The Effects of Psychoactive Prescription Drugs on Driving

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Table of Contents

Executive Summary

Background

Over the past several decades, the impairing effects of alcohol on driving have become common knowledge. More recently, the use of illicit drugs such as cocaine, cannabis and methamphetamine have become the focus of increasing concern for its impact on road safety. However, it is less well understood that some psychoactive prescription drugs can also affect driving. Psychoactive prescription drugs, such as opioids, sedative-hypnotics and stimulants, are associated with serious harms including injury and death. In an effort to address these and other harms, the Canadian Centre on Substance Abuse (CCSA), together with over 40 partners, released *First Do No Harm: Responding to Canada's Prescription Drug Crisis*, a 10-year pan-Canadian strategy that outlines 58 recommendations for collective action in a number of key areas, including prevention, education, treatment, monitoring and surveillance, enforcement, and legislation and regulation.

The current review explores the extent to which psychoactive prescription drugs can adversely affect the cognitive and motor functions essential for the safe operation of a motor vehicle and thereby increase the risk of crash involvement. More specifically, the objectives of this report are:

- To review and summarize the scientific literature on the impairing effects of psychoactive prescription drugs on the skills and abilities required to operate a vehicle safely;

- To examine the epidemiological evidence on the extent to which psychoactive prescription drugs are used by drivers and increase the risks of crash involvement; and

- To identify approaches for enhancing the safety of drivers who use psychoactive prescription drugs in Canada.

The evidence reviewed in this report will help to inform policies and practices aimed at reducing injuries associated with driving impairment involving psychoactive prescription drugs.

Method

A search of scientific journals and grey literature was conducted using a combination of key terms and phrases to identify papers related to the effects of common psychoactive prescription drugs on driving as well as the prevalence and risks associated with these drugs in relation to driving.

Findings

Psychoactive prescription drugs cause changes in brain functioning. Such changes can disrupt normal cognitive and psychomotor performance through a variety of mechanisms. For example, depressant drugs slow the speed at which the brain receives, processes and responds to environmental information, reduce the effectiveness and efficiency with which decisions are made and impact motor control. On the other hand, stimulant drugs speed up brain activity and can create a situation where decisions are made impulsively, greater risk is taken, and normal sleep and rest periods are disrupted. As the stimulant drug's effects wane, fatigue and sleepiness effects can cause inattention and carelessness. Although the manifestation of drug effects varies, the different mechanisms have the same net effect: a decrease in the quality of cognitive and psychomotor effort that goes into the driving task, creating substandard driving performance and elevating the risk of crash involvement.

The consequences of driving while impaired by psychoactive prescription drugs are becoming increasingly evident. Numerous studies that have examined the results of toxicological tests on the blood of drivers involved in serious road crashes have found evidence of psychoactive prescription drug use. In particular, drugs that slow the function of the brain in a manner similar to that of alcohol, such as sedatives and tranquilizers, are the drugs most often detected. In addition, it is not uncommon that these drivers have combined medications with other prescription drugs, illegal drugs, alcohol or combinations of all three.

Determining the degree of risk posed by drivers who have used psychoactive prescription drugs can be challenging. Despite a variety of factors that limit the validity of the findings of these studies, the weight of the evidence indicates that the use of sedative drugs increases a driver's risk of crash involvement. This increase is particularly a concern within the first two weeks of a patient starting a medication. Some hypnotic medications and opioid pain relievers have also been shown to be associated with increased crash risk in some circumstances. In many of these studies, it is not known whether the drug was prescribed by a healthcare professional and taken as directed, or used illicitly.

Discussion

Even in the absence of a complete understanding of the role of psychoactive prescription drugs in road crashes, there is sufficient evidence to begin implementing policies and practices to reduce the road safety risks posed by the use of these medications. Existing controls and regulations governing the distribution of prescription drugs provide considerable opportunities for prevention. Products could be systematically tested for impairment potential. Healthcare professionals could provide patients with specific information about the advisability or safety of driving while taking specific products. Product labelling could be standardized, providing clear guidance to consumers. The way forward requires interdisciplinary involvement in discussion and consultation to develop and implement an integrated set of policies and practices to reduce the road safety risks associated with the use of psychoactive prescription medications. The First Do No Harm strategy provides a forum and network for such discussions and collective action.

Introduction

Psychoactive prescription drugs can have a beneficial impact on health and well-being. Pharmacological research is continually developing new medicines to treat a host of ailments and alleviate the symptoms of others. Unfortunately, some of these same medications can have adverse effects, particularly when used improperly. For example, opioid pain relievers, stimulants and sedative-hypnotics are associated with a risk of adverse effects and harms, which can include addiction, overdose and death, all of which place a significant burden on health care, social services and public safety systems (National Advisory Committee on Prescription Drug Misuse, 2013). Physical and mental impairments from these drugs can also lead to unsafe driving and traffic crashes, resulting in injuries and deaths. This report explores the issue of impairment and crash risk associated with the use of psychoactive prescription drugs.

In an effort to address the harms associated with psychoactive prescription drugs, the Canadian Centre on Substance Abuse (CCSA), together with over 40 partners, released a *First Do No Harm: Responding to Canada's Prescription Drug Crisis*. This 10-year pan-Canadian strategy outlines 58 recommendations for collective action in a number of key areas, including prevention, education, treatment, monitoring and surveillance, enforcement, and legislation and regulation. CCSA continues to provide leadership and coordination to ensure the effective implementation of the strategy.

Over the past decade, the issue of drug-impaired driving has emerged alongside the persistent problem of alcohol-impaired driving. Although not necessarily a new problem, the use of drugs by drivers has come to the forefront of public attention most likely as a consequence of three factors. First, the number of deaths attributable to alcohol-impaired drivers continues to fall (Brown, Vanlaar, & Robertson, 2015). This fact does not suggest that the alcohol-crash problem has gone away, but after over 30 years of demonstrable progress, public interest has perhaps waned and has been re-focused on a new priority — the influence of drug use on driving. Second, the growing number of jurisdictions that have legalized the use of cannabis for medical or recreational purposes or both has raised concerns about driving after cannabis use. Finally, recent changes in police enforcement practices, developments in oral fluid drug testing and increased drug testing of drivers involved in serious crashes have helped to identify drug-impaired drivers, highlighting the magnitude of the issue.

For the most part, the focus of the attention afforded to drug-impaired driving has been on impairment as a result of the use of illicit substances such as cannabis and cocaine. However, drug impairment is not limited to the use of illicit substances. Many prescription drugs, as well as a variety of over-the-counter (non-prescription) remedies, can also have adverse effects on a person's ability to operate a vehicle safely. The potential of medicines to impair driving is not unfamiliar to Canadians. Some medications come with a label or package insert alerting the consumer that the product can cause "drowsiness" or "dizziness" and to avoid or "use caution" when driving or operating heavy machinery until the individual knows "how the medication will affect them." Healthcare practitioners might also specifically advise their patients of the effects of certain medications on driving. The extent to which such warnings are given and patients heed them is unknown.

To some degree, the potential for psychoactive prescription drugs to impair driving seems to have been assigned a lower level of concern among the public than driving after using illicit substances. Clearly, if a substance is illegal, it would be illegal to drive after its use. On the other hand, many drivers might mistakenly feel that unless told otherwise, a drug prescribed by their doctor is inherently safe. Accepting the fact that medications can have undesired adverse consequences that can compromise normal activities might be difficult for many to accept. Hence, to the extent their health condition permits, there is a tendency for people to continue their daily routines while taking

medications largely without concern that their medication might have an adverse effect on their ability to perform complex tasks such as driving, placing themselves and other road users at increased risk on the road.

The use of prescription drugs is common among Canadians. According to Statistics Canada, 41% of Canadians aged 6 to 79 had taken at least one medication prescribed to them in the two days prior to the survey (Rotermann, Sanmartin, Hennessy, & Arthur, 2014). Among those aged 15–24, 26% reported using some type of prescription drug, and this increased to 83% among those between 65 and 79 years of age (Rotermann et. al., 2014). Multiple prescription drug use was also found to increase with age (Rotermann et al., 2014).

Not all prescription medications have the potential to impair the ability to operate a vehicle. In fact, the relatively high incidence of medication use among Canadians reflects use for the management of chronic medical conditions such as heart disease and diabetes (Rotermann et al., 2014); medications for these conditions have no apparent adverse effect on road safety when used as directed. The focus of this report is the use of psychoactive pharmaceuticals — that is, those that have effects on brain function. These drugs include opioid pain relievers, sedative-hypnotics and stimulants. These drugs have effects that can alter one's state of alertness, motor performance and cognitive functioning, even when used as prescribed. The adverse effects, however, can be particularly profound when taken with other medications or alcohol or both. While certain psychoactive over-the-counter cold medications and sleep aids, as well as drugs for the relief of allergy symptoms (e.g., antihistamines) might also cause impairment, they are not a focus of this review.

Whether the person using the drug was prescribed it by his or her physician, accessed it from friends or family, or purchased a diverted product from someone else, the impact can be the same. The primary difference is the reason for use. Whereas most individuals who use psychoactive prescription drugs are seeking the health benefits of medications, the goal of other individuals is often to experience the euphoria associated with many of these drugs or to escape withdrawal. To this end, these latter users often consume higher doses of the drugs or do so with greater frequency or both. This type of use can produce significant impairment and adverse effects, especially when used in high doses.

These effects can also occur among those who use prescription medications for health reasons. Recent studies show very poor rates of compliance with prescription directions in some patient populations such as those with chronic pain (Couto, Romney, Leider, Sharma, & Goldfarb, 2009). Taking additional doses of prescribed medications, using medications prescribed to someone else, and using multiple medications or combining them with alcohol are not uncommon behaviours. The adverse effects of medications on driver behaviour, whether caused by ingestion to experience the pleasurable effects or double-dosing in an attempt to enhance or prolong the therapeutic effects, are qualitatively similar. For this reason, the primary focus of this report is on the potential impairing effects of psychoactive prescription drugs that are primarily intended for the treatment of a health condition, regardless of the circumstances or pattern of use.

This paper reviews the extent to which psychoactive prescription drugs can adversely affect the cognitive and motor functions essential for the safe operation of a motor vehicle and thereby increase the risk of crash involvement. More specifically, the objectives of this report are:

- To review and summarize the scientific literature on the impairing effects of psychoactive prescription drugs on driving;

- To examine the epidemiological evidence on the extent to which psychoactive prescription drugs are used by drivers and increase the risks of crash involvement; and

- To identify approaches for enhancing the safety of drivers who use psychoactive prescription drugs and reducing the incidence of impaired driving related crashes and injuries in Canada.

This report is intended for health and road safety professionals, policy makers and researchers, and will help inform policies and practices aimed at reducing injuries associated with driving impairment involving psychoactive prescription drugs. Based on its review of the current evidence, the report concludes with a discussion of program and policy options that could be explored to help reduce the risks associated with the use of psychoactive prescription drugs and driving.

Method

A search of the published literature was conducted using a combination of key terms and phrases. (See Appendix A for the list of search terms that were used.) Databases such as PubMed, Cochrane summaries, Safety Lit, and Health Evidence were searched to identify papers published between 2010 and 2015 related to (1) the effects of psychoactive prescription drugs on driving or driving-related skills and abilities; and (2) the epidemiology (prevalence and risks) of psychoactive prescription drug use in relation to motor vehicle crashes. The initial search identified a set of 165 articles. Further searches included a wider time span (2000–2015) and specific drug names. Reference lists of identified papers were scanned for additional relevant articles.

To locate grey literature, including technical reports and other publications, web sites of key organizations and groups (e.g., Canadian Association of Mental Health, National Highway Traffic Safety Administration, National Institute on Drug Abuse, DRUID, SafetyLit) and Internet search engines such as Google Scholar and Bing, were used. In addition, the collected proceedings of the International Conference on Alcohol, Drugs and Traffic Safety were searched for relevant literature.

Titles and abstracts were reviewed for relevance and those that were deemed out of scope or that involved prescription drugs not available in Canada or not commonly detected in drivers involved in crashes (e.g., antipsychotics) were eliminated from further consideration.

Rather than present a review of individual prescription drugs, drugs were grouped into the following categories according to the general similarity of their effects, not necessarily their pharmacological classification: sedative-hypnotics (e.g., benzodiazepines and the non-benzodiazepine hypnotics, zopiclone and zolpidem),[1] central nervous system (CNS) stimulants (e.g., amphetamines) and opioids. Over-the-counter antihistamines have been included as well. It should also be noted that although cannabis for medical purposes is available in Canada, it was not included in the present review. (For a review of cannabis and driving, see Beirness & Porath-Waller, 2015.)

For each category of substance, the review includes information on the general effects of the drugs and those effects specifically related to the cognitive and motor skills and abilities needed for the safe operation of a motor vehicle. In addition, where data exist, the extent of the effects in relation to dose, acquired tolerance and the interaction among various substances was also examined to better understand the types of impairments and the conditions under which impairment is either enhanced or mitigated.

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[1] Zopiclone and zolpidem are sometimes referred to as Z-drugs or Z-hypnotics.

Findings

An understanding of the role of psychoactive prescription drugs in motor vehicle crashes requires evidence from two complementary lines of research, experimental and epidemiological. The role of experimentation is to document the nature and extent of deficits in cognitive and motor functioning produced by various doses of specific drugs. The role of epidemiological research is to determine the extent to which the type and amount of specific drugs are associated with, and contribute to, motor vehicle crashes. It was complementary and converging evidence from these two research approaches that firmly established the link between alcohol and road crashes. The same approach is currently being applied to drug-impaired driving.

Establishing the connection between drugs and road crashes, however, has proven to be considerably more complex than for alcohol. For example, alcohol is a relatively simple molecule that can be readily detected and measured in breath samples. In addition, the absorption, distribution and elimination (i.e., the pharmacokinetics) of alcohol are relatively straightforward and well-understood. On the other hand, virtually all other drugs of interest require a sample of blood, urine or oral fluid to be collected and sent to a toxicology laboratory for analysis to determine their presence and concentration. The pharmacokinetics of drugs are considerably more complex than those for alcohol and can involve very different patterns of absorption and distribution, the production of active metabolites, and long and variable elimination rates.

Drug effects can also vary between individuals depending on the dose, route of administration, concomitant use of other medications and/or alcohol, time of day, demographic characteristics (e.g., age, sex), and health status of the individual. In the case of prescription drugs, it is important to examine drug effects on healthy volunteers, as well as a sample of patients with the condition the medication is used to treat, both before the drug regimen has been initiated as well as after the patient has been stabilized on a therapeutic dose of the medication. Of particular relevance is an examination of the effects following initial use of the drug, as well as after a stable dose has been used for a period of time. This dual examination is required because tolerance to the acute effects of some drugs can develop with longer term use, minimizing or even eliminating some of the adverse effects on driving.

A wide variety of psychoactive prescription drugs disrupt the release or reabsorption of neurotransmitters in the brain, which can affect normal cognitive and psychomotor functioning. Depending on the particular drug and the site of action, this effect can have an impact on alertness, perception, concentration, impulse control, the speed at which the brain receives, processes and responds to environmental information, and higher order executive functions such as planning, problem-solving, organizing and reasoning (Julien, Advokat, & Comaty, 2008). All of these mechanisms can adversely affect the quality of mental and physical effort dedicated to the driving task, decreasing performance and increasing the risk of crash involvement.

The following sections review the evidence from experimental and epidemiological studies relevant to the impact of psychoactive prescription drugs on driving.

Experimental Evidence

Driving is a complex task that requires the coordination of a number of cognitive, perceptual and motor skills. Michon (1985) outlines three levels of skills and controls involved in driving: operational, tactical and strategic.

The operational level involves vehicle control skills: steering, braking, tracking, accelerating, decelerating, manipulating vehicle controls and automatic response patterns. These are the fundamental skills required to operate a vehicle. These behaviours must be learned prior to integrating other higher order driving skills.

The tactical level involves manoeuvering skills required for complex action patterns that allow the driver to negotiate the variabilities in the roadway environment. For example, it involves guiding the vehicle through traffic, avoiding obstacles, changing lanes, maintaining headway, adjusting speed and overtaking. Actions at this level are expected to meet the goals set at the strategic level and adapt to circumstances or the outcome of specific manoeuvers.

The strategic level involves planning, route selection, assessment of risks and benefits, critical judgment and dynamic evaluation of the environment, the traffic and the vehicle. At this level, the tasks are primarily cognitive and involve higher order analytical functioning.

Most people are able to learn to integrate the various skills and functions necessary to operate a vehicle safely. With experience, these behaviours can become routine and automatic. However, for even the most proficient drivers, drugs and alcohol can adversely affect the efficient integration and application of these skills.

Experimental studies of the effect of drugs on driving behaviour typically examine performance on tasks that assess the same or similar skills necessary for the safe operation of a motor vehicle: for example, tracking, reaction time, divided attention. The inherent artificial nature of the tasks often leads to questions pertaining to their relevance and validity in relation to actual driving. Driving simulators provide greater perceived validity in that they involve physical and cognitive tasks resembling those actually involved in driving. Driving simulators have become increasingly sophisticated, providing a more realistic experience of operating a vehicle (e.g., National Advanced Driving Simulator) and have become popular as a means to assess behaviour in as realistic a manner as possible, while eliminating the real risks of a traffic environment. A unique approach used at the University of Maastricht in the Netherlands involves conducting drug-impaired driving research in an instrumented vehicle on actual roadways (e.g., Ramaekers, Robbe, & O'Hanlon, 2000). Regardless of the approach, all of these studies provide insight into the effects of drugs on the skills and abilities required to operate a vehicle safely.

Sedative-Hypnotics

The types of drugs in this category have effects similar to those of alcohol. This category includes drugs that have relaxing, anxiety-reducing or hypnotic actions and are commonly used in the treatment of anxiety and insomnia. The general effects of sedative-hypnotics produce a reduction in neural activity and slowed neurotransmission. These effects result in slower reactions to stimuli, slower response times, poor coordination and impaired ability to divide attention. Two different types of drugs are discussed: benzodiazepines (e.g., diazepam, alprazolam, lorazepam) and non-benzodiazepine hypnotics (e.g., zolpidem, zopiclone).

Benzodiazepines

A variety of benzodiazepines are available in Canada. They differ in terms of their efficacy in treating anxiety, muscle tension, seizures and insomnia, and producing sedation. Benzodiazepines also differ in their duration of action with some having relatively long periods of action (i.e., half-life[2] from 40 to

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[2] The half-life of a drug is the time required for the concentration of drug in the body to be reduced by one-half. It is generally taken as an indication of relative duration of drug action.

100 hours) while others are metabolized and rendered inactive relatively quickly (i.e., half-life 2.5–12 hours) (Julien et al., 2008).

In general, benzodiazepines produce a state of relaxation and drowsiness. They can also cause confusion and disruption of short-term memory. These effects can produce dose-related motor and cognitive impairments similar to those caused by alcohol use and can interfere with the ability to operate a vehicle safely.

Quantitative assessments of benzodiazepine effects on driving have been performed for alprazolam, showing significant driver impairment from both immediate release and extended release formulations, most notably weaving within the traffic lane and decreased alertness (Verster, Volkerts, & Verbaten, 2002; Verster & Volkerts, 2004a; Leufkens, Vereeren, Smink, van Ruitenbeek, & Ramaekers, 2007). Assessment of the relationship between benzodiazepine concentrations in blood and the subject's performance in field tests for impairment showed a positive correlation between diminished performance and increasing drug concentration (Smink, Lusthof, de Gier, Uges, & Egberts, 2008; Boucart, Waucquier, Michael, & Libersa, 2007; Bramness, Skurtveit, & Mørland, 2002, 2006).

A meta-analysis of the effect of sleep medications on driving the morning after use (10–11 hours after initiating sleep) showed the use of long-acting benzodiazepines produced significantly greater variation in vehicle lane position compared to performance later the same day (Roth, Eklov, Drake, & Verster, 2014). A double dose also produced significant driving impairment in the afternoon following use (16–17 hours after initiating sleep).

Non-Benzodiazepine Hypnotics

A related group of drugs used for treating insomnia includes zolpidem and zopiclone, often referred to as "Z-hypnotics." As would be expected, these drugs induce sedation and promote sleepiness, which serve to reduce sleep latency and improve sleep maintenance. Clearly, these effects are inconsistent with the safe operation of a motor vehicle. These drugs have a relatively rapid onset of action (30–90 minutes) and are intended to be taken at bedtime to facilitate sleep. Administration of these products at other times is not recommended.

While these medications are very effective in enhancing sleep onset and maintenance, there is clear evidence of dose-related psychomotor and cognitive impairments shortly after administration (Gustavsen, Hjelmeland, Bernard, & Mørland, 2012). Perhaps more importantly, there is concern about residual effects following a period of sleep, typically the next day. A number of studies have examined the effect of these medications on driving the day after use (Gunja, 2013; Leufkens, Lund, & Vermeeren, 2009; Mets et al., 2011; Roth et al., 2014; Staner, et al., 2005; Vermeeren, et al., 2014; Verster, Volkerts, Olivier, Johnson, & Liddicoat, 2007). Systematic reviews and meta-analyses, including many of these studies, reveal significant driving impairment the morning after administration of zopiclone following a full night's sleep. Zolpidem showed no adverse residual effects on driving performance. Administration of either zopiclone or zolpidem in the middle of the night (typically after a period of unsuccessful attempts to sleep) produced significant driving impairment the following morning. Higher doses were associated with greater driving impairment (Leufkens & Vermeeren, 2014; Verster, Veldhuijzen, Patat, Olivier, & Volkerts, 2006).

A phenomenon known as "sleep driving" has also been reported with this class of drugs (Doane & Dalpiaz, 2008; Paulke, Wunder, & Toennes, 2015; Poceta, 2011; Pressman, 2011). This condition, characterized by unconscious driving, without intent and with no recollection of the activity, is controversial and has only been reported anecdotally. These individuals are often stopped by the police and arrested for impaired driving. Case reports indicate a number of related factors including

daytime use of the drug, high blood drug concentrations, use of other medications, concomitant sleep disorders and a history of parasomnia.

Opioids

Opioids include the naturally occurring opiates morphine and codeine, semi-synthetic variants, including oxycodone, oxymorphone, hydrocodone, hydromorphone, dihydrocodeine and buprenorphine, and synthetic opioids such as methadone, propoxyphene, fentanyl, tramadol and meperidine. The opioids reduce sensitivity to pain, and are widely used to relieve acute and chronic pain. The opioids also act on the cough centre in the brain stem and are used as a cough suppressant. The most important use of the opioids outside of the CNS is to relieve diarrhea through their effect on the intestine (Julien et al., 2008).

Opioids depress CNS and respiratory function and induce sedation and sleep. This reduced level of consciousness, which can accompany the loss of the ability to feel pain (analgesia), especially with higher doses or in non-tolerant individuals, can result in impaired performance in tasks demanding cognitive and psychomotor skills such as driving. Pupillary constriction, which is common with opioid use, can affect vision and light/dark adaptation.

Chronic pain itself can be an impairing medical condition. Nilsen and colleagues (2011) examined driving simulator performance among a group of individuals with untreated chronic pain, a group with chronic pain treated with codeine and a group of healthy controls. Those with chronic pain, whether treated with codeine or not, performed more poorly than the group of healthy controls, suggesting that the impairment was related to chronic pain and was not a function of codeine.

Tolerance to the effects of opioids is well documented, and there is some evidence that patients stabilized on moderate doses of opioids have tolerance to some of the impairing effects of the drugs on cognitive and psychomotor functioning (Byas-Smith, Chapman, Reed, & Cotsonis, 2005; Fishbain, Cutler, Rosomoff, & Rosomoff, 2003; Soyka, 2014; Zacny, 1995). A systematic review of studies of patients on opioid maintenance therapy concluded that while opioid-naïve subjects (i.e., new users) were subject to impairment, only some opioid maintenance patients showed slight driving impairment and others showed no impairment (Strand, Fjeld, Arnestad, & Mørland, 2013).

It typically takes several days on a stable dose to acquire the tolerance necessary to counter the drug's effects (Gringauz, Rabinowitz, Stav, & Korczyn, 2001). Changes in dose or frequency of dosing, breaks in dosing or co-administration with other opioids, however, restores the potential for impairment. Patients being treated for chronic pain conditions often take other drugs in combination with opioids, such as muscle relaxants, sleep aids and anti-depressants, which can combine with the effects of the opioid to produce greater impairment.

In summary, therapeutic use of opioids by a naïve user, problematic opioid use even in a tolerant user, or combining opioids with other CNS depressant drugs or alcohol create a significant risk of driving impairment. Supervised chronic administration with a stable dose does not appear to create significant risk of impairment.

Central Nervous System Stimulants

Prescription drugs in this class include amphetamines and methylphenidate, most commonly used to treat attention deficit/hyperactivity disorder (ADHD). Amphetamines are also used in the treatment of narcolepsy. In the past, amphetamines have also been used as an appetite suppressant to promote weight loss and as a fatigue-reducing agent to help maintain wakefulness and vigilance over extended periods of time.

Amphetamines cause a lessening of fatigue, an increase in mental and motor activity, an elevation of mood, and a general feeling of well-being. However, their indiscriminate use in attempts to increase capacity for work or to overcome fatigue is undesirable and not necessarily effective. At high doses, amphetamines produce a euphoria that upon abrupt withdrawal of the drug reverts to severe depression and lethargy.

Amphetamines produce a range of effects on drivers that differ in the acute phase (shortly after drug consumption) and the post-acute phase, when drug withdrawal or abstinence syndrome can be an issue (Logan, 2002). With higher doses of amphetamine, the immediate effects of stimulant use produce intense excitement and euphoria, which can be distracting and disorienting, affecting the degree of attention and concentration on driving. The drugs also produce changes in reaction time, often resulting in faster but less reasoned, more impulsive responses and increased risk taking. Higher doses or chronic use can produce agitation, hyper-vigilance and irritability. Some of the motor effects of the drug result in restlessness, a need to be in constant motion, and problems with balance and coordination. Following intense stimulant use, susceptible individuals can develop paranoia, hallucinations and delusions (Blaho, Logan, Winbery, Park, & Schwilke, 2000).

At low doses, stimulants can offset fatigue and delay the need for sleep (Caldwell, Smythe, Leduc, & Caldwell, 2000). However, the administration of amphetamine does not compensate for the detrimental effects of sleep deprivation (Hjalmdahl et al., 2012). The chronic sleep loss resulting from repeated use creates a rebound or withdrawal effect when drug use stops. Those individuals who use stimulants who are experiencing withdrawal suffer fatigue, extreme sleepiness, anxiety, exhaustion, drug craving, irritability and dysphoria (Logan, 2002). In some respects, this withdrawal phase is similar to the effects caused by CNS depressant drugs, and can have profound effects on driver attention and performance. The range of effects can vary dramatically among individuals depending on dose, route of administration, intensity of use and time since last use.

A number of studies have examined the effects of amphetamines and methylphenidate on the driving performance of individuals with ADHD (Biederman et al., 2012; Cox et al., 2008; Gobbo & Louzã, 2014; Kay, Michaels, & Pakull, 2009; Sobanski et al., 2008). These studies report that therapeutic doses of amphetamine or methylphenidate can improve driving performance and information processing, and reduce driving errors compared to that of untreated patients. However, 16 hours after administration of amphetamine, inattentive on-road driving errors increased, suggesting a possible rebound effect (Cox et al., 2008). In healthy volunteers, amphetamine improved various aspects of attention and suggested possible enhancements in tracking (Silber et al., 2005).

In summary, individuals with untreated ADHD have been shown to exhibit impulsive, fast and aggressive driving behaviours (Barkley & Cox, 2007). The evidence indicates that compliant physician-supervised therapeutic use of the methylphenidate or amphetamines can improve driver performance in individuals with ADHD (Jerome, Habinski, & Segal, 2006). Inappropriate or problematic use of stimulants, including the use of amphetamines in an attempt to compensate for driver sleepiness, can result in impulsive, erratic behaviour, and can be followed by a period of depression and dysphoria that can have detrimental effects on driving.

Antihistamines

Antihistamine medications such as diphenhydramine and chlorpheniramine are readily available in a variety of over-the-counter medications used to treat the symptoms of allergies, common colds, insomnia and motion sickness. These medications can induce sleepiness, sedation and loss of sustained attention (Verster & Volkerts, 2004b), effects similar to those of sedative-hypnotics described in a previous section. So-called "first generation" antihistamines such as diphenhydramine are well-established as having the ability to cause impairment in driver ability (Burns & Moskowitz, 1980; Moskowitz & Wilkinson, 2004). These drugs are often combined with other drugs (e.g., dextro-methorphan) in multi-symptom cold relief formulations that can also produce impairment or drowsiness (Logan 2009). Newer antihistamines such as fexofenadine have been shown to produce less sedation and fewer impairing effects (Ridout & Hindmarch, 2002; Tashiro et al., 2005; Perttula et al, 2014).

Summary

Psychoactive prescription drugs produce changes in the brain that disrupt normal cognition and psychomotor skills. They produce these changes occurs through a variety of mechanisms. For example, sedative-hypnotics slow the speed at which the brain receives, processes and responds to environmental information, reduce the effectiveness and efficiency with which decisions are made, and impact motor control. On the other hand, high doses of CNS stimulants can cause over-stimulation of the brain and create a situation where decisions are made impulsively, greater risk is taken, and normal sleep and rest periods are disrupted. As the stimulant effects wane, fatigue and sleepiness cause inattention and carelessness. Although the manifestation of drug effects varies, the different mechanisms have the same net effect: a decrease in the quality of cognitive and psychomotor effort that goes into the driving task, creating substandard driving performance that elevates the risk of crash involvement.

Dose and route of administration can cause a difference in the intensity of effect, and tolerance to the drug can make it difficult to predict the specific level of effect in an individual drug-using driver. Prescription drugs, when used by a naïve user, after an increase in dose or when used in a problematic way, have the potential to cause impairment. Even responsible use of a medication in an individual who is non-tolerant or through interaction with other drugs or alcohol can create a dangerous decline in driving performance.

Experimental research demonstrating the impairing effects of drugs is, however, only one piece of evidence implicating the potential of psychoactive prescription drugs as a risk factor for driving. It is also necessary to show that drivers use these substances and that these substances are used by drivers who become involved in crashes — that is, epidemiological evidence. The following sections provide a summary of the epidemiological studies in this area.

Epidemiological Evidence

Two types of epidemiological evidence provide information about psychoactive prescription drugs and driving. Descriptive epidemiology examines the extent to which prescription drugs are used by drivers. This evidence includes random surveys of drivers on the road, as well as surveys of drivers involved in crashes. Analytical epidemiology examines the extent to which drivers who test positive for prescription drugs are over-represented in crashes. Both types of studies typically require drivers to provide a biological specimen for analysis of drug content.[3] Breath samples have been used for many years to measure the concentration of alcohol in the blood. Breath samples are easily obtained and can be analyzed on site. There is also a good relationship between the concentration of alcohol in the blood and the extent of impairment. However, assessing drug use is considerably more complex.

An assessment of drug use requires a sample of blood, urine or oral fluid that is sent to a toxicology laboratory for analysis. The choice of specimen is an important consideration. Blood is a preferred sample over urine. Blood analysis provides an approximation of active drug concentrations, which allows assessment of dose range, problematic or compliant use, and potential impairment. Blood drug concentrations, however, do not necessarily reflect drug concentrations in the brain, which is the site of psychotropic drug action. Hence, inferences about drug effects based on blood drug concentrations are subject to considerable variability.

Urine is the least useful specimen in that it reflects recent drug use or exposure, but not necessarily active effects. Some drug metabolites can be detected in urine for hours or days after the acute drug effect has dissipated. In recent years, oral fluid has provided a means to collect relatively non-invasive samples, the results of which can be interpreted in a manner analogous to those of blood. Unfortunately, not all drugs transfer readily from blood to oral fluid (e.g., benzodiazepines) and hence their prevalence can be underestimated in oral fluid samples (Drummer, 2006).

Roadside Surveys

Roadside surveys have been done periodically in various countries over the past decades. First used to assess the extent of alcohol use by drivers, the roadside survey technique has evolved to include the collection of oral fluid samples (in addition to breath samples) to test for the presence of a variety of commonly used drugs (Boase, 2012). The technique involves randomly selecting drivers from the traffic stream and having them provide a sample of breath and oral fluid, the overall purpose of which is to provide an estimate of the prevalence of alcohol and drug use in a random sample of drivers.

One of the earliest roadside surveys examining drug use by drivers was conducted by Krüger and colleagues (1995) in Germany. From the 2,235 oral fluid samples collected, it was determined that 3.6% of drivers tested positive for benzodiazepines and 0.6% tested positive for cannabis. Among the 0.7% of drivers who tested positive for opiates, approximately three-quarters were suspected to have been the result of the use of medically prescribed codeine. Of some note, about one-third of all drug-positive cases were also found to be positive for alcohol.

In 1999, the province of Quebec conducted the first roadside survey in Canada to assess driver drug use (Dussault, Lemire, Bouchard, & Brault, 2000). Just under half of all drivers selected agreed to provide a sample of urine to be tested for drugs. Although oral fluid was also collected, the results were not reported. Analysis of the urine samples revealed an 11.8% drug positive rate. Cannabis (6.7%) and benzodiazepines (3.6%) were the most commonly found substances. The relatively low

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[3] Pharmacoepidemiological or registry-based studies are an exception that, rather than using toxicological analysis of biological samples to determine drug status, instead use prescription records.

rate of compliance with the request for a urine sample, combined with the inherent problems in interpreting the road safety implications of urine drug tests, left questions about the validity of the findings from this study.

These early studies were followed by a series of roadside surveys of alcohol and drug use by drivers in Scandinavia, Europe, South America, the United States and Canada. These surveys are summarized in Appendix B. In addition to the results for psychoactive prescription drugs, the results for alcohol and cannabis are presented for comparison purposes.

In reviewing these studies, it should be noted that the methodological details of these surveys vary considerably across countries, for example in the time of day and days of the week when the surveys were conducted. Surveys also differ in the list of drugs included in the test panel and the detection limits of the drug tests. Response rates also vary. In several European countries, alcohol and drug tests are mandatory, with penalties for refusal. Consequently, response rates are very high. Other surveys are voluntary and drivers can elect not to participate with no repercussions. Hence, comparisons of the results across countries should be made with caution.

Many studies report the prevalence of drivers who test positive for a variety of psychoactive prescription drugs, most notably benzodiazepines, opioids and amphetamines. It is difficult, however, to determine whether the substance was prescribed by a healthcare practitioner and used as directed. Although very high drug concentrations can generally be interpreted as some form of inappropriate use, concentrations within or below the therapeutic range cannot necessarily be equated with medicinal use.

The information in Appendix B also does not include data on the use of more than one drug and/or use with alcohol. Such behaviour is not uncommon and the range of available combinations is large. Using more than one potentially impairing psychoactive prescription drug or combining these drugs with illicit drugs or alcohol adds to the potentially impairing effects.

It is apparent from the roadside survey data presented in Appendix B that psychoactive prescription drug products are present in the general driving population. The range of prescription drugs detected by oral fluid screens is often limited to those most likely to have an adverse effect on drivers (e.g., benzodiazepines, opioids, stimulants and hypnotics). Some studies include tests for the presence of other substances such as antidepressants, anticonvulsants and antihistamines. It should also be noted that some substances of interest, most notably benzodiazepines, are difficult to detect in oral fluid. Furthermore, in the absence of additional testing, the mere presence of a drug should not be interpreted to mean that the driver was impaired. In light of the various limiting factors, roadside surveys provide, at best, an indication of the prevalence of the use of prescription drugs by drivers.

Several general observations from the table are worth noting. Rates of alcohol and drug use by drivers in Europe tend to be lower than in Canada. To some extent, the difference could reflect the fact that European surveys tend to sample from the general driving population at all times of day and all days of the week, whereas in Canada roadside surveys are generally conducted from 9:00 p.m. to 3:00 a.m. on Wednesday through Saturday nights, a reflection of the timeframe during which alcohol and recreational drug use among the driving population is most common. Distributing survey times throughout the week and including daytime data collection provides a more comprehensive and representative picture of the overall prevalence of alcohol and drug use by all drivers.

Including weekdays and daytime hours in the data collection shows that alcohol use by drivers is not common during daytime hours, but serves to highlight the extent of psychoactive prescription drug use (e.g., benzodiazepines) by drivers during daytime hours and on weekdays (Lacey et al., 2009). Indeed, older drivers are more likely than younger drivers to test positive for prescription drugs

regardless of day of the week. This finding would suggest distinct and separate groups of individuals who use drugs and possibly different motivations for drug use. Further research is needed to uncover the characteristics of various subgroups of the population who drive after using different types of drugs. Such information will help efforts to develop targeted prevention messaging and initiatives.

In roadside surveys conducted in Canada and the United States (Beirness & Beasley, 2009, 2010, 2011, 2012; Beirness, Beasley, & McClafferty, 2015; Compton & Berning, 2015; Lacey et al., 2009), the proportion of drivers who test positive for alcohol has been decreasing over the past several years. However, the use of cannabis has been increasing. It is not known the extent to which this latter trend is associated with increased access to cannabis for medical purposes and changing policies (or perceptions thereof) towards the use of cannabis for non-medical purposes. In comparison, the reported prevalence of prescription drugs by drivers is relatively low. The most common classes of prescription drugs found among drivers are benzodiazepines and opioids. Once again, it is not possible to determine the extent to which the prevalence of these drugs in the driving population reflect appropriate medical use or whether the driving behaviour of these individuals was adversely affected by the presence of the drug.

Drivers Involved in Crashes

Numerous studies from around the world have examined the incidence of drugs and alcohol among drivers injured in crashes. In reviewing these studies, it is important to recognize that they use a diversity of methods, procedures, populations, sample sizes and case selection methods, and each of these factors can have an impact on the results. For example, low testing rates among drivers killed and injured in crashes continue to plague the search for a valid estimate of the prevalence of drug use among crash-involved drivers. In jurisdictions where such testing is not required, drivers who are injured in crashes are rarely tested without at least suspicion of drug or alcohol use. This limitation severely restricts the ability to determine the overall prevalence and contribution of substance use in crashes. Hence, attempts to estimate the overall prevalence of drug use among drivers involved in crashes from the existing studies should be done so with considerable caution.

A summary of findings from studies from various countries that have examined the prevalence of psychoactive prescription drugs among drivers killed or injured in road crashes are presented in Appendix C. The results of studies in the countries that participated in the DRUID[4] project in Europe are presented in Appendix D (Isalberti et al., 2011). In reviewing these tables, it should be noted that not all studies tested for the same drugs or necessarily reported the results the same way. The tables present the main drug categories of interest: benzodiazepines, Z-hypnotics (zopiclone, zolpidem), amphetamine and opioids. Antihistamines are rarely reported. Where amphetamine is included, it is recognized that there is a high likelihood that its use is illicit. The results for some substances have not been included in the tables (e.g., cocaine, antidepressants, acetaminophen).

In most cases, it is not possible to infer that drivers who tested positive for specific substances were impaired at the time of crash involvement. A positive drug result merely indicates that the drug was consumed and that it was present in the driver's blood at the time of testing, which can be several hours from the time of the crash. Some individual studies only report drug concentrations above a specified threshold value, particularly countries where per se drug limits[5] have been established for specific substances (e.g., Norway). In such countries, drivers with a drug concentration in excess of the threshold would be deemed to have committed a driving violation.

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[4] The DRUID project is a large multi-site study in Europe. The formal title is Driving under the Influence of Drugs, Alcohol and Medicines.

[5] Per se limits specify a drug concentration above which it is an offence to operate a vehicle, similar to the 80 mg/dL limit in Canada for alcohol (see Canadian Centre on Substance Abuse, 2015).

A common finding in many studies was that drivers injured or killed in crashes tested positive for more than one type of drug. Prescription drugs could be combined with other prescription drugs, illicit substances and alcohol. The drug interactions from this pattern of use create a high-risk situation that is of concern not only for driving, but for health reasons as well.

Not surprisingly, the findings from the studies on crash-involved drivers vary by study and by country. For example, whereas less than 2% of injured drivers in the Netherlands were found to have used potentially impairing prescription drugs (Legrand, Houwing, Hagenzieker, & Verstraete, 2012), these substances were found in a considerably higher proportion of drivers in Canada (Beirness, Beasley, & Boase, 2013; Jeffery, Hindmarsh, & Mullen, 1996; Stoduto et al., 1993) and the United States (Brady & Li, 2014; Romano & Pollini, 2013). The prevalence of benzodiazepines among crash-involved drivers in northern European countries is also higher than that in southern European countries (Isalberti et al., 2011). It is uncertain as to whether this reflects differences in drug use patterns or testing protocols. Whereas many countries have well-developed systems for the routine collection of bodily fluid samples from drivers killed in road crashes to test for alcohol, testing for other substances is less consistent. The testing for alcohol and drugs in drivers involved in non-fatal crashes is routine in some countries, while in others, ethical and privacy concerns often supersede the needs of research and enforcement. Nevertheless, such testing is critical for routine surveillance, monitoring trends and identifying emerging patterns in the substances involved in traffic deaths and injuries.

The prevalence of psychoactive prescription drug use among serious or fatally injured drivers is generally less than that of alcohol and often less than that of cannabis. Nevertheless, prescription drugs that are known to have impairing effects are routinely detected in the blood of drivers involved in serious crashes. While such information provides valuable evidence of the extent to which prescription drugs are involved in road crashes, the key issue is not only how frequently drugs are detected among drivers, but the extent to which consumption of these substances contributed to the crash. The evidence pertaining to this issue is examined in the next section.

Risk of Crash Involvement

The risk of crash involvement associated with the use of specific drugs is determined by comparing the prevalence of drug use among drivers to that among drivers involved in crashes. Two primary approaches have been used to determine the risk associated with drug use among drivers: (a) case-control studies and (b) crash culpability or responsibility studies. A third approach, referred to as pharmacoepidemiology or registry-based studies, has also been used to estimate the risk of crash involvement associated with the use of pharmaceuticals. All three approaches provide valuable information pertinent to the issue. This section examines the strengths and limitations of the various approaches and summarizes the evidence from studies that have used these methods.

Methodological Issues

The case-control methodology used in the study of drug-impaired driving is a direct extension of the method used to determine the relative risk of crash among drinking drivers, which in turn is an adaptation of the design from classic medical epidemiology. Cases are defined as drivers involved, injured or killed in road crashes. The frequency of drugs detected in the cases is compared to the frequency of drugs detected in a comparable group of drivers who have not been involved in crashes. The degree to which drugs are more frequently detected in crash populations is an indication of the extent to which drugs present an elevated risk for drivers.

This method has been instrumental in understanding the risks associated with alcohol use by drivers. In addition, by comparing the quantity of alcohol used among cases and controls, it was possible to

determine the relative likelihood of crash at different blood alcohol concentrations (Blomberg, Peck, Moskowitz, Burns, & Fiorentino, 2009; Borkenstein, Crowther, Shumate, Zeil, & Zylman, 1964). Similar data are fundamental in determining which prescription drugs present an increased risk for drivers.

The application of the case-control method to studying the risk of crash for drivers using drugs is somewhat more complex than for alcohol. First, unlike the situation involving alcohol, the testing for drugs, both among the cases and the controls, is more difficult. Ideally, blood should be obtained from both cases and controls, but obtaining the needed compliance from controls can be difficult and, as a consequence, testing rates can be low, producing unreliable estimates. Among cases, similar problems are experienced, but are often minimized in the case of fatalities. The net result is that the estimates derived from the comparison group often suffer as a result of missing data. Assumptions made about the distribution of drugs in the untested portion of the sample can have profound effects on the interpretation of the estimates of risk.

Second, the type of sample (blood, oral fluid or urine) used to test for drugs has a strong bearing on the certainty that a substance poses a risk for crash involvement. Ideally, if a substance is detected, it should signify that it could reasonably be expected to have had an adverse effect on the driver at or around the time of the crash. Proving this assumption requires an indication of the level of active drug in the driver's blood because the amount of a substance in blood provides the best indication of recent use and the extent of the potential influence on driver behaviour. The study of the role of alcohol in crashes has been greatly facilitated by the fact that blood alcohol levels can be easily and reliably established from breath samples. However, blood levels of other types of psychoactive substances cannot be easily established from breath samples and typically require that toxicological testing be conducted on bodily fluids. Because of the inherent difficulties in obtaining blood samples, particularly from control populations, many studies have used oral fluid as the medium for drug testing. Unfortunately, some drugs do not transfer well from blood into oral fluid (e.g., benzodiazepines), which can result in false negative results. In addition, although oral fluid drug concentrations are often correlated with blood concentrations, they are not necessarily equivalent, and direct comparisons of oral fluid and blood concentrations can be misleading. Nevertheless, oral fluid testing provides a means by which to determine at least drug prevalence in control populations, thereby greatly facilitating efforts to conduct these types of studies.

A third methodological problem that complicates case-control studies is the elapsed time between the crash and the drawing of the specimen for drug analysis. The longer the period of time between the crash and the drawing of the sample, the greater the risk of underestimating the incidence and level of the drug.

The case-control method requires the sample of crash-involved cases to be compared to a sample of drivers who have not been involved in crashes, matched on variables known to be differentially associated with crash involvement: for example, time of day, day of week, location and type of vehicle. Drivers selected for inclusion are usually volunteers and have the option of refusing to participate. Not surprisingly, some studies show that a substantial proportion of drivers elect not to cooperate with invasive procedures such as the collection of blood or urine samples. For example, in the Quebec study, 97% of drivers provided a breath sample, but only half (49.6%) agreed to provide a urine sample to test for the presence of drugs (Brault, Dussault, Bouchard, & Lemire, 2004). Some drivers might refuse because of fear of detection and prosecution; others might simply object to the invasiveness of the procedures or the amount of time required. It should be noted, however, that in several European studies (e.g., Ahlm, Björnstig, & Ostrōm, 2005), very high response rates have been obtained. Undoubtedly, random testing laws and the use of police to conduct the survey served to enhance compliance. In any event, refusal rates that exceed the incidence of drug detection can compromise the validity of the comparisons.

The wide range of psychoactive drugs that can be studied mean that case-control studies require an extremely large number of crash-involved and crash-free drivers. Even when the drivers studied number in the thousands, the relatively low incidence of specific drugs means that drugs often have to be combined into groups with similar effects and comparisons are often reduced to a simple comparison of the presence or absence of the drug or drugs under investigation. Few studies have attempted to determine the extent of increased risk according to the quantity of drug found (Drummer, 2006; Laumon, Gadegbeku, Maint, Biecheler, & the SAM Group, 2005).

Furthermore, should a substance be found to be over-represented in crashes, it cannot be assumed that the mere presence of the substance was sufficient to have contributed to the crash. In fact, the case-control approach merely provides evidence of an association between the drug and crash involvement, and does not imply that the substance induced a degree of impairment sufficient to have contributed to the crash. Other factors associated with drug use, such as the characteristics of the person or their driving style, could also explain the observed association (Terhune, 1986).

An alternative approach, culpability analysis, also referred to as responsibility analysis, has been employed as a means to study the role of drugs and alcohol in motor vehicle crashes (Robertson & Drummer, 1994; Terhune, 1983, 1986). This approach does not require a non-crash-involved control group of drivers and includes information about the attribution of drivers' responsibility for the crash. Judgments about responsibility for causing the crash are made by examining the circumstances and events leading up to the crash. Comparisons are then made between the proportion of drivers according to drug use status and crash responsibility. The contribution of drugs is determined by the extent to which a greater proportion of drug-positive drivers are deemed responsible for the crashes in which they were involved.

Culpability analysis alleviates the difficulty of obtaining fluid samples from an appropriate sample of drivers not involved in crashes. At the same time, however, it loses valuable exposure information about the use of drugs by drivers who are exposed to risk, but have not been involved in a crash. Moreover, the design does not eliminate the challenges of obtaining a valid sample of crash-involved cases that have appropriate toxicological data derived from fluid samples obtained close in time to the crash. As well, the procedure is somewhat subjective and highly dependent on the method of rating crash responsibility, so it is critical that judgments about responsibility are made without knowledge of drivers' use of alcohol or drugs, and that responsibility is assessed by applying a strict set of scoring criteria. Some studies, however, rely on judgements of responsibility made by the investigating police officer. Police judgments of crash responsibility are not necessarily reliable and might be biased by knowledge or suspicion of drug use by the drivers involved.

Culpability analysis has been used successfully in the study of alcohol and driving, and such studies have consistently found alcohol to be associated with higher risk of crash involvement. Culpability analysis of the role of drugs in crashes provides another source of evidence.

Pharmacoepidemiological studies, a variation of the classic case-control approach, have been used to study the role of prescription drugs in road crashes. These studies compare the incidence of crashes among drivers who have (cases) or have not (controls) been prescribed a specific psychoactive drug for the treatment of a disorder. Information from toxicological tests on drivers involved in crashes is not typically obtained or used in the analysis. Hence, it is not possible to verify that cases were actually taking the prescribed medication at the time of the crash, taking it as directed, or taking the medication in the absence of alcohol or other drugs. Nevertheless, the large sample sizes typically involved in these studies reduce the possibility of these factors having a significant influence on the overall results and can provide information about overall risks.

Summary of Risk of Crash Involvement Evidence

Despite the limitations, all three types of studies provide valuable insights into the relationship between the use of prescription drugs and crash involvement. Appendix E presents a summary of these studies. The major findings are presented in terms of the odds ratio (OR) or relative risk (RR) of crash involvement associated with the major types of drugs examined in this report: sedative-hypnotics (benzodiazepines, non-benzodiazepine hypnotics), CNS stimulants (amphetamine, cocaine) and opioid pain relievers (morphine, codeine). Where available, the 95% confidence intervals are also presented.[6]

Among the studies presented in Appendix E, the evidence on the risk of crash involvement associated with the use of psychoactive prescription drugs varies considerably. Although many studies reveal a statistically significant increase in risk, there are other studies that show the risk is no different than that associated with a driver who has consumed neither drugs nor alcohol. The different results could be a result of differences among studies, such as methods, population, country or region, sample size, testing rates and so on. These findings stand in marked contrast to those obtained by studies that have examined the use of alcohol consumption by drivers, which invariably show a level of risk that increases exponentially with the amount of alcohol consumed, regardless of the methods used by the studies (Blomberg, et al., 2009; Borkenstein, et al., 1964; Compton & Berning, 2015). Most studies examining crash risk associated with drug use have not been able to assess the differential risk associated with increasing drug concentration, but have only been able to separate drivers who test positive for the drug versus those who test negative. At most, one study has examined the crash risk associated with different prescribed doses of opioids (Gomes et al., 2013), but did not actually conduct tests to confirm the drug concentration.

Benzodiazepines are among the most commonly prescribed medications, so it is not surprising that they are found among drivers on the road as well as among those involved in crashes. Among the studies that examined benzodiazepines, the weight of the evidence shows increased risk of crash associated with the use of benzodiazepines. The degree of risk, however, depends on the type of benzodiazepine and the duration of its use. For example, long-acting benzodiazepines were associated with higher crash risk than short-acting benzodiazepines. The risks were also higher within the first couple of weeks following the prescription (presumably the start of drug use), but the magnitude of the risk decreased with longer-term use (i.e., 61 to 365 days). This finding suggests that patients can develop a degree of tolerance to the impairing effects of the medication or can learn to adapt their behaviour so as not to be as susceptible to the adverse effects or both.

Two studies provide evidence of increased risk associated with the use of zopiclone and zolpidem (Gjerde, Christophersen, Normann, & Mørland, 2011; Gustavsen et al., 2012). The experimental literature indicates that these hypnotic drugs can have impairing effects that linger into the morning after use of the drug at bedtime, suggesting that users have increased risk of crash involvement even after a night's sleep. It is not clear, however, whether the reported risks are associated with "next morning" drug effects or with improper or recreational use.

Evidence on the risks associated with the use of opioids is also mixed. The experimental literature shows opioids can cause impairment. It also shows that tolerance can develop to opioids relatively quickly with regular use of the same dose. Adherence to a program of medical use of prescription opioids would be expected to result in the development of some degree of tolerance. Tolerance could mitigate the extent of impairment and crash risk. In epidemiological studies, it is often difficult to determine whether the specific opioid detected was used as directed to treat a medical condition or

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[6] Confidence intervals that include the value 1.0 are not considered to be statistically significant.

was used for other purposes. Separating medical use of prescription opioids from other types of use in these studies might help to clarify the extent of the risks associated with opioids.

Fewer studies have examined the crash risk associated with stimulant drugs. The stimulant category often includes illicit stimulants such as cocaine and methamphetamine, and is not restricted to the legitimate use of amphetamine or methylphenidate for therapeutic purposes. In fact, although not a study assessing crash risk, Cox and colleagues (2012) followed a small number of youth with ADHD and found their driving improved after starting treatment with amphetamine. Hence, there is no evidence that therapeutic use of stimulants increases the risk of crash involvement when used as prescribed in the treatment of ADHD.

Several of the studies cited in previous sections and listed in Appendix E noted an increased risk of crash associated with driving after using more than one substance. The findings almost invariably show that drivers who combine the use of alcohol with cannabis (Brault et al., 2004; Drummer et al., 2004; Longo, Hunter, Lokan, White, & White, 2000a, 2000b; Mura et al., 2003; Williams, Peat, Crouch, Wells, & Finkle, 1985), benzodiazepines (Barbone et al., 1998; Benzodiazepine/Driving Collaborative Group, 1993; Brault et al., 2004; Longo et al., 2000a, 2000b; Lowenstein & Koziol-McLean, 2001) or any other psychoactive substance (Brault et al., 2004; Mathijssen & Houwing, 2005; Movig et al., 2004; Swann, 2000) are at significantly increased risk of crash involvement. The use of more than one substance other than alcohol has also been shown to increase the risk of crash involvement (Mathijssen & Houwing, 2005; Movig et al., 2004). Importantly, the risks associated with multiple substance use are typically higher than those associated with the use of a single substance alone. Clearly, drivers who combine more than one psychoactive substance, or a psychoactive substance and alcohol pose a serious threat to themselves and other road users.

Epidemiological studies are rarely able to provide information on whether the substance used was taken as prescribed or used illicitly. Using more of one's medication than prescribed or taking it more often, can increase the adverse effects on driving. Using medication prescribed to another person can be dangerous for a variety of reasons. In addition, using prescription medications for non-medical purposes often involves the ingestion of higher than recommended therapeutic doses or a route of administration intended to achieve a quick, intense effect or both. This type of substance use presents a number of risks, only one of which is to safe driving.

Despite the many methodological challenges, the available analytic epidemiological studies provide evidence of the increased risk of crash involvement among drivers who consume benzodiazepines, non-benzodiazepine hypnotics and opioids. The evidence also shows that the risk associated with alcohol increases exponentially with blood alcohol concentration and appears to be substantially larger than the risks associated with psychoactive prescription drugs. This difference could be the result of methodological differences among studies (particularly compliance with alcohol and drug testing), as well as considerable differences in patterns of use. For example, compliance with a medically supervised regime of prescription drug use could have overall protective effects in terms of crash risk. On the other hand, alcohol consumption is governed primarily by individual choice and often exceeds thresholds at which the effects on driving become increasingly profound. The consumption of large doses of alcohol combined with the social convention of drinking away from home leads to the need for transportation, which places these individuals at risk. It is also clear that the risk of crash involvement is higher when drug use is combined with alcohol or other drugs. Virtually every study that has examined use of multiple drugs or combined use of drugs and alcohol shows an elevated risk of crash involvement. This elevated risk could be the result of the combined effects of the substances consumed or the results of unique interactions among the substances that serve to increase impairment and crash risk.

Discussion and Conclusions

The experimental research evidence leaves little doubt that psychoactive prescription drugs can adversely affect cognitive and motor functions involved in the operation of a motor vehicle. Epidemiological studies show that psychoactive prescription drug use among drivers is not uncommon and that these drivers often become involved in crashes. However, the evidence pertaining to the extent of increased risk of crash involvement associated with the use of psychoactive prescription drugs is less consistent. Whereas the weight of the evidence reveals a significant increase in crash risk associated with the use of these drugs, there are also studies that fail to find such an increase. Overall, the evidence of driver impairment and risk is strong for the use of benzodiazepines, Z-hypnotics and opioids. Less evidence is available pertaining to the risks associated with the use of amphetamine and antihistamines.

The lack of consistent, definitive evidence on the road safety risks associated with the use of psychoactive prescription drugs is most likely related to the many challenges of the research, all of which can have a bearing on the results. For example, differences in the various methodologies used to assess risk, the assumptions and limitations of the studies, the type of bodily fluid sample collected, the drug testing methods used, the characteristics of the populations studied, and drug use and driving practices in the jurisdictions where the studies were conducted can all have a bearing on the results. Caution is also warranted in the interpretation of case-control studies that used different sample media (blood, urine or oral fluid) or non-equivalent cut-off values in testing for drugs.

The experimental literature indicates that not all psychoactive prescription drugs within a category exhibit the same degree of adverse effects. In epidemiological studies, the small number of drivers testing positive for specific drugs, however, often requires that substances with similar types of effects be grouped together for analysis. This aggregation of drugs implies that all substances within a category are associated with the same degree of risk. Until such time as the research is able to provide sufficient evidence on specific substances, differences in the risks associated with individual products will remain unknown.

It is also the case that not all drivers involved in crashes are tested for drugs, nor are drivers selected as controls in case-control studies required to participate. Furthermore, when blood samples are collected, not all potentially impairing drugs are necessarily included in the toxicology test panel. The variation in testing rates and the lack of common procedures in drug testing limits the validity of the estimates of the extent to which drugs contribute to serious road incidents. There is a need for consistency in the list of drugs that should be tested for in traffic-related cases, along with common cut-off values and standard analytic techniques (Farrell, Kerrigan, & Logan, 2007).

In assessing the evidence, it is imperative to recognize that there are inherent differences between the medical use of psychoactive prescription drugs prescribed by a healthcare practitioner for the treatment of a medical condition and the use of psychoactive substances for other purposes. Whereas medical use of prescription drugs is widely viewed as necessary and beneficial, any other use is deemed potentially harmful and dangerous. One of the major factors involved is dose. Although medical use can involve high doses, non-medical use of prescription drugs is often associated with the use of doses higher than those typically prescribed to treat a medical condition.

The distinction between medical and non-medical use can become blurred in some situations. For example, an individual can begin with a prescription for opioids to relieve chronic pain, but over time might develop a dependence on the medication and begin taking more medication than prescribed to obtain the same effects. This dependence might lead to seeking alternative sources for the drug. Distinguishing the different types of drug use in epidemiological studies is extremely difficult and

requires interviews with those using the drugs or inferences about drug concentrations or both. The present study recognizes that the epidemiological research often includes both types of drug use.

Further complicating the interpretation of the research is that in some cases the use of the appropriate psychoactive prescription drugs under the supervision of a healthcare practitioner might actually serve to improve the ability of a patient to operate a vehicle safely by helping to alleviate the effects of the disease (Wingen, Bothmer, Langer, & Ramaekers, 2005). While the rationale is compelling, there is limited research evidence supporting widespread offsetting effects of this kind. Future research needs to include patient populations in the study sample to determine the effect on their driving behaviour that can be attributed to the nature and extent of medications. At this point, generalizations should be avoided and evaluations of such effects be conducted on a case-by-case basis.

The influence of specific risk groups within the population also needs to be considered. For example, young and new drivers might be more susceptible to the impairing effects of drugs. Females are more likely than males to use anxiolytic medications. Older adults and those with chronic illnesses are more likely to take multiple prescription drugs, increasing the risk of adverse effects of drug interactions (Canadian Institute for Health Information, 2014; Ramage-Morin, 2009). Further research is required to better understand the risks of specific groups and the precautions or considerations to help ensure the safe use of medications by these groups.

The Way Forward

While acknowledging the limitations of the existing evidence, there is a need to begin implementing policies and practices to reduce the risks to all road users as a result of the use of psychoactive prescription drugs by drivers.

One of the initial responses to road safety problems such as impaired driving is often enforcement. In Canada, driving while impaired by alcohol or drugs is a criminal offence that carries severe sanctions (Canadian Centre on Substance Abuse, 2016). The law makes no distinction between the type of substance consumed or the reason for taking it. Driving while impaired by a psychoactive prescription medication, whether taken for health reasons or not, is the same offence punishable by the same penalties as driving while impaired by alcohol or an illicit substance. From a public safety perspective, it does not matter why a driver was impaired, but merely that impairment by alcohol or drugs placed the driver and other road users at risk. To some extent, we rely on judges to take such issues into account in sentencing.

Enforcement of impaired driving laws is widespread in Canada. Police services throughout the country operate periodic spot check activities to identify impaired drivers and remove them from the road. While most would agree that arresting drivers impaired by alcohol or illicit drugs is appropriate and warranted, a gentler approach for dealing with drivers who are adversely affected by their prescription medication might find favour with many. Short-term administrative licence suspension to immediately remove the affected driver from the road might be an appropriate response in most of these cases (Canadian Centre on Substance Abuse, 2016). This response could be followed up with a requirement to consult with a healthcare practitioner to determine what action should be taken to prevent subsequent occurrences of impaired driving.

Some countries have adopted an approach similar to that taken with alcohol and have established illegal drug concentration limits while driving for certain prescription drugs. For example, Norway, Denmark and the United Kingdom have set limits on the concentration of several prescription drugs, most notably benzodiazepines. Other countries (e.g., Sweden, Germany) have established a limit of

zero for some drugs. It is, however, often the case that a valid prescription is sufficient to absolve the driver of liability or require evidence that the driver was impaired.

In the case of psychoactive prescription drugs, enforcement should perhaps take a secondary role and the primary response to prevent impaired driving should be prevention. There are many opportunities for prevention. At the outset, it should be noted that prescription drugs are highly regulated products. From the point of product development, to the prescriber, the pharmacist and even the user, prescription drugs are subject to numerous rules and regulations to help ensure these products are used for the intended purposes, as well as to prevent or limit adverse effects. Each of these points also provides an opportunity for prevention.

It is incumbent upon product developers and producers to ensure that their products are not only effective but safe. This safety requires extensive research and clinical trials to determine and report the nature and extent of effects beyond the intended therapeutic effects, often referred to as "side effects." For example, manufacturers must assess the potential effects on an unborn child so that physicians can avoid prescribing medications with known teratogenic effects to pregnant females. No such systematic testing to determine the extent of adverse effects on one's ability to operate a vehicle is currently required, although manufacturers can report any known effects. Such information would be beneficial to guide the prescriber's choice of medication for their patients who drive.

In 2000, the U.S. National Transportation Safety Board recommended that the Department of Transportation establish a list of approved medications that may be used when operating a vehicle (National Transportation Safety Board, 2000). Subsequently, the Department of Transportation convened an expert panel to determine if such a list could be developed and indicate which medications might pose a hazard to driving. The panel developed a structured, standardized protocol for assessing the impairment potential of drugs. This approach would lead to better classification of drugs and provide more meaningful information to prescribers and patients about the impact of drugs on driving (Kay & Logan, 2011). The U.S. Food and Drug Administration has recently recommended that industry adopt this objective approach for evaluating the effects of drugs on driving (U. S. Department of Health and Human Services, 2015).

Government regulatory agencies are charged with the task of ensuring that prescription drugs products are both safe and effective. Of the possible adverse effects reported by drug manufacturers, impairment potential is not necessarily deemed a key concern unless the drug is known to cause sedation or dizziness. However, there is a vast array of impairing effects that goes considerably beyond sedation and dizziness. A potential solution is for regulators to require manufacturers to test all products, or least those that act on the brain, using the protocol for assessing impairment potential developed by the expert panel convened by the U.S. Department of Transportation.

Standardized testing of all existing psychoactive prescription drugs for their impairment potential is an expensive, time-consuming proposition. In the absence of such testing, there have been national and international efforts to develop a rating scheme for medicines for potential impairment based on an assessment of their pharmacological profile, available experimental research, epidemiological findings and clinical experience. Notable among these efforts is the work of the International Council on Alcohol Drugs and Traffic Safety (ICADTS) Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs Affecting Driving Performance. This group developed a system for classifying medicinal drugs according to their potential for causing driver impairment and provided a series of recommendations for implementing the system along with tools to help improve prescribing and dispensing practices (Alvarez, deGier, & ICADTS Working Group, 2001). The classification system includes a long list of prescription drugs that has since been updated and revised (Alvarez, de Gier, Mercier-Guyon, & Verstraete, 2007; de Gier & Alvarez, 2013). Within this classification system,

Level I indicates the drug is presumed to be safe or unlikely to produce any adverse effects on driving. Level II indicates the drug is likely to produce minor to moderate adverse effects and Level III indicates the drug is likely to produce severe effects or is presumed to be potentially dangerous. France, Spain and the Netherlands have implemented this three-tier classification scheme for prescription drugs by way of a clear, easy-to-understand graphic placed on product packaging and inserts to provide the consumer with information about the risk associated with driving after taking the medication.

In addition to the easy-to-understand warnings provided to consumers, this categorization scheme for prescription drugs can serve as the basis for mass communication about prescription drug use and driving impairment. It can also serve to trigger discussions between the patient and the prescriber or pharmacist about the risks of driving while using the medication. The list of prescription drugs with their classification also provides prescribers with information about alternative drugs that could be used for the same condition, but have less impairment potential for patients who have to drive.

Consumers also need to be aware of the potential for prescription drugs to affect their ability to operate a vehicle safely. Unless specifically told by their healthcare practitioner not to drive after taking a particular prescription drug, many might either believe it is safe to do so or simply never consider the possibility of their medication having an effect on their driving. Informed decisions about the safety of driving while using a prescription drug cannot be made in the absence of information on the effects of that drug on the ability to operate a vehicle safely.

There are several opportunities for consumers to obtain information about the potential impact of their prescription drugs on their ability to operate a vehicle safely. The healthcare practitioner is generally in the best position to advise the patient about the risks associated with the prescribed medication. In addition to knowledge of the drug's action, the physician typically has details about the patient's social and medical history, as well as other medications being used. The physician and pharmacist are also able to consider alternative medications that could be used that have less profound effects on driving.

The potential impact of prescription drugs on driving is an important consideration in deciding on which medication is best for the patient. For many, driving has become an essential component of their lifestyle. Simply discontinuing driving while taking prescription drugs can be a difficult decision. Hence, physicians might sometimes be reluctant to advise patients not to drive even for an initial period of time when starting a new medication or increased dose of a medication for fear that the patient will choose not the take the prescription drugs or only take it when convenient, rather than abstain from driving. The concern is a legitimate one and is best dealt with through a discussion between physician and patient.

Pharmacists also have an opportunity to provide further information about the anticipated effects of medications. In addition to verbal cautions, many pharmacists also provide written descriptions of contraindications, how to take medications and adverse effects to be wary of, including effects on cognition and psychomotor performance. Some prescription drugs come with a label on the package warning about the potential dangers associated with driving while taking the medication. Such warnings, however, can be vague and leave the consumer to decide whether to drive based on their perception of how the prescription drug is affecting them. Granted, some consumers will heed the warning and take appropriate caution in making decisions about driving. Unfortunately, the adverse effects of prescription drugs are not always apparent to the user. Others will discount the effects and rationalize driving. Stronger warnings and direct guidance about avoiding driving would be in order.

In conclusion, there is a need for ongoing research to better understand the adverse effects of various psychoactive prescription drugs on driving, the circumstances under which impairment is

likely to occur and the characteristics of those at greatest risk. Even in the absence of a complete understanding of the role of prescription drugs in road crashes, there is sufficient evidence to advance the state of prevention activities. In this context, there is need for interdisciplinary discussion and consultation involving all those with an vested interest in this area (e.g., regulators, prescribers, pharmacists, enforcement, policy makers and consumers) in a process that will use available resources, knowledge and experience to develop and implement an integrated set of policies and practices to reduce the risks associated with the use of psychoactive prescription drugs by drivers.

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Appendix A

Search Terms

- driv*, driving simulator, automobile driv*, motor vehicle driv*, road tests

- drugs and driving, impair*, drug, effects of drugs, influence of drugs, driver impairment

- central nervous system agents, depressants, hypnotic, stimulants, opioids, narcotic analgesic, antihistamine, amphetamine, opiate, benzodiazepine, anxiolytic, Z-drug, Z-hypnotic, psychotropic, psychoactive, prescription drug

- roadside survey, motor vehicle crash, crash risk, relative risk, injury, fatal crash, case-control, drivers at risk, crash-involved

Appendix B

Drug Use among Road Users: Roadside Surveys

Study	Location	Sample	Method	Results
Assum et al. (2005)	Norway	N=410	All days/all times Oral fluid samples collected by police (required)	Opiates 0.2% Benzodiazepines 0.2% Cannabis 0.5% Alcohol 0.0%
Behrensdorff & Steentoft (2003)	Denmark	N=961 (drivers suspected of illegal driving were not included)	70% daytime hours Mainly rural Oral fluid sample requested by police	1.3% positive for illegal drugs 0.7% positive for 1 or more benzodiazepines
Beirness & Beasley (2009)	British Columbia, Canada	N=1,533 78% provided oral fluid (N=1,197)	9 pm–3 am, Wed.–Sat.	Alcohol 8.1% Cannabis 4.6% Cocaine 4.6% Opioids 0.9%
Beirness & Beasley (2011)	British Columbia, Canada	N=2,306 71% provided oral fluid (N=1,781)	9 pm–3 am, Wed.–Sat.	Alcohol 9.9% Cannabis 4.5% Cocaine 2.3% Opioids 1.2%
Beirness & Beasley (2012)	British Columbia, Canada	N=2,513 70% provided oral fluid (N=1,757)	9 pm–3 am, Wed.–Sat.	Alcohol 6.5% Cannabis 4.4% Cocaine 3.3% Opioids 0.8%
Beirness, Beasley, & McClafferty (2015)	Ontario, Canada	N=2,443 80.7% provided oral fluid	9 pm–3 am, Wed.–Sat.	Alcohol 4.0% Cannabis 7.7% Stimulants 2.2% Opioids 1.5%
Berning, Compton, & Wochinger (2015)	United States	N=11,100 71% provided oral fluid (N=7881) 42.2% provided blood (N=7898)	Fri. daytime Fri.–Sat. nights	Weekend nights: Any illegal drug 15.2% Only medications 7.3% Weekdays: Any illegal drug 12.1% Only medications 10.3%
Assum et al. 2005	Scotland	N=1,312	All days, all times Oral fluid samples Police screened drivers for impairment	Cannabis 3.14% Amphetamines 0.49% Ecstasy 4.10% Cocaine 0.98% Opiates 0.02% (excludes codeine) Codeine 1.34%
Dussault, Lemire, Bouchard, & Brault (2000)	Quebec, Canada	N=5,509 41.4% compliance	All days, all times Urine samples	Cannabis 5.2% Benzodiazepines 3.7% Cocaine 1.1% Opiates 1.1% Barbiturates 0.4% Amphetamines < 0.1%
Fierro, Gonzalez-Luque, Segui-Gomez, & Alvarez (2015)	Spain	N=3,302 (2008–2009)	Oral fluid (on-site analysis) Mandatory tests 11 months	Cannabis 5.28% Cocaine 1.28% Amphetamines 0.06% Opiates 0.14% Benzodiazepines 0.17% Alcohol > .05 BAC 4.92%

Study	Location	Sample	Method	Results
Fierro et al. (2015)	Spain	N=2,932 (2013)	Oral fluid (on-site analysis) Mandatory tests April and November	Cannabis 3.13% Cocaine 0.87% Amphetamines 0.12% Opiates 0.03% Benzodiazepines 0.09% Alcohol > .05 BAC 3.41%
Gjerde et al. (2008)	Norway	N=10,816	All days, all times Oral fluid	Zopiclone 1.4% Benzodiazepines 1.4% Codeine 0.8% THC 0.6% Amphetamines 0.3% Cocaine 0.1%
Gjerde et al. (2014)	Norway	N=2,038	Fri.–Sat., 12 pm–12 am Oral fluid	Amphetamines 0.1% Cannabis 1.0% BDZ/Zopiclone 1.7% Opioids 0.4% Alcohol 0.2%
	Brazil	N=3,326		Amphetamines 0.5% Cannabis 0.5% BDZ/Zopiclone 1.0% Opioids 0.0% Alcohol 2.7%
Houwing et al. (2011)	13 European countries	N=48,542	Week days 2 pm–9.59 pm Week nights 10 pm–3.59 am Weekend days 4 pm–9.59 pm Weekend nights 10 pm–3.59 am	Benzodiazepines 0.9% (0.14–2.73) Opioids 0.35% (0.0–1.79) Z-drugs 0.09% (0.0–0.69) Alcohol 3.48% (0.15–8.59) THC 1.32% (0.0–5.99) (numbers in brackets are the range across countries)
Krüger, Schulz, & Magerl (1995)	Germany (Unterfranken)	N=2,234	All days, all times Oral fluid samples	Benzodiazepines 3% Illicit drugs 1% 1/3 of drug cases also positive for alcohol
Lacey et al. (2009)	United States	N=8,384 (nighttime)	Fri.–Sat., 10 pm–12 am, 1 am–3 am Oral fluid 71% Blood 39%	Benzodiazepines 2.0% Opioids 2.95% Amphetamine 0.86% Cannabis 7.66% Alcohol 12.4%
		N=2,525 (daytime)	Fri. 9:30 am–11:30 pm, 1:30 pm–3:30 pm Oral fluid 73% Blood N/A	Benzodiazepines 2.26% Opioids 1.49% Amphetamine 0.56% Cannabis 4.46% Alcohol 1.0%
Mathijssen & Houwing (2005)	Netherlands	N=3,799	All days, all times Urine samples (N=2,873) Blood samples (N=501)	Alcohol 2.3% Cannabis 4.5% Benzodiazepines 2.1% Amphetamines 0.03% Cocaine 0.7% Opiates 6.6% (includes codeine)
Pechansky et al. (2010)	Brazil	N=3,492	Fri.–Sat. 12 pm–12 am	Benzodiazepines 1.04% Amphetamines 1.2% Cannabis 1.5% Alcohol 4.8%

Appendix C

Drug Use among Crash-Involved Drivers

Study	Location	Sample	Method	Results
Ahlm, Björnstig, & Oström (2009)	Northern Sweden	N=102 hospitalized drivers N=56 fatalities	Fatalities: blood & urine Injured: blood (up to 6 hours post-crash)	Substance　Fatal　Injured Alcohol　38%　21% Pharma*　7%　13% Illegal drugs　9%　4% Combinations　5%　7% * benzodiazepines, opioids, antidepressants
Ahlner, Holmgren, & Jones (2013)	Sweden	N=895 driver fatalities	Blood samples	Diazepam 1.8% Zopiclone 1.6% Amphetamine 3.3% Cannabis 3.5% Alcohol 20.8%
Beirness, Beasley & Boase (2013)	Canada	N=9,547	Fatally injured drivers Blood drawn within 2 hours	Sedative-hypnotics 11.2% Opioids 5.4% CNS Stimulants 8.6% Cannabis 16.6% Alcohol 38.5%
Brady & Li (2014)	United States (6 states)	N=7,159 drivers killed in crashes (2007–2010)	Blood samples Driver died within 1 hour of crash	Substance　Male　Female Sedative-hypnotics　3.2%　4.8% CNS stimulants　9.5%　8.9% Opioids　4.0%　7.6% Cannabis　12.3%　7.5% Alcohol　43.7%　27.7%
Brault, Dussault, Bouchard, & Lemire (2004)	Quebec, Canada	N=512 fatally injured drivers	Blood tests	Benzodiazepines 10.4% Opiates 1.8% Amphetamines 0.8% Cannabis 19.7% Alcohol found in 47.5% of drug cases
Carmen del Río, Gómez, Sancho, & Alvarez (2002)	Spain	N=5,745 fatally injured drivers	Blood samples	Benzodiazepines 3.4% Opiates 3.2% Amphetamines 1.2% Alcohol 43.8% Cannabis 2.2%
Drummer et al. (2004)	Australia	N=3,398 drivers killed in crash	Blood samples	Benzodiazepines 4.1% Opioids 4.9% Stimulants 4.1% Other psychoactive drug 2.7% Cannabinoids 13.5% Alcohol 29.1%
Gerostamoulos, et al. (2002)	Melbourne, Australia	N=358 crash victims at trauma centre	Blood samples	Benzodiazepines 14% Opiates 10% Barbiturates 2% Amphetamines 12% Cannabis 36%
Gjerde, Christophersen, Normann, & Mørland (2011)	Norway	N=196 fatally injured drivers (59% of the total)	Blood samples	Benzodiazepines 11.8% Opioids 1.5% Amphetamine 4.6% Cannabis 4.6% Alcohol 25.0%

Study	Location	Sample	Method	Results
Jeffery, Hindmarsh, & Mullen (1996)	Canada	N=391 fatalities	Incidence of drugs among cases submitted to forensic labs	Benzodiazepines 21.4% Stimulants 14.5% Opiates 8.2% Barbiturates 3.1%
Jones, Kugelberg, Holmgren, & Ahlner (2009)	Sweden	N=1403	Drivers killed in crashes Blood and urine	Benzodiazepines 6.6% Zopiclone 0.9% Opiates/Opioids 4.9% Amphetamines 2.8% Cannabis 2.4% Alcohol 22.4%
Legrand, Houwing, Hagenzieker, & Verstraete, (2012)	Belgium	N=348	Injured drivers admitted to ER Blood samples	Benzodiazepines 7.3% Zolpidem/Zopiclone 1.8% Opioids 3.9% Amphetamines 2.6% Cannabis 7.6% Alcohol 42.5%
	Netherlands	N=187	Injured drivers admitted to ER Blood samples	Benzodiazepines 0.0% Zolpidem/Zopiclone 0.5% Opioids 0.5% Amphetamines 2.2% Cannabis 0.5% Alcohol 29.6%
Longo, Hunter, Lokan, White, & White (2000a)	South Australia	N=2,500 injured drivers	Incidence of drugs among injured drivers	Benzodiazepines 2.7% Stimulants 1.3% Cannabis 10.8%
Maio et al. (2000)	Michigan, USA	N=708 motor vehicle crash victims	Frozen serum samples from a previous study tested specifically for benzodiazepines	Benzodiazepines 3% (60% also positive for alcohol)
Mercer & Jeffery (1995)	British Columbia	N=227 fatally injured drivers	Blood samples	Diazepam 5% Cocaine 4% Alcohol 48% Cannabis 13%
Papadodima et al. (2008)	Southern Greece	N=3,167 crash-involved drivers	Blood samples for alcohol Urine samples for drugs	Benzodiazepines 4% Opiates 4% THC 4% Alcohol 29%
Romano & Pollini (2013)	United States	N=16,942	Fatally injured drivers in single vehicle crashes who died at the scene and were tested for alcohol and drugs	Sedative-hypnotics 1.5% Opioids 2.1% CNS Stimulants 7.2% Other 4.1% Multi-drug 4.1% Cannabis 7.1% Alcohol 45.1%
Ricci et al. (2008)	Italy	N=100 crash victims 56 drivers 15 passengers 12 bicyclists 17 pedestrians	Blood for alcohol Urine for drugs	Benzodiazepines 18% Opiates 6% THC 9% Alcohol 31%
Smink et al. (2005)	Netherlands	N=993 crash involved drivers	Blood samples (74% test rate)	Benzodiazepines 10.3% Opiates 4.2% Cannabis 16.9% Alcohol 64.5%
Stoduto et al. (1993)	Toronto, Canada	Injured victims in motor vehicle collisions N=854	Blood & urine samples	Benzodiazepines 12% Cocaine 5% Morphine 5% Cannabinoids 14%

Study	Location	Sample	Method	Results
Walsh et al. (2005)	Maryland, USA	N=108 injured drivers at trauma centre	Urine	Amphetamines 0.9% Methamphetamine 5.6% Opiates 10.2% Barbiturates 3.7% Alcohol 30.6% Cannabis 26.9%

Appendix D

Drug Use among Crash-Involved Drivers: Results from DRUID

DRUG	(a) Drug-Positive Seriously Injured Drivers (%)					
	Belgium	Denmark	Finland	Italy	Lithuania	Netherlands
Benzodiazepines	7.3	6.7	10.2	0.7	3.6	0
Zopiclone/Zolpidem	1.7	1.2	3.8	0	0	0.5
Opiates	3.9	4.7	4.0	5.8	8.1	0.5
Cannabis (THC)	7.6	1.3	5.7	3.7	0.5	0.5
Alcohol (≥10 mg/dL)	42.5	19.7	32.1	23.1	17.7	29.6
	(b) Drug-Positive Fatally Injured Drivers (%)					
	Finland	Norway	Portugal	Spain		
Benzodiazepines	13.3	9.7	1.8	3.9		
Zopiclone/Zolpidem	3.0	4.4	0	3.2		
Opiates	2.1	1.7	2.1	4.1		
Cannabis (THC)	1.3	6.1	0	1.3		
Alcohol (≥10 mg/dL)	31.4	25.4	44.9	19.0		

Appendix E

Studies Assessing the Risks Associated with Drugs in Crashes

Study	Country	Sample	Method	Results
Barbone et al. (1998)	United Kingdom	N=1,731 18 and older drivers involved in road-traffic accident taking psychoactive drug during study period	Case-crossover study	Benzodiazepines OR= 1.62 (risk greater for drivers 30 and younger, at fault, and with a positive alcohol breath test)
Benzodiazepine/Driving Collaborative Group (1993)	France	N=2,852 injured drivers	Responsibility analysis blood samples	Benzodiazepines OR=0.96 (0.8–1.2) Benzodiazepines + alcohol OR=7.2 (3.4–15.2)
Brault, Dussault, Bouchard, & Lemire (2004)	Quebec, Canada	N=512 fatally injured drivers N=5,931 drivers tested at roadside	(1) Case-control (2) Responsibility analysis Urine samples	**Substance / Case-control / Resp.** BZD 3.9 2.5 Opioids 3.1 3.2 Alcohol>0.8 69.9 32.6
Compton & Berning (2015)	United States (Virginia Beach)	N=3,095 crash-involved drivers N=6,190 controls	Case-control	Sedatives OR=1.19 (0.86–1.64) Stimulants OR=0.92 (0.70–1.19) Opioids OR=1.17 (0.87–1.56)
Drummer et al. (2004)	Australia	N=3,398 drivers killed in crash	Responsibility analysis blood samples	Benzodiazepines OR=1.27 .
Drummer (1995)	Australia	N=1,052 fatally injured drivers	Responsibility analysis blood samples	Stimulants OR=2.0 Benzodiazepines OR=2.0 Opiates OR=2.0 Alcohol OR=7.6
Dubois, Bédard, & Weaver (2010)	United States	N=2,541 opioid positive cases N=69,485 controls Drivers involved in fatal crashes (all had 0 BAC)	Responsibility analysis using unsafe driving action as a proxy for responsibility	Opioids OR=1.72 (1.45-2.03) Opioids with Depressants OR=1.31 (1.03–1.67)
Dubois, Bédard, & Weaver (2008)	United States	N=72,026 drivers involved in fatal crashes (BAC=0)	Responsibility analysis using unsafe driving action as a proxy for responsibility	Benzodiazepine short acting OR=1.02 (0.73–1.42) Benzodiazepine intermediate acting OR=1.53 (1.20–1.96) Benzodiazepine long acting OR=1.54 (1.25-1.66)
Dussault, Brault, Bouchard, & Lemire (2002)	Quebec, Canada	N=354 fatally injured drivers N=5,931 drivers at roadside	Case-control Responsibility analysis Urine tests for controls Blood + urine tests for cases	**Substance / Case-control / Resp.** Cannabis 2.2 1.2 Cannabis + alcohol 8.5 2.5 Cocaine 4.9 – BZD 2.5 3.6

Study	Country	Sample	Method	Results
Engeland, Skurtveit, & Morland (2007)	Norway	N=12,865 drivers in personal injury crashes	Pharmacoepidemiological SIR=Standardized incident ratio	**Within first 7 days (men)** Benzodiazepines short acting SIR=4.1 (2.6–6.2) Benzodiazepines long acting SIR=3.1 (2.5–3.8) Opioids SIR=2.0 (1.5–2.5) **Within first 14 days (men)** Benzodiazepines short acting SIR=3.2 (2.2–4.5) Benzodiazepines long acting SIR=2.7 (2.3–3.2) Opioids SIR=1.9 (1.6–2.3)
Gjerde, Christophersen, Normann, & Mørland (2011)	Norway	N=204 driver fatalities N= 10,540 roadside controls	Case-Control Blood for fatalities Oral fluid for controls	Benzodiazepines OR=11.4 (6.7–19.3) Benzodiazepines alone OR=1.6 (0.5–5.2) Opioids OR=5.7 (2.0–16.2) Zopiclone OR=5.4 (2.3–12.6) Zopiclone only OR=2.6 (0.9–7.6)
Gomes et al. (2013)	Ontario, Canada	N=1,930 road trauma cases N=1,819 controls with opioid prescription < 65 years of age	Pharmacoepidemiological	Opioid low dose OR=1.21 (1.02–1.42) Opioid mod dose OR=1.29 (1.06–1.57) Opioid high dose OR=1.42 (1.15–1.76) Opioid very high dose OR=1.23 (1.02–1.49)
Gustavsen, Mørland, & Bramness (2006)	Norway	N=3.9 million persons prescribed medications N=129 crashes	Pharmacoepidemiological SIR=Standardized incident ratio	Zopiclone SIR=2.3 (2.0–2.8) Zolpidem SIR=2.2 (1.4–3.4) Nitrazepam SIR=2.7 (1.8–3.9) Flunitrzepam SIR=4.0 (2.4–6.4)
Hemmelgarn, Suissa, Huang, Bolvin, & Pinard (1997)	Quebec, Canada	N=5,579 67–84 year old drivers involved in a crash where at least 1 person was injured N=18,490 controls	Nested case-control design (prescription information obtained from the provincial agency responsible for administering healthcare services)	Benzodiazepine long acting OR=1.28 Benzodiazepine long acting OR=1.45 (first 7 days of use) Benzodiazepines long acting OR=1.26 (61–365 days use) Benzodiazepine short acting OR=0.96
Li, Brady, & Chen (2013)	United States	N=737 drivers in fatal crashes National Roadside Survey	Case-control	Depressants OR=4.83 (3.18–7.21) Narcotics OR=3.03 (2.00–4.48) Stimulants OR=3.57 (2.63–4.76)
Longo, Hunter, Lokan, White, & White (2000b)	South Australia	N=2279 injured drivers	Responsibility analysis (blood samples)	Benzodiazepines only OR=2.0 Benzodiazepines + alcohol OR=13.4 Stimulants only OR=2.0 Alcohol only OR=8.0
Movig et al. (2004)	Netherlands	N=110 injured drivers N=816 controls randomly stopped on public roads	Case-control design blood and/or urine samples	Benzodiazepines OR=5.05 (1.82–14.04) Opiates OR=2.35 (0.87–6.32)
Mura et al. (2003)	France	N=900 injured drivers N=900 ER patients	Case-control Blood samples	Morphine OR=8.2 Benzodiazepines OR=1.7

Study	Country	Sample	Method	Results
Neutel (1995)	Saskatchewan	N=147,726 drivers with prescription for benzodiazepines N=97,862 controls	Pharmacoepidemiology (no toxicology)	Benzodiazepine short acting OR=3.9 within 4 weeks Benzodiazepine short acting OR=6.5 within 2 weeks Benzodiazepine long acting OR=2.5 within 4 weeks Benzodiazepine long acting OR=5.6 within 2 weeks Other sedatives OR=2.2