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REVIEW

Driving under the influence of new psychoactive substances☆

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Abstract Neurological and psychological symptoms caused by the use of new psychoactive substances (NPS) can have a major impact on an individual's ability to drive. However, there are limited data available on the prevalence of their use by drivers, the risk of a driver being injured/killed in an accident under the influence of NPS and on how driving can be adversely influenced by the consumption of these substances.

Detecting NPS in drivers is complicated in both *in situ* oral fluid testing and in laboratory tests that require advanced technology and analytical methods that must be kept up to date. These limitations, together with the characteristics of these substances, such as the ''legality'' of most of them, grant impunity to those driving under the influence of NPS and represent a real danger to non-consumers.

PALABRAS CLAVE
Nuevas sustancias psicoactivas;
Conducir bajo la influencia;
Análisis

Conducción bajo la influencia de las nuevas sustancias psicoactivas

Resumen Los síntomas neurológicos y psicológicos producidos por el consumo de las nuevas sustancias psicoactivas (NPS) pueden tener un impacto importante en la capacidad de conducir de un individuo. Sin embargo, se dispone de pocos datos de su prevalencia en conductores y del riesgo que supone que un conductor sufra lesiones/muerte en un accidente bajo los efectos de estas sustancias y de cómo realmente la conducción puede verse afectada por la presencia de estos compuestos.

El control de la presencia de NPS en conductores es complicado tanto en los análisis de fluido oral *in situ* como en las confirmaciones en el laboratorio, que necesitan una instrumentación

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avanzada y unos métodos analíticos que hay que mantener actualizados. Estas limitaciones, junto a las características de estas sustancias, como la «legalidad» de la gran mayoría, suponen la impunidad cuando se conduce bajo la influencia de las NPS y un peligro para los no consumidores.

Introduction

Although there are significant differences among different countries due to different cultures and different laws, it is a proven fact that a significant number of drivers of motor vehicles drive under the influence of alcohol and/or illegal drugs.[1,2]

The results from the literature indicate that alcohol and drugs are major problems for road safety. The main finding of the report *Driving Under the Influence of Drugs, Alcohol and Medicines* (DRUID, 2012) was that the greatest risk of suffering severe injuries/death is associated with driving with high concentrations of alcohol (above 1.2 g/l) and alcohol combined with other psychoactive substances.[3] Furthermore, it was proven that between 28% and 53% of injured drivers tested positive for at least one psychoactive substance, and it was estimated that, when multiple psychoactive substances are used, the risk is between 5 and 30 times greater than for sober drivers.[4]

Several countries have adopted laws for driving under the influence of drugs with different approaches to regulation, demonstrating their deterrent effect and the impact on road safety. In some cases, *per se* limits have been established for illegal drugs and, if the concentrations in the blood sample of the driver are above the defined cut-off concentrations, it will be considered as a crime.

In countries such as Germany, there is a two-tier system which allows for a lower level of penalty when the drugs present are above the ''*per se* limits'' and more severe penalties when the driver is really affected.[5] In Spain, since the Law on Road Safety was amended in 2014, zero tolerance has been established for drivers under the influence of drugs.[6]

In order to avoid being legally controlled substances, and to avoid being detected in traditional toxicological tests and analyses, new psychoactive substances (NPS), chemically very different to each other, are constantly changing, presenting stimulant (euphoria), hallucinogenic (dissociative or psychedelic) and/or depressive effects.[7] Recent toxicodynamic studies show that these compounds can also have effects on the ability to drive.[8] The impairment of the cognitive and psychomotor functions that they cause can lead to an impairment of the skills needed to keep a vehicle safely on the road, and therefore generate a risk, although it is not really known to what degree they affect the ability to drive.[9]

In general, the presence of any NPS would affect the ability to adequately control the vehicle, although the effect would depend on the specific substance consumed. The assessment of how driving is affected by NPS is made difficult, among other reasons, by a characteristic of the NPS consumer: the high frequency of poly-drug use which includes combinations of legal NPS (in terms of them not being explicitly prohibited) and illegal NPS, which means that it is difficult to determine if the effect is caused by just one NPS or by the combined effect. This effect, when it presents with other stimulants or with drugs that affect the serotonin receptors, may translate into an increase in their toxicity due to strong catecholaminergic stimulation.[10] Endless studies would be necessary to assess the different combinations at different concentrations. Therefore, the interpretation is broadly speculative and creates difficulties.[11]

With regard to monitoring drivers, in Belgium, France, Spain and Australia the legal framework allows for the use of oral fluid (OF) testing for analyses of driving under the influence, but these rapid tests have still not been developed for NPS and, so far, few systematic assessments of them have been carried out. Moreover, the lack of information both in terms of pharmacology and the number of studies makes the results difficult to interpret.[12]

In addition to this, from the toxicological analysis standpoint, the laboratories are challenged every day by aspects of the NPS phenomenon. On the basis of the substantial inefficacy of most traditional methods of toxicological detection in biological samples to identify new compounds that appear on the market, accurate and reliable methods are required for NPS, with advanced instrumentation, often with limited availability of certified reference materials, among other difficulties.[13]

In this context, and in comparison with publications on clinical symptoms and signs of intoxication from these compounds, there are little data available on the risk of a driver who has taken a specific NPS suffering injuries/death in an accident, or on how driving can really be affected by the presence of these compounds. Some authors conclude that the prevalence data from different studies are difficult to compare, and that ideally, the evolution of the use of NPS must be continued, year after year, in a similar population with a similar methodology and analytical process.[14]

A review of the knowledge on the impact that the consumption of NPS has on driving is presented, selecting

studies from the most common groups: synthetic cathinones and synthetic cannabinoids, and from other compounds such as ketamine and related compounds, phenethylamines and khat alkaloids.

This article highlights the current difficulty of estimating this impact due to the impossibility of *in situ* studies in the OF sample on a routine basis and the consequent lack of monitoring of drivers who are under the influence of these compounds.

Presence of new psychoactive substances in drivers: prevalence and how they affect driving

Prevalence

The results from the literature indicate that alcohol and drugs are one of the most significant problems for road safety. The main finding of the DRUID report (2012) was that the greatest risk of suffering severe injuries/death is associated with driving with high concentrations of alcohol (above 1.2 g/l) and alcohol combined with other psychoactive substances.[3] Furthermore, it was proven that between 28% and 53% of injured drivers tested positive for at least one psychoactive substance, and it was estimated that, when multiple psychoactive substances are used, the risk is between 5 and 30 times greater than for sober drivers.[4]

If, in general, NPS represent a multi-faceted problem, those related specifically to drivers are an open research area.[4,15]

Among the NPS studies related to driving, those on prevalence are limited, as the tests applied roadside have still not been adapted for these compounds and routine *in situ* testing is not performed.

According to data obtained by *The European Monitoring Centre for Drugs and Drug Addiction* (EMCDDA) up to 2014, the prevalence of NPS in drivers suspected of driving under the influence in Europe was as follows: desoxypipradrol (Finland) 1.7%; fluoroamphetamines (Denmark) 15 cases; gamma-hydroxybutyric acid (GHB) (Germany) 2.0%; GHB (Norway) 25 cases; GHB (Sweden) 548 cases; methylenedioxypyrovalerone (MDPV) (Finland) 5.7%; phenazepam (Finland) 3.5% and synthetic cannabinoids (Norway) 3%. This indicates that all the samples also contain other drugs.[16]

The results from Yapa and Drummer, with an LC-MS/MS method capable of detecting 56 synthetic cannabinoids and 32 synthetic cathinones in blood samples, show a low prevalence of NPS in cases of fatal road traffic accidents. Over a two-year period, prevalence was 2.4% compared to 29% from other drugs, in line with the previously published results from Norway and Germany. The authors indicate that synthetic cannabinoids are the most detected compounds in drivers, thereby demonstrating that they affect the ability to drive. In the case of cathinones, controlled studies on their ability to affect the skill necessary for driving are not available (2016).[5]

These authors also reveal the frequency of the presence of these compounds in drivers, in particular the first-generation compounds (1-pentyl-3-(1-naphthoyl)indole [JWH]) and (1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM-2201), with the latter being the most prevalent in the reviewed cases. However, in recent studies, third-generation compounds have also been detected.[10]

The latest study conducted in Belgium by Wille et al.[4] found an NPS prevalence of 7% in blood samples and of 11% in OF, with the following NPS being found: diphenidine (12), ketamine (8), methoxetamine (2), 4-fluoroamphetamine (3), 2-aminoindane (3), methiopropamine (1), a mixture of 5-[2-(methylamino)propyl], 5-(2-ethylaminopropyl)benzofuran, benzofuran (5-MAPB/5-EAPB) (1), alpha-pyrrolidinovalerophenone (α-PVP) (2), α-pyrrolidinovalerophenone (THPVP) (1), mephedrone (1), methedrone (1), 4-methylmethcathinone (1), N,N-diallyl-5-methoxytryptamine (5-MeO-DALT) (1), 4-Acetoxy-N,N-diisopropyltryptamine (4-Acetoxy-DiPT) (1), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA) (1), trifluoromethylphenylpiperazine (1) and ethylphenidate (1).

The prevalence studies highlight the need for adequate analytical confirmation procedures that make it possible to evaluate the impact of the consumption of these substances on an individual's ability to drive, in particular, and among other reasons, due to the constant development of new modified substances.[17] Other characteristics of these substances, such as instability in blood samples, which is the case of cathinones (mephedrone or methylone), mean that they have been detected sporadically in samples from drivers. These results may not be a true reflection of their presence.[18]

Affect on driving

By consuming NPS, the user is seeking similar effects to those of traditional recreational drugs, and it may be that both the pharmacology and the cognitive and motor adverse effects have a certain similarity to these recreational drugs. Although this is a reasonable assumption, it is only an assumption and there may be significant differences that could be revealed in driving simulation studies with voluntary subjects; however, these studies (administering unapproved compounds without safety data to healthy volunteers) would not be ethical and it is unlikely that they will be conducted.

Synthetic cannabinoids

In studies in which their presence is detected in drivers' blood samples, the effects reported include confusion, depression, paranoia and psychosis. In the case of consumption of synthetic cathinones, these can increase the driver's tendency to make decisions with unnecessary risks, as well as affect concentration and cause visual impairment. In particular, abnormalities in behaviour and the ability to drive due to the presence of methylenedioxypyrovalerone have been reported.[19]

Another study on seven drivers, in whom synthetic cannabis products were found, reveals that their consumption can cause an effect similar to that generated by tetrahydrocannabinol (THC), and, although it was published in 2013, the authors highlight the need for sensitive a analytical procedures for these compounds and their

metabolites and conclude that both the police and forensic toxicologists need to familiarise themselves with the effects of use and be aware of the problem for driving.[5]

Nevertheless, in the case of synthetic cannabinoids, the general conclusion of the published literature shows a greater risk of adverse effects and of the effect on the ability to drive than that caused by the consumption of cannabis, which is in itself already known not to be compatible with safe driving.[20]

Driving under the influence of these compounds has been recognised to cause physiological changes and to affect users, who manifest deficiency, red bloodshot eyes, tachycardia and hypertension, with consistent presence of convergence insufficiency.[21]

Deficiencies in the ability to drive are due to effects of central sedation and impairment of the fine motor skills which are necessary to keep the vehicle on the road, as well as other dangerous adverse reactions such as high blood pressure, tremor, seizures and hallucinations and paranoid behaviour.[22] In drivers affected by the consumption of synthetic cannabinoids who underwent examination, the comparison of the effects of synthetic cannabinoids ($n = 16$) and cannabis ($n = 25$) revealed that synthetic cannabinoids significantly increased the frequency of confusion, disorientation and incoherence.[11]

Synthetic cathinones

The first case of death with detection in biological samples from drivers who drove under the influence was in 2011. Since then, the presence of these compounds has been confirmed in post-mortem samples from drivers and in those in whom the driver's behaviour ranged from incoordination to lack of response and/or breakdown, with physical symptoms such as glazed, bloodshot eyes with contracted pupils and slurred speech.[23] The typical adverse effects observed after consumption are cardiac, neurological and psychological symptoms, such as agitation, difficulty breathing, palpitations, dizziness, confusion, panic, paranoia, as well as auditory and visual hallucinations. When compared with cocaine and amphetamine, both MDPV and α-PVP have proven to be much more potent norepinephrine-dopamine reuptake inhibitors.

The subjective effects of consumption include increased energy, euphoria, empathy and increased libido, while adverse effects include tachycardia, confusion, agitation, insomnia, aggression, hallucinations and hypertension.[24] The psychophysical tests used in the assessment of the ability to operate motor vehicles performed in individuals under the influence of MDPV demonstrated considerable functional impairment of psychomotor abilities in 84% of those tested and in 7% to operate motor vehicles. The abnormalities observed included difficulty defining the current time, walking in a straight line, turning around and verbal expression.[25] However, there have been no controlled studies to date which examine the effect of synthetic cathinones on the ability to drive.[13]

Khat alkaloids

Even though there is sufficient evidence to suggest that they may be a contributor to road traffic accidents, and taking into account that they are commonly chewed by drivers in Ethiopia and other countries in Eastern Africa and the Arabian Peninsula, their effects continue to be underestimated.[26] Their consumption has effects on the autonomic nervous system similar to those experienced with amphetamines, such as a slow pupil reaction to light, dry mouth and increased heart rate. The clinical effects observed after the chewing of khat include a stimulation phase and a depression phase. Impairment of the psychophysical functions, such as effects on the nervous system, trembling, restlessness, nervousness, daze, apathy, dullness, impairment of attention, walking or standing on one leg, may have an impact on driving.[27]

Ketamine

Also considered an NPS, it causes impairment in different neurocognitive and psychomotor functions which are relevant for driving. The psychotropic effects and other effects, such as slurred speech, vomiting, confusion, drowsiness, reduced motor activities, lack of coordination, dystonia and ataxia with stiffness or motor paralysis, could reasonably justify a greater risk of driving under the influence and an increased number of errors related to impulsiveness, a behaviour associated with unsafe driving. Furthermore, changes in perception, in eye movements and in visual performance suggest an impairment in the ability to follow the road or capture the movement of objects, such as the presence of other vehicles.

Ketamine may affect perception of the passage of time and a deficit in attention. With regard to executive functions, several studies have found an increased reaction time with various tasks after the administration of ketamine.[28]

Methoxetamine

Structurally related to ketamine, it presents similar effects. In the first documented case of methoxetamine in a whole blood sample, signs of slurred speech with difficulty speaking without being able to form proper sentences, bloodshot eyes, blank expression, lack of comprehension and uncontrollable motor movements, excessive sweating, muscle tone so stiff that the driver could barely get out of the vehicle because he could not control his legs or straighten his back, confusion when speaking and fixed gaze as if the driver was not aware of what was happening were reported. One of the individuals accompanying him reported that he had consumed methoxetamine, which was confirmed afterwards in the laboratory.[29]

Substituted phenethylamines

We refer to the case of a driver who developed sudden rage as a consequence of ingesting 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe). He drove his car off the road and started to destroy the interior of the vehicle before dying. These compounds are extremely potent at low concentrations, with hallucinogenic effects by triggering a serotonergic avalanche after consumption.[30] In another case, in which the driver confessed to consuming 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethan-1-amine (25C-NBOM), the manifestations were daze, confusion and lack of understanding of instructions due to an altered mental

state. He also had increased heart rate and dilated pupils, although he did not display stiffness or seizures, as has been reported in other cases of intoxication by this compound.[31]

Monitoring of the presence of new psychoactive substances in drivers

The growing quantity of NPS has brought about a new challenge in testing for recreational drugs.

In some legislation on road safety, it has been established that drug tests should be carried out on drivers who have been injured in a car accident or who show signs of being affected which are not consistent with the use of alcohol. Samples are tested for a wide variety of compounds that potentially impair the ability to drive, including therapeutic prescription drugs with effects on the central nervous system, common illegal drugs, as well as NPS.[18]

However, the testing measures against driving under the influence of drugs often start with an OF roadside test using an *in situ* examination focusing on classic recreational drugs: cannabis, opioids, cocaine and amphetamine. In some countries, in the case of a positive result, a blood sample is taken afterwards for confirmation using liquid chromatography-tandem mass spectrometry detection.[10] In Spain, for positive results *in situ*, testing is confirmed in another OF sample in the laboratory, and, in cases involving an accident, a blood sample is used for confirmation.

OF is offered as a non-invasive sample for roadside screening which enables direct supervision of the sampling[32]; detection of compounds in the OF indicates recent consumption of drugs. Studies conducted have demonstrated that qualitative findings in OF are consistent with findings in whole blood, especially when metabolites are taken into account. However, for most drugs, the correlations of the OF/blood concentrations are not good for all compounds, and the blood concentration of a compound cannot be estimated from its OF concentration.[33]

Although the OF is considered a useful matrix for testing drivers *in situ*, the methods used continue to demonstrate a lack of sensitivity and, to ensure adequate reliability, they need confirmation by GC–MS or LC–MS, even when the commercial kit with the best sensitivity and reproducibility results is used.[34] If, in general, the devices are not considered sufficiently sensitive and accurate for cannabis, although acceptable for other recreational drugs, they have nevertheless been improved compared to those used in the projects *Roadside Testing Assessment* (ROSITA 2) and DRUID, although the declared limits are still too high for correct assessment of driving under the influence of drugs through the OF test, in particular for THC and cocaine.[35]

Numerous studies on recreational drugs in OF indicate that in this matrix, drugs tend to be found as a parent compound, which would be favourable for the case of synthetic cannabinoids, facilitating the inclusion of new compounds. However, these synthetic cannabis products are structurally different from THC and will not respond to the same roadside devices that are routinely used for cannabis.[3]

In the case of these compounds, studies on their presence in saliva have been conducted for AM-2201 and JWH-018 after their consumption. AM-2201 is excreted in saliva in small quantities, while if it is smoked it remains in the oral cavity. In the other case studied, it has a detection window of between 5 and 12 h after smoking.[36] However, according to the literature consulted, a systematic evaluation of this topic has not been conducted, and controlled *in vivo* studies would be necessary, which, generally and for ethical reasons, are not available. This results in limited information on the presence of NPS in OF, as well as their detection windows.[19]

With regard to roadside devices, the study conducted by De Castro et al.[37] should be highlighted. The authors evaluate the effectiveness of the devices used in Spain for *in situ* testing for synthetic cathinones: methedrone, methylone, mephedrone, MDPV, fluoromethcathinone and fluoromethamphetamine and two synthetic piperazines: 1-(3-chlorophenyl)piperazine (mCPP) and 1-(3-Trifluoromethylphenyl)piperazine (TFMPP). Their results indicate that the presence of these compounds at high concentrations could give rise to a false positive for methamphetamine, although it may not be confirmed with the traditional testing methods, as they generally do not include new psychoactive drugs. On the other hand, with a positive reactivity of these compounds to methamphetamine having been confirmed, these devices may be used as long as the laboratory has its analytical method validated consistent with the method that the authors present for its determination.

These authors refer to other studies that broaden the range of NPS to synthetic cannabinoids as well as cathinones, with a confirmatory method that enables the use of half the volume of OF as that used by them, in which the applicability of a series of devices for NPS used for recreational drugs *in situ* is demonstrated.[37] Other articles conclude that special devices should be developed for synthetic cathinones as the concentrations necessary for positive results are too high in relation to those expected in forensic cases.[38]

The latest review on the matter, conducted by Øiestad et al.,[12] highlights that there are few effectiveness studies on devices specifically aimed at NPS for their detection *in situ*.

This leads us to the idea that, if a negative result is obtained in the preliminary tests conducted by the traffic police to detect the presence of alcohol and classic narcotic substances in a driver, the driver may be under the influence of one or multiple other psychoactive agents, the presence of which is not detected by the majority of tests *in situ*, which may mean that the driver develops a sense of impunity and therefore drives with a greater likelihood of being involved in a road traffic accident.[15]

As has been indicated previously, confirmation is required for positive results with an analytical method intended to detect NPS, as they are not detected in traditional toxicological analyses.

In general, NPS determinations are carried out using analytical strategies that enable the characterisation of unknown compounds based on the use of advanced high-resolution analytical techniques along with computer tools.[39] A first option would be to implement a targeted (specific) method *versus* another non-targeted (more general) method. The targeted methods often use the highly sensitive multiple reaction monitoring (MRM). This promotes the main drawback of OF, which is the limited volume of the sample. When the general methods are

applied, the preparation of the sample should also be general and not exclude compounds.

Current development of ambient ionisation techniques, such as desorption electrospray ionisation (DESI) or direct analysis in real time (DART), may be of interest to ensure elucidation of unknown structures, without requiring a multi-step sample preparation technique.[10]

Some prevalence studies advise that investigations should focus on the development of methods covering a broad spectrum of these new substances which are also constantly changing. In addition, forensic toxicology should take into account the possibility of various structural isomers, difficult to distinguish using the generally-used chromatographic and spectrometry techniques.[17]

The complexity that the analysis of NPS entails is further compounded by the lack of knowledge of the active, toxic and lethal concentrations. Furthermore, in view of the literature consulted in other reviews, it can be observed that the concentrations overlap significantly in cases such as driving under the effects, chemical submission, recreational use and deaths, which means that toxicologists, coroners and forensic pathologists do not know how to interpret the range of individual results. There are also large gaps regarding the dose, tolerance, metabolism, duration and intensity of the effects and presence in different biological fluids, which in the case of driving under the influence would mainly be OF.[40,41] Due to the possible impact of acute or chronic tolerance, the concentrations found in drivers do not necessarily reflect the degree of the effect, which also makes it difficult to establish concentrations which are dangerous or which affect driving.[25]

Notwithstanding the above, for the confirmations mentioned and following the international trend for NPS, in the case of Spain, given that the tolerance is zero, for the routine confirmation the qualitative detection without need for the quantitative determination would be sufficient, although a minimum content of analyte in the sample should be established that must at least be detected and confirmed. This does not negate the use of advanced analytical techniques and continuous maintenance and updating of the methods.[40,42]

Considerations

Given that no special devices for the *in situ* OF testing of NPS have been developed to date, the vast majority of NPS that may affect driving will not be detected.

We also find ourselves with the problem that very few NPS are controlled substances due to their characteristics, but, for those that are controlled, it is possible that they will not be detected with the current system of *in situ* testing, unless they are in very high concentrations.

Therefore, and as a strictly personal opinion, it would be interesting to perform a study on the prevalence of the presence of these substances in drivers in the Spanish population, with the necessary devices, establishing the usefulness of the OF sample for NPS. Furthermore, it would be interesting to assess the need for a protocol to follow when dangerous driving is detected, or when during a traffic stop, the driver presents signs of driving under the influence, with a negative routine alcohol and drugs test.

Although the risk for driving is not established due to a lack of specific studies for each individual NPS, we already have clinical and forensic data that show their harmful effects to health, as well as effects that can result in dangerous driving.

We are aware of the existence of hundreds of NPS in a changing market that are considered harmless by a large portion of the population, in particular young people. Along with other characteristics, this facilitates high consumption considered a worrying public health problem that, in the case of driving under their influence, is extrapolated to road safety, also posing a threat to non-consumers.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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