Cannabis and traffic collision risk: findings from a case-crossover study of injured drivers presenting to emergency departments

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ABSTRACT

Objective: This study examined whether acute cannabis use leads to an increased collision risk.

Methods: Participants were 860 drivers presenting to emergency departments in Toronto and Halifax, Canada, with an injury from a traffic collision, between April 2009 and July 2011. Cannabis and other drug use were identified either through blood sample or self-report. A case-crossover design was employed with two control conditions: a fixed condition measuring substance use during last time driving, and whether the driver typically uses cannabis prior to driving. Collision risk was assessed through conditional fixed effects logistic regression models.

Results: Results revealed that 98 (11%; 95% CI: 9.0-13.1) drivers reported using cannabis prior to the collision. Regression results measuring exposure with blood and self-report data indicated that cannabis use alone was associated with a four-fold increased (OR 4.11; 95% CI: 1.98- 8.52) odds of a collision; a regression relying on self-report measures only found no significant association.

Conclusions: Main findings confirmed that cannabis use increases collision risk and reinforces existing policy and educational efforts, in many high-income countries, aimed at reducing driving under the influence of cannabis.

INTRODUCTION

Data from high income countries indicate that rates of driving under the influence of cannabis are on the rise, a finding corroborated in studies based on self-report and bodily fluid sample (blood, urine), with drivers from the general public, those injured or those killed in collisions (MacDonald et al. 2003; Zhu et al. 2010; Jones et al. 2008; EMCDDA 2008; Beirness and Beasley 2011). Rates are highest amongst young drivers (19 years of age and younger), where the prevalence of driving under the influence of cannabis has reached and, in some instances, surpassed rates of driving under the influence of ethanol (Asbridge et al. 2005; Fergusson et al. 2008).

The primary psychoactive component in cannabis is THC (Δ9 tetrahydrocannabinol), which typically produces euphoria, relaxation, and changes in perception at low doses, and at higher doses, deficits in attention span and memory, psychomotor function, and pain relief (Kalant 2004; Hall and Degenhardt 2009). From the perspective of road safety, the central question is whether cannabis use increases collision risk. Three recent systematic reviews and meta-analyses have considered this question (Li et al. 2012; Asbridge et al. 2012; Elvik 2012).

Li and colleagues (2012) examined nine studies that included measures of cannabis use from self-report, urine, or blood, though some studies did not capture acute cannabis use. They reported a pooled odds ratio of 2.66 (95% CI: 2.07, 3.41). Asbridge and colleagues (2012) also selected nine studies for inclusion, with all studies having measured acute (recent use, within the preceding two hours) cannabis consumption in blood (and one via self-report) and adjusting for the presence of other drugs. They reported a pooled odds ratio of 1.92 (95% CI: 1.31, 3.36), though the association varied by study design (case control versus culpability studies) and

collision severity (injury versus fatal collisions). Finally, Elvik (2012) examined the association

of cannabis and collision risk in 42 studies of varying quality that included measures of cannabis

use from self-report, urine, and blood, and not all measured acute consumption. Elvik found an

association between cannabis use and property damage collisions (OR 1.48; 95% CI: 1.28, 1.72)

but not for fatal (OR 1.31; 95% CI 0.91, 1.88) or injury collisions (OR 1.26; 95% CI: 0.99, 1.60);

associations were weakened when publication bias was considered.

The divergence in findings across studies points to a lack of robust epidemiological data on the

role of cannabis on collision risk (Asbridge et al. 2012; Elvik 2012; Laumon et al. 2005) due, in

large part, to issues of methodological quality and weak study design. Foremost is the inadequate

measurement of cannabis use which often fails to capture acute pre-collision consumption. Many

studies only measure inactive THC metabolites in urine or blood, which can show positive

results in the body for weeks after consumption and have no clear relationship to impairment and

ability to drive (Kalant 2004; Ramaekers et al. 2004). A second concern is that many studies of

collision risk fail to include a control group of motorists not involved in collisions that have been

randomly stopped and tested for drug use (MacDonald et al. 2003), affecting the identification

of relative risk estimates. Finally, many studies fail to adjust for confounders, particularly the

combined presence of ethanol and other drugs used with cannabis (MacDonald et al. 2003;

Perez-Reyes et al. 1988; Mura et al. 2003; Dussault et al. 2002).

There is, therefore, a need for additional studies of the association of cannabis consumption on

collision risk in view of the scope and quality of the existing scientific literature and identified

gaps. Employing a case-crossover design of injured drivers presenting to emergency

departments after a traffic collision, we assess the role of acute cannabis consumption on

collision risk (by comparing to a control time; see below). We avoid the limitations described

above through a toxicological analysis isolating active THC metabolites in whole blood, adjusting for the presence of other psychoactive substances, and controlling for confounding from measured and unmeasured sources through our within-person study design.

METHODS

Participants

Participants were injured drivers presenting to an emergency department after being involved in a traffic collision. Eligibility for inclusion in the study is being a driver, 16 years and older in Halifax, 18 years and older in Toronto, and presenting to hospital within twenty-four hours of the collision event. Drivers included not only those individuals operating standard highway motor vehicles (cars, vans, SUVs, trucks, motorcycles) but also bicycles and scooters.

Between April 2009 and June 2011, injured drivers were recruited from three Canadian hospitals. The Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia, is the largest adult tertiary care hospital in Atlantic Canada and the only adult tertiary care centre in Nova Scotia. St. Michael's Hospital in Toronto is an inner-city trauma centre with a high proportion of collisions involving major traumas. Humber River Regional Hospital in north-central Toronto is a large, acute-care hospital, with a collision patient population who largely suffer from less severe injuries.

Participants were recruited using a time sampling strategy. Different four-hour time slots were randomly selected, with the probability based on occurrence density (i.e. times with higher occurrence of presentations due to collision having a greater chance of being selected). Time

sampling methods have been successfully used as part of the WHO Collaborative Study on Ethanol and Injuries (Borges et al. 2006).

Recruitment of drivers occurred in two ways. First, when drivers suffering serious injuries arrived at the emergency department, a member of the research team (research nurse or paramedic) responded along with the clinical care team. As seriously injured drivers were often unconscious upon arrival, blood samples (maximum 6 mL whole blood) were obtained via a waived consent process – a temporary period where active informed consent to collect data from a patient is not required, yet data collection is necessary and time sensitive. Waived consent is accepted as an exception to informed consent under Canadian ethical policies. Informed consent to use the blood was then obtained once the driver was conscious and able to make an informed decision. Given the rapid decline in active metabolites in blood, samples used to estimate active THC metabolite (11-hydroxy delta-9-THC) , which lasts in blood for approximately two hours, must be collected as close to the time of collision as possible to draw inferences regarding acute cannabis use pre-collision (Ramaekers et al. 2004).

Seriously injured drivers were approached after they received treatment, either in the emergency department or in the ward after being admitted. Separate consent was obtained to participate in the study and to use the blood sample (with the sample destroyed if consent was denied). If the driver consented to participate, they were screened for mental competence, as determined by the Mini-Mental State Examination, and the interview was completed.

The second recruitment method applied to less severely injured drivers who were identified through the emergency department computer system. A similar recruitment procedure to that for seriously injured drivers was employed, though drivers were approached in the waiting room.

After obtaining consent and screening for mental competence, a blood sample was drawn and the interview was completed.

Study design

We employed a case-crossover methodology, a variation of the case-control design, which is an epidemiological design well suited to the study of transient effects on the risk of rare acute events (Maclure 1991), and has previously been employed to study factors influencing collision risk (Redelmeier and Tibshirani 1997; Gmel et al. 2009; Maclure and Mittleman 2000). In a case-crossover design each subject serves as their own control, thus it departs from cases only designs which are seen as a limitation of previous studies of cannabis and collision risk. An even greater strength of the within-person design is that it eliminates confounding from most known and unknown personal characteristics, including age, gender, driving experience and ability, personality or sociodemographic characteristics, and other fixed effects. Moreover, the case-crossover design eliminates the problem of control-selection bias (Maclure and Mittleman 2000) and increases study efficiency.

For the case period, cannabis, ethanol, and other drug consumption (benzodiazepines and cocaine) were assessed (through blood sample or self-report) within the six hours before the collision. For drivers who consented to provide a blood sample, we defined acute cannabis use as any positive THC level (>0.2 ng/mL). Our primary outcome was based on blood sample results, if present, and self-report results otherwise, and measured dichotomously. Our measure of acute ethanol consumption was similarly operationalized

The control condition necessary to quantify risk is established by asking cases about their past exposure. Two different control periods were used to operationalize past exposure (Maclure 1991): For the first control condition, cannabis and ethanol use were assessed retrospectively for the same time interval (i.e. 6 hours) during the last time the driver drove a similar vehicle around the same time of day. The second control condition was the self-reported usual frequency of driving under the influence of cannabis over the preceding six months. The use of multiple control conditions has the benefit of reducing control time bias (Maclure and Mittleman 2000), increasing the validity of study findings, and addresses differences in cannabis use patterns (infrequent versus regular users).

Interview

The interview drew on questions from the WHO Collaborative Study on Ethanol and Injuries (Borges 2006), and assessed: 1) a socio-demographic driver profile (i.e. age, gender) and injury history; 2) events surrounding the collision, including cannabis, ethanol and other substance use, and crash location, injury type, and severity; 3) cannabis and ethanol use, and general driving information for the control period; 4) usual patterns of substance use over the past six months, including harmful use measured through the Alcohol Use Disorders Identification Test [AUDIT (Saunders et al. 1993)] and the Cannabis Use Disorders Identification Test [CUDIT (Adamson and Sellman 2003)]. The AUDIT and CUDIT are short, validated, ten-question scales developed to determine if an individual's consumption of alcohol or cannabis may be harmful (scale scores range from 0-40). All consenting drivers received $50 Canadian for participating in the study, irrespective of whether or not they completed the interview.

Blood samples

Active THC metabolite (11-hydroxy delta-9-THC) was measured in blood if the driver had presented to the emergency department within six hours of their collision. Whole blood samples, regardless of consenting procedure, were immediately sent to their respective hospital lab where the blood serum (maximum 3.6mL) was obtained (via spinning/separation), and samples were frozen (at a minimum -20 C) in cryogenic plastic vials until being sent to the lab for analysis.

Pharmacologically active THC concentrations were obtained using gas chromatography-mass spectrometry. The analysis of serum for THC and its two major metabolites, hydroxy-THC and carboxy-THC, involved purification by solid phase extraction followed by derivatization and analysis by gas chromatography-mass spectrometry detection. The limit of detection was 0.2 ng/mL with the analytical range up to 50 or 100 ng/mL, as needed. Internal standards used were the deuterated compounds for each analyte. Unchanged THC was recorded in ng/mL. Blood ethanol concentrations were determined through headspace gas chromatography and recorded in grams/100mL. All blood analysis was completed at the laboratory at the Centre for Addiction and Mental Health in Toronto, Canada.

Control for Confounding

In addition to the within-person design, we address potential confounding of other drugs with the inclusion of measured ethanol concentrations and screening (through gas chromatography-mass

spectrometry) for the presence (not analytic) of benzodiazepines and parent cocaine, two drugs often found in studies of impaired drivers. Descriptive statistics for the sample are provided in Table 1.

INSERT TABLE 1 HERE

Statistical analysis

We estimated conditional fixed effects logistic regression models to account for the within-person structure of the case-crossover approach (Maclure and Mittleman 2000; Marshall and Jackson 1993). The conditional logistic regression model is specified as:

$$Yij = B0 + B1Xij + Ui + Eij$$,

where Yij, Xij are the outcome and exposure measures for the it i^{th} pair with j referring to the individual within the ith pair, Ui denotes non observed sources of fixed variation that influence the outcome of the ith subject and Eij is a random error term.

Our main model measures cannabis impairment alone, identified either through any positive THC (>0.2 ng/mL) in blood or through self-report, if no sample was present (n=763). Approval

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for the study was obtained from the institutional ethics review boards from all participating hospitals, universities, and centres.

We also performed sensitivity analyses on our main model employing different inclusion and exclusion criteria, based on: 1) whether cannabis was measured via blood or self-report only; 2) employing usual frequency control period; 3) whether other substance use was controlled for; and 4) whether respondents "lied" about their pre-collision cannabis use. Potential lying was evident in respondents who provided indications of cannabis use from blood and self-report. Considerable discordance was observed, where cannabis use pre-collision was indicated in the blood sample but not through self-report (n=52).

RESULTS

In total, 3,033 drivers presenting to emergency departments in Halifax and Toronto due to a traffic collision were approached to participate in the study (see Figure 1). Of these, 1,848 patients were deemed ineligible, due to: being a passenger rather than driver, young age, poor mental or physical competency, death, discharge or leaving without treatment, language barrier, or having a collision that occurred outside the study window. This left 1,185 eligible drivers, of which 860 (73%) consented to participate in the study, and 368 (43% of those consenting) agreed to provide a blood sample. Only limited differences were observed between those who provided a blood sample and those who did not (Table 1); a higher proportion of those who provided a sample were Canadian born, resided in Halifax, and reported higher levels of problem ethanol and cannabis use, and past six months driving under the influence of cannabis.

INSERT FIGURE 1 HERE (Flow Chart for driver recruitment, Canada, 2011)

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Among eligible drivers, 98 (11.3%; CI 9.2-13.4%) reported using cannabis prior to the collision; when restricted to the 368 drivers who provided a blood sample, nearly one in five (19.8%; CI 15.7, 23.9%) had positive levels of THC. As Table 1 indicates, relative to cannabis-free drivers, those who used cannabis prior to the collision were more likely to be male (91%), Canadian born (92%), poorly educated, and less likely to be employed. A greater proportion of cannabis-related collisions occurred in the evening /night; no differences were observed in collision severity or collision location. Finally, a higher proportion of those who were involved in a cannabis-related collision regularly drove under the influence of cannabis, and reported higher CUDIT and AUDIT scores.

Table 2 presents results from conditional fixed effects regression models assessing the association of cannabis use with collision risk. Our main model measures pre-collision cannabis use via blood and, where blood is not available, through respondent's self-report. Results indicate that cannabis use alone (i.e. without the use of other substances) was associated with a four-fold increase in the odds of collision (OR 4.11; 95% CI: 1.98- 8.52). This association persisted when usual frequency controls (Model 2) were employed instead of last time driving, while an increased effect size was observed (Model 3) when cannabis was used in conjunction with other substances (OR 6.30; 95% CI: 3.23-12.3). Results were also similar for motor vehicles and bicycles.

Other sensitivity analyses provided mixed findings. Cannabis was associated with an increase in the odds of a collision when measured via blood sample (Model 4) only (OR 12.0; 95% CI: 3.70- 38.9), but demonstrated no association when measured via self-report (Model 5) only (OR 0.58; 95% CI: 0.23-1.48). As noted above, this was due to discordant responses between blood and self-report measurement, where a subset of drivers with positive THC in blood self-reported that

they had not used cannabis pre-collision. This was verified when we reran our main model

removing discordant responses (Model 6) and found no association between cannabis and

collision risk (OR 0.55; 95% CI: 0.19-1.66).

INSERT TABLE 2 HERE

We replicated cannabis analyses with a similar set of questions on ethanol use pre-collision

(measured via blood and self-report) and during control periods (bottom half of Table 2). Ethanol

consumption was associated with an increase in the odds of a crash (OR 3.89; 95% CI: 1.86-

8.09). More importantly, the association was consistent in all models; whether ethanol

consumption was measured via blood (Model 4) or from self-report (Model 5), whether last time

driving or usual frequency control (Model 2) periods were employed, and when discordant

responses were removed (Model 6). The later finding was likely the result of the limited

disagreement between respondents' self-reported pre-collision ethanol consumption and their

blood sample results.

DISCUSSION

In a sample of 860 injured drivers presenting to emergency departments due to a traffic collision,

controlling for other substance use, acute cannabis consumption, measured through blood sample

or self-report, was associated with a four-fold increase in the risk of a traffic collision, and the

association remained when employing a usual frequency control condition. Our results are

consistent with recent studies and reviews (Li et al. 2012; Asbridge et al. 2012; Bogstrand et al.

2012) that report a positive association between acute pre-collision cannabis consumption and

increased collision risk. The likelihood of a collision was higher when cannabis was used in

conjunction with other drugs (ethanol, benzodiazepines, cocaine); a finding consistent with other laboratory and epidemiologic studies (MacDonald et al. 2003; Perez-Reyes et al. 1988; Mura et al. 2003; Dussault et al. 2002). While ethanol is the drug most commonly found in studies of collision-involved drivers (Dussault et al. 2002; Drummer et al. 2003; Gonzalez-Wilhelm 2007), in the current study ethanol (n=74) was present in fewer injured drivers than cannabis; this has been observed elsewhere in studies of younger drivers (Asbridge et al. 2005; Fergusson et al. 2008).

Sensitivity analyses, however, revealed some inconsistencies in the association contingent on how acute cannabis use was measured pre-collision. Acute cannabis, when measured in blood, was strongly associated with an increased crash risk, whereas cannabis measured through respondent self-report showed no association with collision involvement. This divergence can be explained by the inconsistent reporting from a subset of respondents who tested positive for THC in blood, yet indicated that they had not used cannabis pre-collision during the interview. Interestingly, this discrepancy was not observed in an examination of pre-collision ethanol consumption and, as such, the association of acute ethanol consumption with and increased risk of a collision was consistent across all models, whether measured in blood or self-report.

How might we interpret these findings? One possibility comes from recent research demonstrating that active THC metabolites can be measured in blood days after last consumption among chronic, heavy cannabis users (Karschner et al. 2009; Bergmaschi et al. 2013). While studies indicate that impairments in psychomotor performance due to cannabis are observed at concentrations of 1 ng/mL (Drummer et al. 2003; Laumon et al. 2005; Ramaekers et al. 2004), the precision of the measurement of acute cannabis consumption among chronic users may result in drivers who had not used cannabis pre-collision (within the six hour pre-collision) but

who tested positive for THC in blood. This does not address the subsequent question of whether residual THC is accompanied by neurocognitive and motor impairment, though the limited evidence available suggests that impairment persists (Bergmaschi et al. 2013; Pope et al. 2001).

A more immediate explanation resides in the illicit nature of cannabis consumption in Canada. While it is illegal to drive under the influence of any impairing substance, including cannabis or ethanol, the general consumption of ethanol is legal while the consumption of cannabis is not. As such, respondents may feel uncomfortable, either morally or through fear of legal action, in admitting cannabis consumption – despite assurances of anonymity and confidentiality. Validation studies comparing self-report to objective measures of illegal behaviour have produced mixed findings (depending on the degree of illegality, age of the population), with some reporting a high degree of agreement and others much less so (Mensch and Kandel 1988; Ledgerwood et al. 2008; Loo et al. 2012). A lack of concordance between self-report and biologic measures of acute pre-collision cannabis use may help to explain inconsistencies in reviews of studies examining the role of acute cannabis use on collision risk (Elvik 2012; Bates and Blakely 1999).

The question then, with respect to the current research, is which estimates should we focus upon? We believe that blood sample results combined with self-report helps to improve the accuracy of information regarding exposure status (Loo et al. 2012; Origer and Schmit 2012). As such, our main model, which measure exposure to cannabis primarily in blood and, when not available, in self-report, offers the most reliable and valid estimate of the association of acute cannabis consumption and collision risk.

Beyond risk, our study points to the high prevalence of cannabis use among injured drivers involved in traffic collisions. Overall, 11% of injured drivers reported using cannabis before driving, though when looking only at those who provided a blood sample the prevalence was 20%. This is the highest observed rate of THC positive collisions in studies of injured Canadian drivers (Dussault et al. 2002; Stoduto et al. 1993). For comparison purposes, the recent BC Roadside survey reported that 5.8% of 2,442 drivers stopped randomly at the roadside, and not involved in a collision, tested positive for cannabis (Beirness and Beasley 2011).

Our observed rates are also comparable to international results. In a review of 17 studies involving 14,668 fatally injured drivers and 10 studies involving 4,843 non-fatally injured drivers, Macdonald et al. (2003) reported that the average proportion testing positive for cannabis across studies was 7.8% for fatally injured drivers (range 1.4 to 27.5%) and 11.9% for non-fatally injured drivers (range 5 to 16.9%). More recent international studies report varying rates for the presence of cannabis in samples drawn from collision-involved drivers [range 6 to 29%] (Laumon et al. 2005; Mura et al. 2003; Gmel et al. 2009; Mura et al. 2005).

This study has limitations. First, blood samples were provided by only 43% of consenting drivers. Given that 20% of drivers who provided a blood sample tested positive for THC suggests our estimates are likely conservative. Second, our control conditions are only measured via self-report and thus under-reporting of cannabis consumption is likely. Related, while two control periods were included to account for the inherent recall bias associated with case-crossover designs, such bias cannot be completely eliminated (Gmel 2010; Zeisser et al. 2012; Yu et al. in press). Third, we were unable to collect more detailed data on driving behaviour, including information on the specific type of motor vehicle involved in the crash and, as well as driving experience and , as such, cannot adjust for these in our analyses. Finally, the drivers

included in our study represent only injured drivers presenting to emergency departments, and associations may not hold for non-injured drivers involved in collisions, injured drivers who refused to participate, and drivers from the general population.

Despite these limitations, our findings address important gaps in the existing research and represent an important contribution to the epidemiologic literature on the association of cannabis use with collision risk. The effect size of our estimate demonstrates the strength of the association of acute cannabis consumption on collision risk, and reaffirms the negative role played by cannabis in contributing to the traffic collision burden. Our results reinforce existing efforts in many high income countries to reduce rates of driving under the influence of cannabis and improve road safety, through policy, education, and enforcement. From the perspective of public health, increasing access to and utilization of medical marijuana in many jurisdictions, coupled with a high general prevalence of cannabis use, suggests that concerns about driving under the influence of cannabis, and associated collision risk, will persist (Hall and Degenhardt 2009; Borges et al. 2006; Saunders et al. 1993; Adamson and Sellman 2003).

REFERENCES

Adamson SJ, Sellman JD (2003) A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol dependent clinical sample. Drug Alcohol Rev 22:309–315.

Asbridge M, Hayden JA, Cartwright JL (2012) Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 9;344:e536. doi: 10.1136/bmj.e536.

Asbridge M, Poulin C, Donato A (2005) Driving under the influence of cannabis and motor vehicle collision risk: evidence from adolescents in Atlantic Canada. Accid Anal Prev 37(6):1025-1034.

Bates MN, Blakely TA (1999) Role of cannabis in motor vehicle crashes. Epidemiol Rev 21:222-232.

Beirness DJ, Beasley EE (2011) Alcohol and drug use among drivers: British Columbia Roadside Survey 2010. Canadian Centre on Substance Abuse, Ottawa ON.

Bergamaschi MM, Karschner EL, Goodwin RS, Scheidweiler KB, Hirvonen J, Queiroz RH, Huestis MA (2013) Impact of prolonged cannabinoid excretion in chronic daily cannabis smokers' blood on per se drugged driving laws. Clinical Chemistry 59(3):519-526.

Bogstrand ST, Gjerde H, Normann PT, Rossow I, Ekeberg O (2012) Alcohol, psychoactive substances and non-fatal road traffic accidents - a case-control study. BMC Public Health 12:734.

Borges G, Cherpitel C, Orozco R, Bond J, Ye Y, MacDonald S et al (2006) Multicenter study of acute alcohol use and non-fatal injuries: data from the WHO Collaborative Study on Alcohol and Injuries. Bull World Health Org 84(6):453-460.

Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn JR, Robertson MD, Swann P (2003) The incidence of drugs in drivers killed in Australian road traffic crashes. Forensic Sci Int 134(2-3):154-162.

Dussault C, Brault M, Bouchard J, Lemire AM (2002) The contribution of alcohol and other drugs among fatally injured drivers in Quebec: some preliminary results. In Mayhew DR, Dussault C (eds) *Proceedings of the 16th International Conference on Alcohol, Drugs and Traffic Safety*. Société de l'Assurance Automobile du Québec, Quebec, pp 423-430.

Elvik R (2012) Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. [E-pub ahead of print]. Accid Anal Prev. doi: 10.1016/j.aap.2012.06.017

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2008) Drug use, impaired driving and traffic accidents: Insights no 8. Office for Official Publications of the European Communities, Lisbon.

Fergusson DM, Horwood LJ, Boden JM (2008) Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. Accid Anal Prev 40(4):1345-1350.

Gmel G, Kuendig H, Rehm J, Schreyer N, Daeppen JB (2009) Alcohol and cannabis use as risk factors for injury – a case-crossover analysis in a Swiss hospital emergency department. BMC Publ Health 9:40.

Gmel G (2010) Case-crossover designs for alcohol use: the potential for more than one bias. J Stud Alcohol Drugs 71:620–621.

Gonzalez-Wilhelm L (2007) Prevalence of alcohol and illicit drugs in blood specimens from drivers involved in traffic law offences. Systematic review of cross-sectional studies. Traffic Inj Prev 8(2):189-198.

Hall W, Degenhardt L (2009) Adverse health effects of non-medical cannabis use. Lancet 374:1383-1391.

Jones AW, Holmgren A, Kugelberg FC (2008) Driving under the influence of cannabis: a 10-year study of age and gender differences in the concentrations of tetrahydracannabinol in blood. Addiction 103(3):452-461.

Kalant H (2004) Adverse effects of cannabis on health: an update of the literature since 1996. Prog Neuropsychopharmacol Biol Psychiatry 28(5):849-863.

Karschner EL, Scwilke EW, Lowe RH, Darwin WD, Pope HG, Herning R et al (2009) Do Δ9-tetrahydrocannabinol concentrations indicate recent use in chronic cannabis users? Addiction 104(12):2041-2048.

Laumon B, Gadegbeku B, Martin J-L, Biecheler MB, SAM Group (2005) Cannabis intoxication and fatal road crashes in France: population based case-control study. BMJ 331:1371-77.

Ledgerwood DM, Goldberger BA, Risk NK, Lewis CE, Price RK (2008) Comparison between self-report and hair analysis of illicit drug use in a community sample of middle-age men. Addictive Behaviors 33(9):1131-9.

Li M-C, Brady JE, DiMaggio CJ, Lusardi AR, Tzong KY, Li G (2012) Marijuana use and motor vehicle crashes. Epidemiol Rev 34:65–72.

Loo RL, Chan Q, Brown IJ, Robertson CE, Stamler J, Nicholson JK, et al (2012) A comparison of self-reported analgesic use and detection of urinary ibuprofen and acetaminophen metabolites by means of metabonomics: the INTERMAP study. American Journal of Epidemiology 175(4):348-358.

MacDonald S, Anglin-Bodrug K, Mann RE, Erickson P, Hathaway A, Chipman M, Rylett M (2003) Injury risk associated with cannabis and cocaine use. Drug Alcohol Depend 72:99-115.

Maclure M, Mittleman MA (2000) Should we use case-crossover design? Annu Rev Publ Health 21:193-221.

Maclure M (1991) The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 133:144-153.

Marshall RJ, Jackson RT (1993) Analysis of case-crossover designs. Stat Med 12: 2333-41.

Mensch BS, Kandel DB (1988) Underreporting of substance use in a national longitudinal youth cohort individual and interviewer effects. Public Opinion Quarterly 52(1):100-124.

Mura P, Chatelain C, Dumestre V, Gaulier JM, Ghysel MH, Lacroix C et al (2005) Use of drugs of abuse in less than 30-year-old drivers killed in a road crash in France: a spectacular increase for cannabis, cocaine and amphetamines. Forensic Sci Int 160:168-172.

Mura P, Kintz P, Ludes B, Gaulier JM, Marquet P, Martin-Dupont S et al (2003) Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. Forensic Sci Int 133:79-85.

Origer A, Schmit JC (2012) Prevalence of hepatitis B and C and HIV infections among problem drug users in Luxembourg: self-report versus serological evidence. J Epidemiol Community Health 66(1):64-68.

Perez-Reyes M, Hicks RE, Bumberry J, Jeffcoat AR, Cook CE (1988) Interaction between marihuana and ethanol: effects on psychomotor performance. Alcohol Clin Exp Res 12:268-76.

Pope H, Gruber A, Hudson J, Huestis M, Yurgelun-Todd D (2001) Neuropsychological performance in longterm cannabis users. Arch Gen Psychiatry 58:909-15.

Ramaekers JG, Berghaus G, van Laar M, Drummer OH (2004) Dose-related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 73:109-119.

Redelmeier DA, Tibshirani RJ (1997) Association between cellular-telephone calls and motor vehicle collisions. New Engl J Med 336:453-58.

Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M (1993) Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption - II. Addiction 88:791-804.

Stoduto G, Vingilis E, Kapur BM, Sheu WJ, McLellan BA, Liban CB (1993) Alcohol and drug use among motor vehicle collision victims admitted to a regional trauma unit: demographic, injury, and crash characteristic. Accid Anal Prev 25:411-420.

Yu Y, Bond J, Cherpitel CJ, Stockwell T, MacDonald S, Rehm J (2013) Evaluating potential bias using the case-crossover usual frequency method to estimate risk of injury due to alcohol. Epidemiology 24(2):240-3.

Zeisser C, Stockwell TR, Chikritzhs T, Cherpitel C, Ye Y, Gardner C (2013) A systematic review and meta-analysis of alcohol consumption and injury risk as a function of study design and recall period. Alcohol Clin Exp Res 37(Suppl 1):E1-8.

Zhu M, Zhao S, Rice TM, Coben JH (2010) Trend analysis of drug-related motor vehicle crashes in the United States. Injury Prev 16:A159.