acute intoxication and have been related to the duration, frequency, dose and age of onset of cannabis use [63]. Moreover, a prolonged exposure to cannabis has been demonstrated to result in impaired P50 sensory-gating in long-term cannabis users [64]. Cannabis consumption has also been shown to induce acute changes in brain activity involving centers linked with saliency detection, self-oriented mental activity, and task performance [59]. Then, acute and chronic use of cannabis has been shown to impair psychomotor functions, memory and attention, often in a dose-dependent manner [18]. These cognitive and psychomotor changes (loss of motor control, psychomotor speed, executive function, motor impulsivity, manual dexterity, visual processing, short-term memory, working memory, perception and balance [18]) affect driving performance and lead to increased risk taking [59].

The utility of marijuana in specific medical conditions has been studied at length, but its effects on driving performance and risk of motor vehicle collision remain unclear. The healthcare provider should be informed of the potential risks of driver safety prior to prescribing this psychotropic drug to give anticipatory guidance for appropriate use. The only review on this topic had demonstrated that patients should abstain from driving for 8 h if they achieve a subjective "high" from self-treatment with smoked marijuana and should be aware of the cumulative effects of alcohol and other psychoactive xenobiotics [65].

Controlled, experimental studies using simulated and on-road assessment techniques have demonstrated that recent cannabis use can influence fundamental driving skills: increased reaction time, decreased driving speed, impairment in memory, divided attention ability, tracking, and motor functions such as lane positioning, lateral and longitudinal vehicular control and reaction time [5,59,60,66–76]. Some studies have also focused on how personality or individual differences may impact the effects of cannabis on driver behavior and performance. A very recent research work has demonstrated that drivers high in trait impulsivity may be more sensitive to the effects of THC

[77].

With the growing worldwide trend towards the decriminalization of recreational and medicinal cannabis use, there has been a renewed focus on the risks associated with driving under the influence of cannabis [67,78,79]. For this reason, numerous studies investigated the correlation between driving under the influence of cannabis (DUIC) and the risk of various unfavorable traffic events (UTEs), such as collision, injury, or death. Elvik et al. have observed that cannabis use increases the risk of being involved in fatal RTCs with a relative risk of 1.26 (95 CI 0.88–1.81), 1.10 (95% CI 0.88–1.81) for collisions with injuries and 1.26 (95% CI 1.10–1.44) for crashes resulting in property damage [3]. A series of published systematic reviews [80] and meta-analysis [81] strongly suggest an association between DUIC and UTEs. However, most of them had important limitations [82–85]. For example, there is no differentiation between testing for tetrahydrocannabinol (THC) and its core metabolite (THC-COOH) [84], a water-soluble substance easily excreted [86] and detectable in body fluids giving a positive test for cannabis use for several days (or even weeks in heavy users), in absence of active component [87,88], wrongly believing that the person is DUIC. Additionally, in the terminal elimination phase of the metabolite, a single subject may produce consecutive specimens that could be tested positive, negative, and again positive, making it very hard to differentiate a new episode of consumption from a previous cannabis exposure [89]. Moreover, there is always some delay between UTE and the moment of collecting biological samples, which makes the simple determination of the relationship between cannabis use and collision risk very difficult. Other limitations are the self-reporting method for analysis of the association between cannabis use and UTEs, underestimating the actual proportion of cannabis users [83,85].

Therefore, research is inconclusive on THC's association with crash risk [81,90–92] as also observed in the first large scale case control study in the United States [22]. Obtaining a definite answer is difficult, as these studies often had conflicting results and the research methodology was regularly prone to biases. A recent meta-analysis suggests that the overall effect size for DUIC on UTEs is not statistically significant [82]. Daily cannabis users develop tolerance to some drug effects, but the extent to which this diminishes driving impairment is uncertain. A very recent study assessed this issue by testing the driving performance in adults age 25–45 years with different cannabis use histories: occasional users (1–2 times per week), daily users and non-users. A car-based driving simulator was used to obtain two measures of driving performance, standard deviation of lateral placement (SDLP) and speed relative to posted speed limit, in simulated urban driving scenarios at baseline and 30 min after a 15 min ad libitum cannabis smoking period. The study revealed a decrement in driving performance that was statistically significant only in the occasional users in comparison to the nonusers. Direct contrasts between the occasional users and daily users were not statistically significant. Daily users drove slower after cannabis use as compared to the occasional use group and non-users. The study results do not conclusively establish that occasional users exhibit more driving impairment than daily users when both smoke cannabis ad libitum [93]. Moreover, it has been shown that inhalation of cannabis leads to a rapid increase in blood THC concentrations with a delayed decrease in vigilance and driving performance, more pronounced and lasting longer in occasional cannabis consumers than in chronic cannabis consumers [59]. Chronic users of cannabis often present a long-term cognitive impairment that may persist even after a period of abstinence and has been stated that chronic frequent smokers may have concentrations higher than 2 ng/ml even after 7 days of abstinence [94]. Notwithstanding, it must currently be considered a field worth further assessment.

Several studies have specifically investigated the link of THC levels and impaired driving [18]. Over the years, some studies have tried to assess cut-off values for THC. The criteria on which cut-offs have been proposed are predominantly clinical, epidemiological or a combination of both [5,6,50–52]; expert opinions [53,54,95] as well as analytical approaches [55,57] have also contributed. In detail, THC concentrations between 5 and 10 ng/ml showed a significant impairment in performance tests (Critical tracking task, stop signal task, Tower of London) in about 75–90% of all observations: it was therefore stated that the lower and higher limits for observing any impairment were 2 and 5 ng/ml [5]. In the Ferrari at al. study [50] the legal cut-offs of their territory were adopted. With reference to what has been proposed by Vindenes et al. [51] and by experts, there are similar considerations to those presented in the section on amphetamines. In detail, Walsh et al. [53] reported a value of 1 ng/ml, whereas Vindenes et al. [51] 1.3 ng/ml and Wolff et al. [52] 5 ng/ml. Studies have assessed the coexistence of THC and alcohol [52]: in such cases, the cut-off value proposed was 3 ng/ml. According to Drummer and Odell [95], a concentration of THC higher than 5 ng/mL would strongly suggest that the deceased was impaired. Other studies reported that THC concentrations between 1.5 and 3 ng/mL are believed to be the minimum concentrations for impaired behavior, and users at these concentrations could be considered to be under the influence of cannabinoids [57,96]. However, the identification of such limits is controversial and not straightforward, since these limits are not demonstrably indicative of impaired driving ability in all individuals and, unlike other drugs, cannabis in some countries is regulated as a legal substance within certain limits and under certain circumstances. In contrast to alcohol, fewer studies have been conducted on cannabis and driving impairment, therefore no evidence has been found to date for the identification of international agreed cut-off points. Complicating even further this picture are the different effects induced by the substance, which vary according to the type of user (occasional/chronic) and the fact that the relationship between blood levels and impaired driving lacks a clear and proven direct correlation. Moreover, passive exposure to cannabis smoke may induce effects on behavior and psychomotor skills, and have legal consequences, including the risk of being falsely considered as a cannabis user. A recent review identified specific biomarkers of passive exposure in urine, blood, oral fluid, hair, and sebum. In everyday life conditions, 11-nor-delta-9-THC-carboxylic acid (THC-COOH) urinary level should be detected below the positivity threshold used to confirm active smoking of cannabis, especially after normalization to creatinine level. Measuring delta-9-tetrahydrocannabinol (THC) and THC COOH in blood is an appropriate alternative for appraising passive exposure as low and very low concentrations of THC and THC-COOH, respectively, should be measured. In hair, oral fluid (OF) and sweat/sebum emulsion, no THCCOOH should be detected. Its presence in hair argues for regular cannabis consumption and in OF or sweat for recent consumption [97].

As mentioned above, the metabolism of cannabinoids is highly variable in different subjects: therefore, at the same concentration, a person may be under the influence, while another may have normal driving ability [98]. In addition, it is known that the concentration in blood of THC decreases rapidly after use, but the clinical effects take longer to dissipate [98]. This, associated with the fact that sampling is done sometimes even hours after the event, may significantly alter the results [82]. For this reason, simply identifying cannabis use in a driver is not enough to justify the assumption of an increased risk for UTEs. When such a result is obtained, it should be corroborated with either quantitative data regarding cannabis use, or a clinical assessment of the driver, before establishing his fitness to drive. A positive test for cannabis (i.e., blood) does not necessarily imply that drivers were impaired, as THC/metabolites might be detected in blood a long time after impairment, especially in chronic cannabis users [82].

2.4. Opioids

Opioids are primarily used as licit drugs in the treatment of moderate to severe pain [99,100]. At the same time, both natural, synthetic and new synthetic opioid (e.g., fentanyl and derivatives) are a class of psychotropic substances that are widely used out of medical indication [18,101,102]. Common side effects of opioid administration include fatigue

[103], sedation, dizziness, nausea, vomiting, constipation, respiratory depression as well as physical dependence and tolerance [104]. Side effects vary between different molecules and are generally most pronounced during the first few days after starting opioid therapy, before tolerance develops [18,105,106]. Through a variety of mechanisms, opioids cause adverse events in several organ systems. Evidence shows that chronic opioid therapy is associated with constipation, sleep-disordered breathing, fractures, hypothalamic-pituitary-adrenal dysregulation, and overdose. However, significant gaps remain regarding the spectrum of potentially opioid-related adverse effects [107]. Opioids are also thought to worsen the performance of psychomotor tasks due to their sedating and mental-clouding effects. However, a study demonstrated that long-term use of opioids does not significantly impair cognitive ability or psychomotor function [108].

The increasing trend in analgesic use in the population [103,109,110] has raised concerns, especially for opioid analgesics [111–113] that can cause side effects such as cognitive deficits (short and long-term memory impairment) [103], impaired vision, drowsiness and slow response to stimuli [113]. These symptoms have been the reason of concern in traffic safety due to their potential effect on driving ability. The effect of opioids on driving performance has been discussed in different reviews that suggest that opioids do not impair driving skills [113–116]. However, use of opioid analgesics was associated with greater odds of committing an unsafe driving act [103]. The majority of reviews included studies that lacked an adequate reference group and failed to control for relevant confounders, such as concomitant illness or the consumption of alcohol or other psychoactive medications/drugs, and Authors were unable to find consistent evidence supporting the notion of a relationship between opioid use and intoxicated driving, crashing, or dying in RTCs [113]. A very recent review argues that illicit assumption, the use of opioid drugs in combination with other psychoactive medications and the initiation of opioid therapy are clearly associated with impairment of neurocognitive and psychomotor functions as they pertain to complex tasks including driving-related functions and/or operation of a motor vehicle [117].

Morphine is the most important and frequently used substance among opioids. However, few data have been reported about morphine and driving impairment in the literature. A meta-analysis revealed that a single dose of morphine of up to 5 mg has caused very few effects on driving performances tasks while higher doses corresponded to alteration of various tasks, but no clear direct dose-effect relationship was observed [18]. Despite this, Elvik et al. [3] estimated that the relative risk of fatal collision with the use of opiates was 1.68 (95% CI 1.01–2.81), 1.91 (95% CI 1.48–2.45) for collisions with injuries 4.76 (95% CI 2.10–10.80) for crashes resulting in property damage.

Over the years, some studies have tried to assess cut-off values for morphine. The criteria on which cut-offs have been proposed are predominantly clinical [18], epidemiological [6, 50 or a combination of both [51,52]; expert opinions and analytical criteria have also contributed [53–55]. Cut-offs from clinical studies are mostly experimental, using driving simulators to assess impairment in different driving tasks [18]. Walsh et al. proposed a value of 10 ng/ml [53], whereas Vindenes et al. 9 ng/ml [51] and Wolff et al. 80 ng/ml [52]. Other studies have assessed the coexistence of morphine and alcohol [52]: in such cases, the cut-off value was 40 ng/ml. Later, a systematic review of experimental studies defined that plasma morphine concentration of 14.3 ng/ml could represent a threshold concentration, under which there is little related road traffic risk. Moreover, a single dose of 5 mg intravenous morphine and analgesic equivalence doses of fentanyl, hydromorphone, oxycodone and oxymorphone did not present traffic-relevant effects [18].

2.5. Cocaine

Cocaine is a highly addictive drug characterized by central nervous system stimulant properties and is considered the most popular abused drug in Europe after cannabis [18]. It is estimated that there are currently more than 20 million cocaine users around the world [118] and results from recent wastewater analyses have revealed an upward trend in benzoylecgonine – and therefore in cocaine – consumption in Europe. Cocaine stimulates the central nervous system with subjective effects that usually last 1–2 h generally consisting of euphoria, hyperkinesia, urge to talk, increased self-assurance and increased readiness to take risks [119], followed by a withdrawal period which lasts 24 h characterized by opposite effects such as exhaustion, fatigue and tremors [120,121]. However, to date, because cocaine shows a significant risk of addiction, few experimental studies have investigated the cognitive effects of acute cocaine use in naïve users, due to ethical issues [122]. In fact, most of the literature considers long-term effects of repeated use assessed when the drug is no longer in the body.

At low doses, it is believed to lead to increased vigilance, arousal and attention [123] and it has been stated that intranasally administered cocaine enhances response inhibition and a speed component in psychomotor tasks [124–128]. Regarding acute effects, in addition, Spronk et al. proposed a comprehensive review and observed that the evidence that cocaine alters attention is mixed [129] and inhibitory control (Go/Nogo task rather than inhibition on response initiation) appears to be improved by cocaine intake; no effects were found on recall and recognition. They concluded that it remains unclear how cocaine affects cognition in naïve individuals.

Repeated and prolonged use has been associated with vascular psychological consequences, as well as central nervous system changes [123]. Moreover, impairment in sustained attention, impulsivity, verbal learning/memory, cognitive flexibility, visuospatial perception, response inhibition, working memory and psychomotor performances are well-documented in those individuals repeatedly exposed to cocaine [129–135], although some studies have not been uniform, stressing conflicting results explained by methodological differences and limitations of the studies [136,137]. Moreover, sex related differences in cognition have been observed by administrating a neuropsychological battery to abstinent recreational cocaine users and to non-drug-using controls, finding that in cocaine users male performed better than female on visuospatial perception [138].

Stimulant use disorders have been associated to structural brain alterations [134,139–143], consisting of altered gray matter volume or density in several brain areas (especially frontal, temporal, insular cortices as well as caudate and putamen), regions associated with emotions, self-regulation, disinhibition, insight, habit forming and craving [144]. This leads to the hypothesis that the differences in cognitive assessments observed between individuals with addiction to these substances and healthy individuals were due to these alterations. However, it is difficult to assess whether differences are a consequence of prolonged stimulant use or instead reflect preexisting traits that confer vulnerability to abuse and dependence: polydrug abuse in clinical population constitutes an additional confounding factor in determining causality [145]. Significant correlation between gray matter density and measures of cognitive performance among stimulant-using population have been observed [146–148]. Several studies have observed that duration of abuse may be linked to the magnitude of structural differences and specifically that decreased gray matter was related to duration of use in orbitofrontal, insular, parahippocampal and anterior cingulate cortices and cerebellum [149–153].

Negative correlations have been reported between cumulative cocaine dose and cognitive performance; moreover, it appears that individuals who began cocaine use prior to 18 years of age show greater cognitive impairment than those with a later onset of use [154]. It has also been observed that with abstinence some recovery in gray matter and cognitive impairment occurs, especially for attention and memory performance [135,146,153,155,156], even if early onset of use has been associated with reduced recovery of working memory [155]. In attention, working memory, memory and executive functions domains, recreational cocaine users exhibit significant impairments similar to individuals with cocaine use disorder [154]. It is still unclear whether

longer-term, recent and daily use may cause greater impairment of cognitive abilities.

Considering the above, Jedema et al. recently performed a study on rhesus monkeys, using neurocognitive performance-matched groups coupled with longitudinal imaging acquisition at baseline before any drug exposure, after 12 months of intravenously drug or water self-administration (maximum 3 mg/kg/die and total cumulative dose 600 mg/kg with negligible variation between individuals) and finally after 2 years of imposed drug abstinence: it has been observed that 1 year of relatively moderate cocaine exposure caused gray matter density structural differences and that the magnitude of these correlates with accompanying cognitive deficits and altered cognition in cognitive flexibility/inhibitor control and visual working memory. No relationship has been observed between structural changes and stimulus discrimination [157]. Additional element of relevance was that despite long-term abstinence some structural changes remained. However, the exportability of such results on human beings is debated.

Regarding specifically driving ability, epidemiological studies have observed that cocaine use increases the risk of being involved in RTCs [158–160], with a relative risk of involvement of 2.96 (95 CI 1.18–7.38) for fatal collisions, 1.66 (95% CI 0.91–3,02) for collisions with injuries and 1.44 (95% CI 0.93–2.23) for crashes resulting in property damage [3]. It has been stated that in the first 1–2 h of intake, cocaine induces impaired ability to react properly, poor concentration and judgements and over-confidence in driving skills which may increase the likelihood of taking unnecessary risks; likewise, it could be very dangerous to drive in the period just after, given the feeling of fatigue to the point of drowsiness and the onset of possible tremors [50].

A few studies have observed that cocaine can partially diminish performance impairments caused by alcohol consumption. The combined use of cocaine and alcohol decreases psychomotor impairment and improves performance on cognitive tests compared with alcohol alone and also reduces the subjective feeling of drunkenness [161,162]. There is no clear evidence that chronic combined use of alcohol and cocaine can cause additive effects on the brain, as cocaine dependent individuals have shown equal or greater neurocognitive impairment than those abusing both alcohol and cocaine [139,163,164].

Cut-off values for amounts of cocaine in blood have been proposed in the literature, with range from 10 up to 80 ng/mL, depending on different expert opinions [51,55,56]. The criteria on which cut-offs have been proposed are predominantly clinical [18] or epidemiological [6, 50] but also a combination of both [51,52]. Expert opinions and analytical criteria have also contributed [53–55]. Despite the above mentioned cut-offs, even 2 ng/ml have been associated with being involved in a car accident [50] and should also be considered that there may be an underestimation of the effects of cocaine in the "crush" period, which can last up to 24 h, as mentioned characterized by fatigue and tremors, in which the concentration in the blood will be reduced but with neurological effects still active. In summary, emphasis has been placed on the need to assess the reliability of the cut off limit of 10 ng/ml [50].

A summary of acute and chronic effects attributed to the substances analyzed is presented in Table 1.

Table 1
Summary of acute and chronic effects attributed to alcohol, amphetamines, cannabis, opioids, cocaine.

Substance	Acute effects	Chronic effects
Alcohol	Euphoria, sweating, chills, confusion, seizure, altered consciousness, nystagmus, balance disturbance, drowsiness, declined decision-making ability, altered automated driving performance (speed control and weaving, reaction time, vision, tracking, concentration, comprehension and coordination), eventually death	Cancer, liver disease, kidney disease, cardiovascular disorder, respiratory disease and mental impairment
Amphetamines	Increased mood and energy boosting, psychotic symptoms, violent behavior, suicidal tendencies, improved psychomotor skills (for low doses), impaired cognitive functions (working memory and movement perception), improved neuropsychological skills (tracking, impulse control) and reaction time, hypersomnolence at the end-of-binge, negative impact on automated driving performances (lateral and speed control), improved cognitive performance of amphetamine abusers (visuospatial perception, sustained attention, and response speed).	Neurotoxicity (convulsion, loss of coordination, mood changes, stroke) and cardiotoxicity (arrhythmias, heart attack, high blood pressure)
Cannabis	Euphoric and relaxing effects, cardiovascular toxicity, cognitive and psychomotor changes (loss of motor control, psychomotor speed, executive function, motor impulsivity, manual dexterity, visual processing, short-term memory, working memory, perception and balance, decrease in vigilance).	Long-term cognitive impairment, memory problems, impaired encoding, storage, manipulation and retrieval mechanisms, impaired P50 sensory-gating
Opioids	Fatigue, sedation, dizziness, nausea, vomiting, constipation, respiratory depression, cognitive deficits (short and long-term memory impairment), increase in lane-keeping variables (inappropriate line crossings and weaving of the vehicle)	Constipation, sleep-disordered breathing, fractures, hypothalamic-pituitary-adrenal dysregulation
Cocaine	Euphoria, hyperkinesia, urge to talk, increased self-assurance, increased readiness to take risks, increased vigilance, arousal and attention, improved inhibitory control, poor concentration and judgements and over-confidence in driving skills.	Vascular and psychological consequences, central nervous systems changes (altered gray matter volume or density in several brain areas associated with emotions, self-regulation, disinhibition, insight, habit forming and craving), impairment in sustained attention, impulsivity, verbal learning/memory, cognitive flexibility, visuospatial perception, response inhibition, working memory and psychomotor performances.

3. Discussion

Driving is a complex task subject to continuous processing of stimuli from one's own body and the outside world. Many substances can alter brain function, with the possibility of altering different aspects of driving performance when psychoactive substances are taken.

Alcohol is the psychoactive substance most frequently identified in the blood of drivers deceased in road-traffic crashes. Cannabis, cocaine, opiates, amphetamines represent the most prevalent classes of drugs found in the blood of RTC drivers, even if other different classes have been found [18]. It is well-established that DUIA and DUID are risk factors for becoming involved in a RTA [2,165], even it is considered

difficult to estimate the number of RTCs caused by alcohol and drugs [55].

Forensic issues relating to the assessment of the impact of drugs on driving performances are mainly represented by the adequacy of the biological matrix in objectively measuring the presence of drugs and metabolites, the reliability of the detection method and "cutoff values" that can be applied to refer to driving impairment [3,55,56].

Blood is indisputably the best available matrix of choice when investigating DUID cases, due to its temporal window of detection and close correlation with the active component within brain structures. Validated analytical methods, such as mass spectrometry, are unanimously required for evaluation: GC-HS and HPLC-MS/MS are the preferred instrumental choice [50] to identify and quantify several psychoactive substances in blood.

However, the main problems arise when discussing the cut off values for establishing the presence of impaired driving. In recent years, a few systematic literature reviews and meta-analyses have been performed on the effects of drugs and the risk of accident involvement, but these studies deal only with a single drug or few drugs [80,81,166–172]. Despite the fruitful proliferation of studies on the subject, at present only a few substances have been reported to have a clear dose/concentration dependent impairment, but for many this relationship is still unclear. Elvik et al. [3], performing a meta-analysis of 66 studies on amphetamines, analgesics, benzodiazepines, cannabis, opiates and medical drugs found that the use of these drugs while driving was associated with a fairly modest increase risk of accident involvement. However, there are reasons to remain sceptical about many findings reported in the same paper, as stated by the Authors themselves, because it was not clear whether the drugs were actually used while driving, there was no information regarding the situation or circumstances in which drugs were used, laboratory analysis were not always performed and many studies were considered to be of modest quality. The Authors actually stated in their conclusions that the evidence is not strong enough to conclude that the use of drugs are causally related to the increased risk of RTC, although there are fairly consistent statistical associations.

A further concern is that in the literature sometimes it is assumed that statistically significant differences are also clinically significant: this leads to conclusion about impairments that are therefore based on statistical differences with respect to a limited number of tasks [137] with no comparison against a normative baseline that takes into account the demographic characteristics of the individual. Previous studies also stressed that other problems are related to the lack of clarity as to which task subtest are adequately assessed and inadequate statistical analysis [173]. Furthermore, it should be noted that the culpability status is almost always unknown, creating an interpretative bias caused by researchers treating culpability ORs as equivalent to crash ORs [174,175], an issue of pivotal importance in the interpretation of previous literature.

It is well-known that there is a great variability between studies, and some Authors argued that many studies have methodological flaws, particularly with regard to controlling for potentially confounding factors [168,169]. Past driving history, medicinal drug history, type of road and weather events may also contribute to RTC, but these variables are usually not taken into account in previous studies. Difference in sample sizes and sample characteristics e.g. polydrug use, sample timing, severity of use, route of administration, psychiatric comorbidities, biological characteristics of the individuals, lifestyle differences, demographic background, genetic predispositions and environmental factors add complexity to measuring the impact of drug use in cognitive performances and RTCs. In polydrug use, common in the forensic practice, is then difficult to determine the contributions of each specific substance to cognitive performance. In general, it should be stressed that most studies are unable to determine the premorbid level of cognitive functioning. Ethical considerations constitute a huge element of discussion that obviously inhibit researchers from administering doses of drugs that, while they would be of interest to science in a certain sense, would be ethically unacceptable and non proposable.

In summary, in order to claim that a risk factor is causally related to an increased risk, the possibility that the increased risk was caused by different risk factors has to be excluded, which, in practice, is never possible, as it is not possible to obtain complete control for all confounding factors in observational studies [3]. To date, as for the chaos property, our ability to assess and discuss drug-related cognitive impairment in court is severely limited by the complexity and singularity of the human being, especially when "low" concentrations are involved. This is because complete prediction of cognitive impairment in the individual does not seem to be feasible.

In this context, three main legal approaches have been proposed. The first is the *impairment approach*, which is based on the identification of signs of impairment in the driver (usually detected through the assessment of horizontal and gaze nystagmus, walk and turn, and one leg stand test) [176]. Such approach is clearly not useful in fatal crashes since the impossibility of testing for signs of impairment in the individual and the extensive unresolved scientific discussion regarding the relationship between specific drug concentrations and driving impairment, as previously discussed. Even in non-fatal cases, having trained professionals at the scene to detect symptoms of impairment is an important limiting factors: in fact, clinical examination must be performed at the time of the crash by trained personnel (not a simple situation in everyday life) and may in any case present a certain subjectivity of the examiner if not performed with a standardized method and accompanied by validated scores. Currently this approach has been considered ineffective in DUIA deterrence [177]. To overcome these problems, approaches to set a concentration threshold for some psychoactive drugs have been proposed and some countries have proposed legal limits for illicit drugs, usually referred to as the "*per se*" approach. *Per se* approach is based on the identification and detection of a drug in biological fluid samples from a driver above a specified cut-off concentration [51,52]. Limits can be proposed on the basis of analytical parameters (limits of quantifications [LOQs] of laboratories, which vary over time depending on improvements in analytical methodologies). Regarding this approach, some countries have also proposed the "zero tolerance" approach which represents a complete ban on the use of a specified drug whilst driving [178] based on LOQs or limits of detections (LODs), the latter defined as the lowest concentration of the drug that the analytical procedure can reliably differentiate from a concentration of zero or the smallest measured content from which the presence of the analyte can be inferred with reasonable statistical certainty [179]. The "zero tolerance" approach on active compound can be considered the most protective of public health, solving the problem upstream when there is no clear scientific evidence on the effects of substances, eliminating the problem of inter-individual variability and harmonizing legal measures. It is also useful in cases of new drugs where cut-offs have not yet been proposed. On the other hand, it does not take tolerance into account, and it is extremely strict (e.g. accidental exposure and/or legitimate use within a medical prescription are not considered). Progressing technical improvements may also make it possible to detect traces of substances in such small quantities that they cannot cause any cognitive impairment [54]. Limits can also be fixed by law based on recommendations of scientific experts regarding concentrations that cause driving impairment [51,52,55,179], on the basis of the lowest concentration where an effect on driving is observed or concentrations considered indicative of risk of accident. However, with regard to the limits proposed as causative of an increase in risk of RTC/driving impairment, which is a sort of "scientific cut-off", regardless of the fact that the human being is roughly the same in each country, the proposed cut-off limits are very different (Table 2) and prone to open debate: severe criticisms has been raised about the viability of such cut-offs [180], and this variability is something that can be interpreted as an implicit demonstration of the inadequacy of such a system, given the lack of uniformity in legislation and especially in the scientific literature. Legal limits are therefore currently difficult to propose on a purely scientific basis, given that at

Table 2
Proposed cut-off limits.

Substance	Minimum value (Favretto et al., 2018) [55] [ng/ml]	Maximum value (Wolff et al., 2013) [53] [ng/ml]	GTFI[a] (2017) [55] [ng/ml]	DRUID[b] PROJECT [54] [ng/ml]	Vindenes et al., 2012 [51] [ng/ml]	Walsh et al., 2008 [52] [ng/ml]
Cocaine	1	80	2	10	24	10
THC	0.5	5	1	1	1.3	1
Morphine	1	80	2	10	9	10
Codeine	1		2	10		10
MDMA	1	300	2	20	48	20
Amphetamine	1	600	2	20	41	20
Methamphetamine	1	200	2	20	45	20

[a] GTFI: Italian Group of Forensic Toxicology.
[b] DRUID: Driving under the influence of drugs, alcohol and medicines.

present, positivity is often only indicative of substance use but not necessarily of proved drug-impaired driving. Clearly this approach, if procedures, limits and reporting methods are established, makes the prosecution process easier and more standardized, unlike the "impaired approach". Actually, *per se* laws are also encouraged by the U.S. National Drug Control Strategy but to date few studies have investigated the effectiveness of such approach [177,181]. The fact that not everyone involved in traffic crashes undergoes toxicological testing makes it complicated to measure the real impact; moreover, the finding of an increase in the prevalence of illegal drug driving following the enactment of drug laws does not necessarily indicate changes in road safety. In fact, variation on road conditions, vehicle safety, road enforcement (e.g. police resources) and different procedures in coding and reporting systems may also contribute to results not being easily comparable: therefore the assessment of the legal effects of the legislation should consider multiple aspects without which the interpretation may be misleading. This being the case, many studies have observed an increase in fatal crashes in cannabis-positive individuals after decriminalization of cannabis [182–186], although the findings are not always consistent with each other [187,188]. At present, it seems imprudent to comment on what is the most effective legal initiative for the DUIC. However, of interest in this respect is the study of Araz et al. which using NSDUH data has recently calculated, using system dynamics modeling considering also influence of road environment and travel demand, that the use of *per se* laws have a negative effect on drugged driving fatalities over time, as previously observed for alcohol-impaired driving. The cost-effectiveness of such policies is not yet clarified, but is certainly an area in need of research [181]. The last approach is the "mixed system", which combine the impairment approach with *per se* limits (also known as "two-tier system"). This approach could be considered to be the most protective for the subject, as it integrates the toxicological data with the clinical evidence of a real altered cognitive state, but it also entails the same limitations mentioned in the two previous approaches.

It should be noted that in toxicological evaluations of subjects who died at the time of the crash, blood tests indicate the concentrations at the time of death; when it comes to subjects who suffer non-lethal injuries, the toxicological evaluation is even more complex because the timing of detection is not constant: Busardò et al. [56] recommend that blood sampling should be preferably performed within 3 h from the event, but some substances, such as THC, have a pharmacokinetics so rapid that this interval could be sufficient to reduce their concentration in the blood below the cut-off values. Thus, in fatal RTCs where death occurs rapidly or almost immediately after the RTC, autopsy blood sampling would allow assessment of the concentration present at the time of death with possible assessment of cut-off thresholds; in non-fatal RTCs this goal would also depend on the rapidity of blood sampling, making it even more variable. However, it has to be taken into account, for a legislative as well as insurance purposes, that cognitive impairment in corpses is not measurable, drug concentration in blood may have different effects in different individuals, there is no linear concentration-effect relationship for most drugs, drug tolerance is not predictable, some drugs have a rapid metabolism (e.g. THC), polydrug abuse (with additive or supra-additive effects) is frequent but scientifically not well studied and improbable that it will be easily studied in the future: therefore it is difficult to establish cut-off values for active molecules. Factors that in non-fatal RTC would be added to the other problem on the frequent delay between the judicial authority stop because of a RTC and blood collection, notwithstanding the uniqueness represented by each human being.

The use of state-of-the-art detection limits (laboratory LODs) for illicit drugs therefore seems to be the most "fair" and public safety-oriented approach, even if it is the strictest policy a State can propose. Under this approach, any amount of illicit drug above the LOD in a driver's blood would lead to prosecution. However, there is no uniformity among laboratories performing forensic analyses, sometimes even in the same country [55]. In this perspective, identifying predetermined and internationally agreed criteria and/or statistical confidence levels is mandatory but it is an attainable goal. Obviously, accidental exposure and legitimate use of medical prescription should be further discussed and analyzed individually. The criticism of this approach is that it would negatively impact some substance users, e.g. chronic THC smokers or individuals who have smoked a single marijuana cigarette a few days prior to testing, even in the absence of any proven impairment to driving. Related to this aspect, a further significant unresolved problem regarding harmonization between countries is the fact that in some countries some substances are legal while in others they are not (e.g. cannabis, but actually also alcohol). In this regard, cannabis presents even greater problems than alcohol since it does not show linear pharmacokinetics; being fat-soluble with rapid uptake into fat cells and slow release thereafter, there are no valid elements to determine, given a blood concentration, the amount of cannabis taken nor the time of intake. Field sobriety tests currently used also do not have good sensitivity for distinguishing cognitive impairment induced by cannabis use [189] constituting another important field of research.

However, "risk thresholds" (a drug concentration threshold indicating a certain risk of accident associated with driving under the influence of a drug above that threshold), also potentially considered "anti-crash laws" [190] are destined to remain just approximations [52] or, as previously stated, "a mirage" [180], which may not be of valuable help in such a public safety issue, also because having a drug concentration below a certain risk threshold does not automatically mean that the drug cannot be the explanation for the RTC. However, also in this area, it seems that further research is worthwhile, not least because impairment studies may be of help for additional or graduated sanctions/penalties.

4. Conclusion

A zero tolerance approach based on LODs for illicit drugs and/or their active metabolites, with limits regularly revised by a panel of experts, does not take tolerance into account, but it sends a signal that use of drugs/polydrugs and driving are incompatible [51], and to date it

seems a policy that should be considered to harmonize judicial processes, given the failure of previous approaches to reduce RTC. This belief is in agreement with Favretto et al. who pointed out that leaving a driver unprosecuted following the detection of any amount of illicit drugs could appear to condone drug use and therefore should be preferable to penalize a driver regardless of the level of drugs detected in blood even though there may not have been a demonstrable concrete threat to public safety [55]. Having a legal limit for an illegal substance can also be considered a paradox [55]. Harmonization of illicit drug legislation is a difficult but estimable and achievable goal, and the "zero tolerance" approach seems to be the best justified approach so far. The course of action to be followed with the prosecution of cannabis in countries where its use is legal is still a controversial and unresolved issue, given the pitfalls in identifying a toxicological finding indicative of cognitive/driving impairment and the current lack of sensitivity of impaired-based approaches, which point to the need for further research.

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Declaration of competing interest

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