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Review Article

Benzodiazepines and driving pharmacological and legal aspects

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ABSTRACT

Objective: Benzodiazepines are a group of psychotropic drugs that are frequently prescribed. There are many published studies indicate that these drugs can affect driving ability. These studies are either epidemiological or experimental. Some efforts have been made recently toward the establishment of legal limits for benzodiazepines in the blood of drivers. **Methods:** A systematic review of the published literature was performed using PubMed and Medline databases, together with additional non-peer reviewed information sources, including books, and publications of state authorities in different countries concerning the effects of benzodiazepines on driving ability. The search terms used were "benzodiazepines," "driving under the influence," "impairment," "traffic accidents," and "legislation." **Results:** The results of the collected epidemiological and experimental studies were presented and evaluated. In many cases, the results of different studies are controversial due to the fact that they have no uniform protocols. The efforts to establish legal limits for benzodiazepines remain to be proven effective. **Conclusions:** There is significant evidence that benzodiazepines affect negatively driving ability. Suggestions on how the problem of driving under the influence of benzodiazepines should be faced are made. Both physicians and pharmacists should advise their patients of the impairing effects of benzodiazepines, particularly in relation to drowsiness and sedation, and the implication of these effects on driving skills. Zero-tolerance legislation for benzodiazepines seems impracticable as these drugs are used extensively. The implementation of per se legislation by adopting legal limits would more properly secure traffic safety.

KEY WORDS: Forensic Sciences, forensic toxicology, benzodiazepines, driving under the influence, impairment, legislation, traffic accidents

INTRODUCTION

Benzodiazepines were introduced in the 1960s for the treatment of insomnia and were the most frequent prescribed psychotropic drugs worldwide [1,2]. They are used today for treating a variety of symptoms, including anxiety, insomnia, muscle spasm, stress-related disorders, epilepsy, or as a pre-operative medication [3-5]. As their efficacy and tolerability are generally good, especially in the short term, they are used extensively by a large number of people [5]. Benzodiazepines are legally prescribed to patients to treat medical disorders and conditions; hence, they are more widely available and accessible to the general public than illicit drugs, making it difficult for epidemiological research to capture the hidden target populations that may be using prescription drugs for non-medical purposes [6]. As far as it concerns the self-reported prevalence of benzodiazepines, there is a lack of data in the general population. In 2007, global consumption of anxiolytics was ranged between 21 and 25 billion defined daily doses for statistical purposes (S-DDD). In 2009, statistical data showed that Europe has the highest average consumption of both for sedative-hypnotics and for anxiolytics, expressed as S-DDD per 1000 inhabitants per day [7]. According to the Substance Abuse and Mental Health Services Administration (2012), the most common prescribed benzodiazepines in the USA for 2009 were alprazolam, clonazepam, lorazepam, diazepam, and temazepam [8]. During the years 1998-2007, an increase on benzodiazepine prescriptions was observed in the USA ranging from 17% for diazepam to 114% for clonazepam [9]. In England, primary care prescribing of benzodiazepine has been relatively constant between April 2008 and April 2012, ranging between 10.9 and 11.1 million prescriptions annually. The prescribing of benzodiazepine hypnotics (flurazepam, loprazolam, lormetazepam, nitrazepam, and temazepam) has declined over the 4-year period, while that of benzodiazepine anxiolytics (alprazolam, chlordiazepoxide, lorazepam, and oxazepam) has increased slightly, but prescribing has increased most for benzodiazepines that can be used for other purposes (clobazam, clonazepam, diazepam, and midazolam) [10]. Given that benzodiazepines are prescribed to outpatients, it is reasonable to conclude that patients taking these drugs qualify as regular drivers and are likely susceptible to driving under their influence [11].

Benzodiazepines are considered central nervous system (CNS) depressants and act on the spinal cord as well as in many

areas within the brain, including the cerebellum (important for balance and co-ordination), limbic areas, and cerebral cortex (thought and decision-making, movement, and sensation) [3,12]. Due to this action, it is clearly mentioned in the summary of product characteristics of all benzodiazepines that these drugs can severely impair driving ability.

The effects of benzodiazepines depend on the duration of action of each one [13]. Their half-life is a significant determinant of their duration of action, but also of their residual effects [5,13]. The various benzodiazepines do not differ markedly in their pharmacodynamics, but they show pharmacokinetic differences resulting in variations in their time course of action [14].

Benzodiazepines can be classified according to their half-life time (T1/2), as short-acting (<8 h), intermediate-acting (8-24 h), and long-acting (>24 h) [15,16]. Benzodiazepines also differ in time of onset (Tmax) and whether they have active metabolites or not [Table 1] [15].

Benzodiazepines can be also classified according to their therapeutic indications, as anxiolytics, or hypnotics [17]. They cause sedation, and when they are used as hypnotics they are administered at bedtime. When sedation lasts into the following day or when these drugs are inappropriately used, sedation becomes an adverse effect. This sedation can be a major cause of traffic accidents [15].

Benzodiazepines have been found to significantly impair driving ability the morning following bedtime administration that exceed the effects of 0.5 g/L blood alcohol concentration, which is used as legal limit in several countries around the world. Impairment sometimes remains significant in the afternoon (16-17 h after administration) especially when twice the recommended dose is used [15,18,19]. However, not all benzodiazepine hypnotics show the same pattern of impairment. For example, impairment with nitrazepam was more pronounced in the afternoon than during the morning tests [15]. Many studies also report a significantly increased traffic accident risk for those using benzodiazepine anxiolytics [2,16,18,20,21]. The use of benzodiazepines with a long half-life has been associated with a significant increase in crash risk, although the risk was slightly lower after continuous use for up to 1 year. Conversely, there was no such elevated risk for drivers using benzodiazepines with a short half-life [14]. Among the intermediate-acting benzodiazepines, alprazolam, and lorazepam caused marked impairment, and less so for lormetazepam and temazepam. Long-acting benzodiazepines such as flunitrazepam, clonazepam, and diazepam showed a clear impairment effect. A few benzodiazepines should generally be regarded as unlikely to have a residual effect the morning after night-time use. The choice of hypnotic molecules with the shortest half-lives and the fewest residual effects on behavioral efficiency has become a challenge in the context of road safety [5,13].

Table 1: Therapeutic blood concentrations and pharmacokinetic parameters of benzodiazepines [15,16,39]

Benzodiazepines	Therapeutic blood concentrations (ng/mL)	T1/2 (h)	Tmax (h)	Active metabolite (s)
Hypnotics				
Triazolam	2-20	1.5-5.5	1	+
Temazepam	100-1000	7-11	0.8	-
Loprazolam	3-10	8	2-5	-
Lormetazepam	1-20	10	1-2.5	-
Flunitrazepam	5-15	16-35	1.2	+
Nitrazepam	20-200	18-34	2	+
Flurazepam	0.5-30	47-100*	0.5-2	+
Anxiolytics				
Oxazepam	100-1000	4-15	2-3	-
Alprazolam	20-60	12-15	1-2	-
Diazepam	100-1000	20-100*	1-2	+
Lorazepam	20-250	12-16	2	-
Clonazepam	20-60	30-40	0.5-1	-
Bromazepam	80-170	8-19	1-4	+
Chlordiazepoxide	700-2000	6-27	1-2	+

*T(1/2) includes those of the active metabolites

Some studies suggested that the negative effect of benzodiazepines on driving ability is dose-related and depends on their blood concentrations. A concentration dependent deterioration of performance is also observed after acute intake of these drugs [17,22]. Although, acute exposure to benzodiazepines is known to impair driving skills, chronic exposure is thought to be relatively safe due to tolerance developing [17]. It should be noted that after chronic and sub-chronic use of benzodiazepines, partial or complete tolerance to the impairing effects on driving may develop [23], as a consequence of the physical dependence that is produced by benzodiazepines [5]. Longo *et al.* showed that first-time users of benzodiazepines have a significantly higher risk of crash involvement within 2 months of first filling a prescription for a benzodiazepine [14].

The aim of this paper is to review the results of the published epidemiological and experimental studies concerning the effects of benzodiazepines on driving ability of individuals, to discuss their role in traffic accidents, as well as the existing legislation on driving under the influence of benzodiazepines.

METHODS

A systematic review of the published literature was performed using PubMed and Medline databases, together with additional non-peer reviewed information sources, including books and publications of state authorities in different countries concerning the effects of benzodiazepines on driving ability. Our review included epidemiological and experimental studies, as well as systematic and meta-analysis reviews on the subject. The search terms used were "benzodiazepines," "driving under the influence," "impairment," "traffic accidents," and "legislation."

Influence of Benzodiazepines on Driving Ability

Driving under the influence of drugs (DUID) other than alcohol is considered to be an increasing cause of traffic accidents worldwide [18]. Most drugs that act on CNS usually alter

its function. This alteration causes behavioral modification that may impair driving performance by diminishing perception, alertness, visual acuity, judgment, decision-making, and responses to external stimuli [17,18,24-26]. When benzodiazepines are taken simultaneously with other sedative drugs on CNS, as usually happens with elder people, a synergistic effect may develop which can influence significantly the driving performance [16,27]. Indeed, benzodiazepines are the most common detected in driver fatalities and in many cases they are detected in combination with at least one other drug, namely alcohol [28].

During the last decades, the use of pharmaceutical and psychotropic substances, including benzodiazepines, by victims of traffic accidents increased significantly [21,27,29-49]. All the above studies clearly show that prescribed drugs, like benzodiazepines, may impair driving performance similarly to the illegal ones, and thus become a risk to road traffic safety. Among these drugs, benzodiazepines hold a significant position. The above statement is verified by the fact that drivers that use these drugs fail at the standardized field sobriety tests. Normally, these tests are focused on alertness (orientation and behavior), balance control, reaction time, divided attention, the critical flicker fusion test, cognitive tasks such as memory tasks, subtraction tasks, motor function (Romberg's test, walking, and walking after turn), and ocular side effects of drugs (nystagmus and pupil size). The results of the above-mentioned studies indicated that increased concentrations of benzodiazepines had an increasingly negative influence on behavior, walking, walking after turn, and Romberg's test, and there was no significant relation between the concentration of benzodiazepine and the effect on pupil size, nystagmus, or disturbed orientation [4,50].

Many epidemiology studies have been conducted during the last 20 years, in order to investigate the prevalence of benzodiazepines among the driving population and their contribution, as a causative agent, to traffic accidents by studying the frequency of this use as well as the culpability of the drivers under the influence of these drugs [2,24,26,27,32,33,35,42,44,46,51-56]. Many benzodiazepines have also been shown, during experimental studies, to impair certain psychomotor tasks (depending on the benzodiazepine itself, dose, half-life, and individual differences) showing a "hangover" effect next morning. Therapeutic doses of benzodiazepines usually slow simple reaction time when testing occurs within a few hours after administration of a single dose. This impairment typically diminishes after sleep. The impairment may continue into the following day or even for more days when long half-life benzodiazepines are administered under a continuous dosing schedule. Visual-motor coordination tasks like tracking are affected by therapeutic doses of hypnotic benzodiazepines only a short time after administration [13,15,19,57-68].

The most frequent detected benzodiazepines in biological fluids (blood, oral fluid, or saliva) from drivers worldwide are diazepam, nordiazepam, temazepam, oxazepam, flunitrazepam, alprazolam, and clonazepam [4,22,24,27,31,38,39,41,42,44,47-52,55,69-71]. Bramness *et al*. grouped the blood concentrations of benzodiazepines found in suspected DUID or alcohol in four groups, with drug levels designated as "therapeutic," "mildly," "moderately," or "highly elevated" [Table 2]. They found that the impairment of the drivers was higher when blood levels of specific benzodiazepines such as diazepam, oxazepam, and flunitrazepam were significantly higher [4].

Table 2: Blood concentrations of benzodiazepines [4]

Benzodiazepine	Blood concentration (ng/mL)			
	Therapeutic	Mildly elevated	Moderately elevated	Highly elevated
Diazepam	≤310	340-650	680-1000	≥1020
Oxazepam	≤1110	1150-2260	2290-3410	≥3440
Flunitrazepam	≤3	6-9	13-16	≥19
Nitrazepam	≤55	85-140	170-230	≥250
Alprazolam	≤37	40-77	80-117	≥120
Triazolam	≤7	7-13	14-20	≥21
Clonazepam	≤48	51-98	101-148	≥152

Several epidemiological studies have documented that the use of benzodiazepines constitute a considerable risk to traffic safety when they are used therapeutically, and probably at a much higher degree when they are misused. This involves not only the risk for traffic accidents [4,50,70,72] but also culpability [14,51,52,73], risk of accident injury [18,26,40,43,46,47,72], and necessity for hospitalization after crash [21]. It is not very clear if hypnotic and anxiolytic benzodiazepines can equally increase the risk of a traffic accident (expressed as odds ratios) [72] or not [17,20]. It is a fact though that hypnotic benzodiazepines are normally taken at night, at bedtime and so, they have a little effect next day, whereas anxiolytic drugs are taken during the day [17].

Reviewing the effects of benzodiazepines on driving ability, it has to be taken into account the fact that these drugs are usually used by elderly people [2]. Driving ability of these people is already influenced by age and the relative effect of benzodiazepines has to be added. The risk for drivers older than 65 years is higher when they take longer-acting and larger quantities of benzodiazepines especially within the 1st week after treatment initiation. Moreover, older people must be more cautious especially when they mix benzodiazepines with alcohol or other sedative drugs [2,17,20,74]. In general, younger people take hypnotics intermittently, while older people tend to take them long term. For this reason, tolerance is the more often developed by older people. On the other hand, young drivers may, in general, have different driving patterns, and the use of hypnotics may in turn influence them in a more unsafe manner. It cannot be excluded that young people with sleep problems have a higher concomitant use of alcohol and/or illegal drugs than the older insomnia patients [2]. In any case, it seems that a higher risk for traffic accidents under the influence of benzodiazepines is observed among young males [2,17,27,72].

Smink *et al.* reviewed 66 studies concerning different driving populations, from the general population to accident-involved road users (with or without injury) and to fatally injured, accident-involved drivers, admitted to a hospital. They

concluded that the greatest accident risk is associated with the use of long half-life benzodiazepines, increasing the dosage and the first few weeks of use of benzodiazepines. Clear evidence of increased culpability associated with benzodiazepine use was not documented as the divergent study populations and comparison groups, and the variety of methods used to express the outcome of interest, hampered comparison between results [75].

It is well-established that multiple drug use and drug alcohol combinations, among vehicle drivers, increase the risk for a traffic accident. The risk of being involved in or responsible for an accident increases when another psychoactive substance (usually alcohol and/or cannabis) is taken in combination with a benzodiazepine [23]. The combination of benzodiazepines with other CNS depressant drugs, such as alcohol, or opioid analgesics, results in additive impairing effects on psychomotor performance and greater relative risk of accidents [16,27]. Drummer *et al.* concluded that when drivers use benzodiazepines in combination with cannabis, stimulant, opiate, and miscellaneous psychoactive drug groups show a strong and significant culpability when involved in traffic accidents [73].

Elvik performed a meta-analysis of 66 studies containing a total of 264 estimates of the effects on accident risk of using illicit or prescribed drugs, including benzodiazepines, when driving. The results of this meta-analysis show pretty convincing evidence on the negative effects of benzodiazepines on driving and increased crash risk [76].

Although, there is strong epidemiological evidence that benzodiazepines can influence negatively driving ability, very limited experimental evidence exists to confirm the exact nature of the impairment that these drugs cause to drivers that use them. A significant number of laboratory studies have showed that administration of benzodiazepines impairs psychomotor function, with resulting effects on motor speed and visual/motor co-ordination. It was also found that benzodiazepines increase reaction time, reduce vigilance, impair divided-attention tasks, and impair cognition which is possibly the most significant adverse effects on driving skills [13,15,19,57-68]. The impairment caused by benzodiazepines can be observed immediately after initial administration and can last up to the next morning after ingestion [13,15,19,58,59,61]. Such an effect was not observed with temazepam [67]. The experimental studies performed until now have not studied the whole group of benzodiazepines, but only the most common used. More specifically, the most studied benzodiazepines are diazepam, oxazepam, temazepam, flurazepam, flunitrazepam, triazolam, alprazolam, lorazepam, bromazepam, nitrazepam, lormetazepam, medazepam, loprazolam, flutoprazepam, and brotizolam. In most studies, there is a clear correlation between blood benzodiazepine levels and response of the drivers, although, some older studies did not find such a relationship [57,77] or suggest that benzodiazepines at low doses have little effect on driving performance [15,60,62,63].

Legislation

The rising prevalence of driving under the influence of illegal and medicinal drugs and its potential impact on traffic safety have raised awareness among media, scientists, and policy makers all over the world and prompted calls for more effective control. Reducing the number of motor vehicle crashes caused by drugs impaired drivers is a serious issue that should be faced by government agencies. In order to determine whether a driver, involved in an accident or stopped at a roadside checkpoint, is impaired or under the influence of benzodiazepines, or any other drug, there are three basic legal approaches used by the current laws in different countries. In the effect-based or impairment approach, the fitness of the drivers is observed, and possible influences on his or her ability to drive safely are assessed. The other two approaches can be considered as per se approaches. The first approach is the zero-tolerance case where the detection of any concentration of the drug in driver's blood is an offense and thus is penalized. It is easily understood that the legal limit technically is the limit of detection of the applied analytical method. This way the legal limit is a result of the detectability of a drug rather than the impairment caused by it. It has to be mentioned here that the adoption of a zero-tolerance policy penalizes the presence of any drug or metabolite in blood, at any concentration. This does not necessarily mean that an actual impairment of driving skills is present. It has also to be mentioned that the presence of any drug or metabolite in urine, but not in blood, is not sufficient evidence to bring a prosecution even though the person can still be charged with using a banned substance. If such a policy will be adopted and any concentration of benzodiazepines in blood above the detection limit (zero-tolerance) would be illegal, this would make unimpaired patients on low therapeutic benzodiazepine dosage impossible to drive. In the other version of the per se approach, a science-based limit is used to define the "tolerable" concentration of a drug or its metabolites in driver's blood. Such a case is the case of alcohol. In the case of drugs, such laws should specify legal or "acceptable" concentrations for each drug in the blood. A driver is assumed to be "impaired" or "under the influence" if he or she exceeds that limits [22,78].

In real life, all the existing DUID legislation refers to impaired drivers, which means that the impairment approach is the one that meets the relative objectives. The lack of standardized methods for estimating or measuring the impairment caused by consumption of a specific drug and the fact that impairment may arise from several other, synergistic, factors like fatigue or consumption of alcohol or CNS affecting drugs are severe shortcomings to its adoption. Field sobriety tests are less sensitive to modest impairment, something that makes the assessment of driver's impairment in such cases arbitrary and legally disputable. This is expected as field sobriety tests are not designed to detect impairment, but rather give a probability that a driver is under the influence of a substance. The impairment approach is used by the legislation of many European countries, despite the fact that no clear definition of "impairment" appears to exist. That is why an integrated interpretation of blood drug concentration in combination with clinical and other observations has been applied for many years worldwide [22,78].

Several European countries, including Sweden, France, Finland, Germany, Belgium, Poland, Portugal, and Switzerland have introduced zero-tolerance laws for driving under the influence of illicit drugs and medicines that can influence driving ability [79]. The Swedish, German, and Finnish laws also apply to medicines such as benzodiazepines when consumed without a lawful medical prescription and in supra-therapeutic doses [23].

In the United States, all the states, except Texas and New York, use the phrase "under the influence" in their laws. In general, they use two approaches to identify a drugged driver: (a) The behavioral approach (impairment) and (b) the analytical approach that involves the chemical testing of biological fluids for drugs. All DUID laws involve one or both of these approaches. Incapacity to drive safely is linked to the drug ingested (and detected) and the prosecutor must show a connection between drug ingestion and the incapacity of the driver. Some states (Arizona, Georgia, Indiana, Illinois, Iowa, Michigan, Minnesota, Nevada, N. Carolina, Ohio, Pennsylvania, Rhode Island, Utah, Virginia, and Wisconsin) have passed "per se" laws in which it is illegal to operate a motor vehicle if there is any detectable level of a prohibited drug, or its metabolites, in the driver's blood. Other state laws define "drugged driving" as driving when a drug "renders the driver incapable of driving safely" or "causes the driver to be impaired." One state (Nevada) has determined that driving with specific cut-off levels of certain prohibited drugs or substances other than alcohol is a per se violation of its DUID statute [78]. Although, benzodiazepines are included in the prohibited drugs, no cut-off levels have been established for this class of drugs.

In 2011, Denmark established legal limits for 35 benzodiazepines in the blood of drivers. These limits ranged from 0.002 (triazolam) to 0.100 (e.g., diazepam) mg/kg blood [80]. In 2012, a similar action was suggested to be taken in Norway where impairment concentrations of seven benzodiazepines in whole blood were proposed. The respective range was 1.3 ng/mL (clonazepam) - 172 ng/mL (oxazepam) [81]. Recently, the UK government approved limits for sixteen different drugs, illicit and generally prescribed, including six benzodiazepines. These benzodiazepines and their respective limits are: Clonazepam (50 μg/L), diazepam (550 μg/L), flunitrazepam (300 μg/L), lorazepam (100 μg/L), oxazepam (300 μg/L), and temazepam (1000 μg/L). The relative regulations will come into force in the autumn 2014 [82]. Similar efforts would be useful to be made by more countries, if not by all, worldwide.

DISCUSSION

Benzodiazepines are scheduled substances worldwide. Despite that, they are used extensively as prescription drugs for the treatment of different pathologic conditions like anxiety or insomnia. It is well-understood that under the current socioeconomic conditions, benzodiazepines have become actually lifestyle drugs due to their anxiolytic properties [83]. Moreover, their role in the treatment of insomnia remains significant. On the other hand, their effects on driving ability and the relative possibility for increased culpability in the case of traffic accidents are vague.

Reviewing the findings of experimental and epidemiological studies, a negative influence of benzodiazepines on driving skills, a dose-dependent impairment, and an increased accident risk can be concluded due to the dose-related impairment of reaction time, sedation, and impairment of psychomotor function they produce [17]. Nevertheless, determining the relation between benzodiazepines use and traffic accidents is complex because of many important selection factors that are doubtlessly present [18]. Epidemiological and experimental studies provide conclusions that are heterogeneous and not robust enough to prove that such consumption represents a crash risk factor of significant magnitude [4,50,84]. In general, it is difficult to formulate a coherent picture concerning the effects of these drugs on psychomotor performance due to the variations in testing parameters, testing, and dosing schedules between studies [85]. These studies show conflicting results due to differences in the methodology of determining drug use, different estimation of accident severity, lack of a dose-response relationship between the dose taken of a benzodiazepine and its effects on accident risk, and poor control for a significant number of confounding factors described by Elvik [76].

Vindenes *et al*. suggested that in order to assess drug concentrations associated with increased risk for traffic accidents, an evaluation of the already published experimental studies should be performed according to four criteria. More specifically, traffic relevant tests (i.e., measuring sedation, drowsiness, divided attention, continuous perceptual-motor coordination, speed and accuracy of decision-making, vigilance, and short-term memory) should be performed, alcohol should be used as reference drug, pharmacokinetic data should be presented and the participants in the study should be at least eight [81].

Epidemiological studies normally do not give conclusive results mainly due to methodological problems such as: Selection bias, small numbers of subjects, subjective elements that are involved in evaluating culpability and misclassification of the outcome. Failure to adjust for other significant confounders, such as fatigue, speed, tolerance, residual effect, and concurrent alcohol consumption in combination with the lack of information about case history or about chronic or single dose make things more difficult [4,18,50,53,73]. Moreover, the selective control groups do not always accurately represent the general population, and, accordingly, the results may under- or over-estimate the prevalence of drugs in these groups. It has also to be recognized that the use of drugs by drivers does not necessarily mean that the drug was a causal factor in the crash. The over-representation of drivers testing positive for drugs could be because of other external factors [52]. Despite all the above drawbacks, epidemiological studies provide valuable insight into benzodiazepines effects across drivers.

On the other hand, experimental studies have the disadvantage that they may not accurately predict the effects of drugs under actual driving conditions [20,73] and do not indicate the

magnitude of the effect [52]. Due to ethical considerations it is not possible to administer high enough benzodiazepine doses to obtain the benzodiazepine concentrations often found in real life situations. The studies in most of the cases are single dose experiments. The subjects included in the experimental research are less often experienced users, excluding possible tolerance as a part of the studies. It could thus be argued that findings from such experimental studies would have limited relevance for real-life impairment that benzodiazepines can cause inexperienced users [86].

Several studies indicated that an almost linear relationship between blood benzodiazepines concentration and its effects on driving ability [22,50]. Smink *et al.* indicated that increasing concentrations of benzodiazepines have an increasingly negative influence on behavior, walking, walking after the turn, and Romberg's test [50]. There was no significant relation between concentration benzodiazepine and effect on pupil size, nystagmus, or disturbed orientation. Bramness *et al.* (2002 and 2003) investigated the benzodiazepine concentration-impairment effect relationship and pave the way for a discussion on legal limits for benzodiazepines in relation to driving. They found a clear concentration-impairment relationship and noticed that the type of benzodiazepine detected did not differ significantly between the impaired and not impaired group but the concentrations were significantly different. This means that blood drug concentrations are of limited value to assess impairment, as the impact of acute and chronic tolerance could be of such a magnitude that obscures a concentration-effect relationship [4,22].

Longo *et al.* found a statistically significant linear relationship between benzodiazepine concentrations and culpability. However, the observation that benzodiazepines were usually detected at sub-therapeutic or therapeutic levels does not mean that drivers were unimpaired. The magnitude and the duration of impairment depends on various factors such as the type of benzodiazepines (hypnotic or anxiolytic, and short or long duration of action), time of administration, dosage, tolerance developing, and combination with other psychoactive drugs, or alcohol [52]. This is another drawback for the studies where no differentiation is made between the benzodiazepines, although it is known that benzodiazepines might differ considering their residual effects and accident risk [28]. Drummer mentioned that common therapeutic doses of diazepam, flunitrazepam, flurazepam, flutoprazepam, loprazolam, lorazepam, nitrazepam, and triazolam can impair skills associated with safe driving, and this applies particularly to the longer-acting benzodiazepines when tested the morning after a night-time dose, and when subjects are tested within hours of a dose of most benzodiazepines. The shorter-acting benzodiazepines oxazepam, lormetazepam and to a lesser extent temazepam show little or no significant adverse effects on psychomotor skills the morning after a night-time dose [87].

Although there are many published studies, experimental or epidemiological, that discuss the influence of benzodiazepines on driving ability, normally they do not follow the same protocol, and so, it is difficult to conclude in the same results. The current experimental literature remains unclear and that limitations to studied methodologies have resulted in inconsistent findings [28]. This is more obvious by the meta-analyses that have been tried occasionally in order to evaluate the effects of benzodiazepines on driving ability [15,19,76,88,89].

Suggestions for Future Research

Epidemiological studies are normally required to answer actually two fundamental questions that experimental studies cannot adequately address: How frequently do people DUID under normal driving circumstances, and what is the relationship between the effects of drugs as seen in a laboratory and road crashes [52]. Such studies would measure the effect of drug use on driving performance and accident risk under real-life conditions and are thus suited to correlate the concentrations of a drug use indicator to an actual risk [90]. More information is also needed to establish limits that indicate impairment of benzodiazepines and therefore are incompatible with driving behavior and further experimental research is required [76] to elucidate the mechanisms underlying any observable driving impairment, and to address clinically relevant questions such as:

- How does the long-term use of benzodiazepines affect driving ability?
- What are exactly the residual effects of benzodiazepine use on driving ability?
- What are the levels of impairment after low, therapeutic or sub-therapeutic doses of benzodiazepines?

Despite the non-conclusive results of the so far epidemiological and experimental studies on the benzodiazepines concentration-impairment relationship, some scientists have recommended the establishment of blood concentrations limits for driving after use of benzodiazepines as per se evidence of impairment [22,50]. Until the establishment of such blood concentration limits for benzodiazepines, the zero-tolerance approach seems to be the best way to deal with driving under the influence of these drugs. The evaluation of the degree of the impairment at the moment of the accident is difficult [91]. Trained police officers should perform field sobriety tests and evaluate driving ability of an individual while a specially trained physician should examine the suspect, look for signs and symptoms of drug influence and evaluate the degree of impairment right after the accident. It has to be mentioned here that as police officers are not able to detect disease or injury, medical input is always required. On the other hand, the impairment by benzodiazepines is generally difficult to prove in court by standard sobriety tests due to the fact that these tests are somewhat insensitive for the assessment of the influence of drugs [92].

More studies on the relationship between dose, blood concentration, and impairment effects are needed in order to establish limits indicating levels of impairment that are incompatible with driving [22,50]. Computer-simulated driving can be proved a useful tool to research benzodiazepines-related impairment of driving abilities [93]. In any case, both physicians and pharmacists should advise their patients of the impairing effects of benzodiazepines, particularly in relation to drowsiness and sedation, and the implications of these effects on driving

skills such as reaction time, attention, and vigilance [91]. The patients should be prescribed evening doses of the shortest-acting hypnotics whenever possible. The patients who take longer-acting compounds or daytime doses of any hypnotic should be advised of the potential for impairment, even in the absence of subjective symptoms. These patients should also be advised to avoid driving, particularly during the initial phase of dosage adjustments. Moreover, physicians should balance medical need with the possibility of abuse and diversion, as well as the necessity to comply with state, federal, or country regulations [94].

CONCLUSION

Increased risk for traffic accident involvement or related injury has been reported after using benzodiazepines in both young and elderly patients. In order to definitively establish a causal association between benzodiazepines use and motor vehicle crashes a more thorough elucidation of the behavioral and cognitive effects of benzodiazepines are needed. A more thorough investigation of the relationship between benzodiazepines biomarkers and intoxication or functional impairment is also necessary, while at the same time a more correctly designed experimental studies on the impact of benzodiazepines on driving performance and behavior should be conducted. Such studies will contribute to science-based government policies and law enforcement practices on benzodiazepines and driving and will help the policy makers to the establishment of more effective prevention efforts and cost-effective prevention strategies in connection with appropriate legislative and enforcement measures. Recent efforts have been made toward the establishment of a per se legislation concerning allowable blood concentrations of benzodiazepine in drivers. More efforts should be made in the future toward this direction based on more solid scientific evidence.

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