

cost. By limiting the therapeutic options for a significant number of patients, the secondary epidemic of drug resistant HIV represents a major clinical and public health problem.

The UK Group on Transmitted HIV Drug Resistance is a collaboration between the UK Collaborative Group on HIV Drug Resistance, the UK Collaborative HIV Cohort Study, and the UK Register of HIV Seroconverters. Members of the writing group are Patricia Cane, Ian Chrystie, David Dunn, Barry Evans, Anna Maria Geretti, Hannah Green, Andrew Phillips, Deenan Pillay, Kholoud Porter, Anton Pozniak, Caroline Sabin, Erasmus Smit, Jonathan Weber, and Mark Zuckerman; affiliations are on bmj.com. We thank Tommy Lui (Stanford) and Patrick Woodburn for help with various aspects of the analysis, and the clinicians, virologists, data managers, and research nurses in participating centres who assisted with the provision of data.

Contributors: See bmj.com.

Funding: The UK HIV drug resistance database is funded by the Department of Health; the views expressed here are those of the authors and not necessarily those of the Department of Health. UK CHIC (grant G0000199) and the UK Register of HIV Seroconverters (grant G9324150) are funded by the Medical Research Council, United Kingdom.

Competing interests: None declared.

Ethical approval: This study was approved by the UK multi-centre research ethics committee and relevant local research ethic committees.

1 Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med* 2002;347:385-94.

- 2 Grant RM, Hecht FM, Warmerdam M, Liu L, Liegler T, Petropoulos CJ, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA* 2002;288:181-8.
- 3 Eron JJ. The role of resistance testing in treatment-naïve HIV-infected individuals. <http://www.clinicaloptions.com/hiv/treatment/testing/#eron> (accessed 1 May 2005).
- 4 Gale CV, Myers R, Tedder RS, Williams IG, Kellam P. Development of a novel human immunodeficiency virus type 1 subtyping tool, subtype analyzer (STAR): analysis of subtype distribution in London. *AIDS Res Hum Retroviruses* 2004;20:457-64.
- 5 UK Register of HIV Seroconverters Steering Committee. The AIDS incubation period in the UK estimated from a national register of HIV seroconverters. *AIDS* 1998;12:659-67.
- 6 Johnson VA, Brun-Vezinet F, Clotet B, Conway B, D'Aquila RT, Demeter LM, et al. Update of the drug resistance mutations in HIV-1: 2004. *Top HIV Med* 2004;12:119-24.
- 7 Release notes for HIVseq, HIVdb, HIValg. <http://hivdb.stanford.edu/pages/asi/releaseNotes/> (accessed 1 May 2005).
- 8 Sabin CA, Hill T, Lampe F, Matthias R, Bhagani S, Gilson R, et al. Treatment exhaustion of highly active antiretroviral therapy (HAART) among individuals infected with HIV in the United Kingdom: multicentre cohort study. *BMJ* 2005;330:695-8.
- 9 UK Collaborative Group on HIV Drug Resistance and UK CHIC Study Group. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. *AIDS* 2005;19:487-94.
- 10 UK Collaborative Group on HIV Drug Resistance. Estimating HIV-1 drug resistance in antiretroviral treated individuals within the UK. *J Infect Dis* 2005;192:967-73.
- 11 HIV and AIDS in the United Kingdom quarterly update: data to the end of December 2004. *Commun Dis Rep CDR Wkly* 2005;15(8).
- 12 Wensing AM, van de Vijver DA, Angarano G, Asjo B, Balotta C, Boeri E, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005;192:958-66.
- 13 Foley E, Watson-Jones D, Loveday C. Extensive antiretroviral therapy resistance in an HIV-infected Zimbabwean patient in the UK. *AIDS* 2003;17:2404-5.

(Accepted 27 September 2005)

doi 10.1136/bmj.38665.534595.55

Cannabis intoxication and fatal road crashes in France: population based case-control study

Bernard Laumon, Blandine Gadegbeku, Jean-Louis Martin, Marie-Berthe Biecheler, the SAM Group

Abstract

Objectives To evaluate the relative risk of being responsible for a fatal crash while driving under the influence of cannabis, the prevalence of such drivers within the driving population, and the corresponding share of fatal crashes.

Design Population based case-control study.

Participants 10 748 drivers, with known drug and alcohol concentrations, who were involved in fatal crashes in France from October 2001 to September 2003.

Main outcome measures The cases were the 6766 drivers considered at fault in their crash; the controls were 3006 drivers selected from the 3982 other drivers. Positive detection of cannabis was defined as a blood concentration of Δ^9 tetrahydrocannabinol of over 1 ng/ml. The prevalence of positive drivers in the driving population was estimated by standardising controls on drivers not at fault who were involved in crashes resulting in slight injuries.

Results 681 drivers were positive for cannabis (cases 8.8%, controls 2.8%), including 285 with an illegal blood alcohol concentration (≥ 0.5 g/l). Positive cannabis detection was associated with increased risk of responsibility (odds ratio 3.32, 95% confidence interval 2.63 to 4.18). A significant dose effect was

identified; the odds ratio increased from 2.18 (1.22 to 3.89) if $0 < \Delta^9$ tetrahydrocannabinol < 1 ng/ml to 4.72 (3.04 to 7.33) if Δ^9 tetrahydrocannabinol ≥ 5 ng/ml. The effect of cannabis remains significant after adjustment for different cofactors, including alcohol, with which no statistical interaction was observed. The prevalence of cannabis (2.9%) estimated for the driving population is similar to that for alcohol (2.7%). At least 2.5% (1.5% to 3.5%) of fatal crashes were estimated as being attributable to cannabis, compared with 28.6% for alcohol (26.8% to 30.5%).

Conclusions Driving under the influence of cannabis increases the risk of involvement in a crash. However, in France its share in fatal crashes is significantly lower than that associated with positive blood alcohol concentration.

Introduction

Consumption of cannabis diminishes the faculties needed for vehicle driving,^{1 2} but it is unclear if it increases the risk of car crashes. The low number of

French National Institute for Transport and Safety Research (INRETS), Epidemiological Research and Surveillance Unit in Transport, Occupation and Environment (UMRESTE), 25 avenue François Mitterrand, F-69675 Bron Cedex
Bernard Laumon
senior researcher

continued over

BMJ 2005;331:1371-4



This is the abridged version of an article that was posted on bmj.com on 2 December 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38648.617986.1F>

INRETS/Université
Claude Bernard
Lyon 1 (UCBL)/
Institut de Veille
Sanitaire
(InVS)/UMRESTTE
Blandine
Gadegbeku
research engineer
Jean-Louis Martin
senior researcher
Marie-Berthe
Biecheler
senior researcher

Correspondence to:
B Laumon
bernard.laumon@
inrets.fr

drivers positive for cannabis, and the common association of cannabis and alcohol, hamper the detection of effects entirely attributable to cannabis.³

In 1999, before considering changes in drug legislation, the French government wished to obtain reliable data on the role of cannabis in the occurrence of crashes. Systematic research was organised in France, from October 2001 to September 2003, into drug consumption in drivers involved in fatal road crashes.

Methods

Study population and drug detection process

We included all fatal crashes resulting in immediate death (including pedestrian fatalities) in the study. All the drivers involved were taken as soon as possible to the hospital for compulsory urine testing to detect four major drug families (cannabis, amphetamines, opiates, and cocaine). If the test was positive or impossible a blood sample was taken. This information was associated with the blood alcohol concentration in the police reports.

These reports provided 10 748 drivers who had had full tests for drugs and alcohol. We considered urinary screening for cannabis as positive above a concentration of 50 ng/ml of acid tetrahydrocannabinol. We considered blood tests for cannabis (using gas chromatography-mass spectrometry) positive above a concentration of 1 ng/ml of Δ^9 tetrahydrocannabinol. We considered drivers negative if their urine tests were negative or their blood concentrations below these thresholds. However, during the analyses of dose and effect, we no longer considered non-null below threshold concentrations as “negative.”

Objectives and study design

Cannabis intoxication may favour fatal crash occurrence in two ways: either by increasing the risk of causing a crash (resulting in death), or by increasing the risk of being killed (in a crash caused by another driver) because of greater vulnerability. Our analysis dealt only with the first hypothesis. We sought a dose effect relation between responsibility and cannabis dose, took potential confounding factors into account (focusing specifically on alcohol), and evaluated the representativeness of the cases and controls.

Assessment of responsibility

We determined responsibility of the driver by adapting the method proposed by Robertson and Drummer,⁴ which takes into account the different factors liable to reduce driver responsibility (see bmj.com). We also asked experts to evaluate the responsibility for a representative subsample of 2683 drivers in a crash involving two or more vehicles. We carried out these two evaluations without considering alcohol and drug intoxication or related factors, such as sex and age.

Selection of cases and controls

The cases were the 6766 drivers at fault, including those responsible for their own death. We selected the controls from the 3982 drivers not at fault (figure) (see bmj.com for details of exclusion criteria).

Validation of cases and controls

We used the police national database of injury crashes (all crash severities) to identify the 112 181 drivers not at fault who were involved in a crash resulting in slight injury (a group we assumed best to represent the driving population). We standardised the prevalence for our control group according to cannabis related factors that were found to be significant between the two groups to estimate the prevalence of cannabis in this group and made the same comparison for alcohol (see bmj.com for validation of cases).

Confounding factors

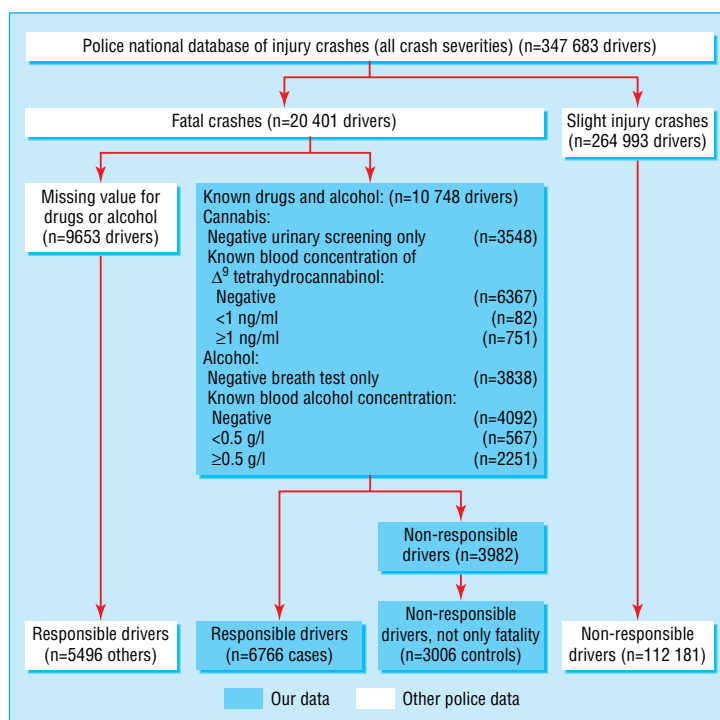
We adjusted for alcohol levels (and a dose effect was sought for alcohol and cannabis), the other three families of drugs, the driver’s age and sex, the type of vehicle driven, and the time of crash. For estimates of the attributable risk see bmj.com.

Results

Of the 9772 drivers studied, 681 were positive for cannabis (7.0%) and 2096 for alcohol (21.4%), including 285 for both (2.9%). The other three families of drugs were, proportionally, more often associated with cannabis than with alcohol (see bmj.com). Men, more often involved in crashes than women, were also more often positive for both cannabis and alcohol, as were the youngest drivers, and users of mopeds and motorcycles. Positive detection was more commonly associated with night time crashes.

Cannabis was significantly related to responsibility of the driver (table 1).

Amphetamines, cocaine, and alcohol were also significantly related to responsibility, although opiates were not. We highlighted a significant dose effect for cannabis (and for alcohol), adjusted or not for alcohol (respectively for cannabis, see bmj.com).



Flow of included drivers through the study

Table 1 Drivers' responsibility associated with drugs and alcohol. Values are numbers (percentages) of drivers unless otherwise indicated

	Cases (n=6766)	Controls (n=3006)	Unadjusted odds ratio (95% CI)
Blood concentration of drugs:			
Δ^9 tetrahydrocannabinol ≥ 1 ng/ml	596 (8.8)	85 (2.8)	3.32 (2.63 to 4.18)
Amphetamines ≥ 50 ng/ml	42 (0.6)	5 (0.2)	3.75 (1.48 to 9.47)
Cocaine ≥ 50 ng/ml	20 (0.3)	2 (0.1)	4.44 (1.04 to 19.0)
Opiates ≥ 20 ng/ml	56 (0.8)	27 (0.9)	0.92 (0.58 to 1.46)
Blood concentration of alcohol ≥ 0.5 g/l	2016 (29.8)	80 (2.7)	15.5 (12.4 to 19.5)

Case drivers and control drivers also differ according to sex ($P < 0.05$), age ($P < 0.001$), vehicle type ($P < 0.001$), and time of crash ($P < 0.001$).

Comparing our controls with drivers not at fault involved in a slight injury crash allowed us to identify their distinguishing characteristics: driver's sex and age; type of vehicle; and place, time, and type of crash. The prevalence of cannabis in our controls was 2.8%, compared with 2.9% when standardised for these variables; both these prevalences were 2.7% for alcohol.

The adjusted fraction of fatal crashes attributable to cannabis (present at any dose) was 2.5% (4.3% when adjusted only for alcohol). The adjusted fraction for alcohol was 29% and 31% when adjusted only for cannabis. When considering only blood alcohol concentration over 0.5 g/l, it was 25% and 27% respectively (table 2).

Discussion

The risk of responsibility for fatal traffic crashes while driving under the influence of cannabis has a significant dose effect that shows a causal relation between cannabis and crashes.

Strengths of the study

We did not exclude any drivers at fault and therefore took into account the overall increase in cannabis related risk in causing crashes fatal to either the individual or to others. This explains why we found higher risks than in studies that include only fatally injured drivers.⁵⁻⁶ The increased fatality risk of drivers not at fault under the influence of cannabis or alcohol is a phenomenon that deserves further investigation. It can be partly explained by greater exposure to the secondary risk of death in a crash, via higher vulnerability (such as the use of motorised two-wheelers), riskier behaviour⁷⁻⁸ (such as not wearing seat belts), or

Table 2 Adjusted fractions of attributable risks of fatal crashes associated with blood concentrations of Δ^9 tetrahydrocannabinol and alcohol. Values are percentages (95% confidence intervals)

Substance and concentration	Adjusted for Δ^9 tetrahydrocannabinol or alcohol	Multivariate model*
Δ^9 tetrahydrocannabinol > 0.0 ng/ml	4.3 (3.4 to 5.3)	2.5 (1.5 to 3.5)
Alcohol:		
> 0.0 g/l	31.2 (29.8 to 32.5)	28.6 (26.8 to 30.5)
≥ 0.5 g/l	26.8 (25.6 to 28.0)	25.2 (23.5 to 26.9)

*Includes blood concentrations of Δ^9 tetrahydrocannabinol and alcohol, driver's age, type of vehicle, and time of crash.

What is already known on this topic

Cannabis consumption, even in low doses, hampers certain faculties necessary for driving a vehicle

Epidemiological studies provide conclusions which are heterogeneous and not robust enough to prove that such consumption represents a crash risk factor of significant magnitude

What this study adds

The risk of responsibility for fatal road crashes while driving under the influence of cannabis has a significant dose effect that shows a causal relation between cannabis and crashes

Reliable estimates of the share of fatal crashes attributable to cannabis and alcohol enable comparison of the respective road safety issues

socio-economic disparities (such as the age of their vehicle),⁹ and partly by a reduced ability to avoid a crash.

Comparison with other studies

We used alcohol as a plausibility indicator for the results obtained for cannabis: our study concurs with previous studies on crash risk related to alcohol.^{5-6 10-11} We were therefore able to confirm the confounding role of alcohol, although we were not able to highlight any interaction: consumption of both cannabis and alcohol would only multiply the risks related to consumption of either cannabis or alcohol alone, without specific potentiation of the effects of one by the other. This result consolidates several previous experimental and epidemiological studies.¹²⁻¹⁵ The existence of a dose effect gives credence to a causal relation between cannabis and road crashes.

Consumption of cannabis increases the risk of responsibility for fatal traffic crashes, while remaining significantly lower than the risk associated with alcohol.

Limitations of the study

It was not possible to perform an adjusted analysis of the effects of amphetamines, cocaine, and opiates, mainly because of the small number of drivers positive for these substances. This highlights, however, that these drugs are not a major issue in France at the moment. Psychoactive medical drugs were sought only in the case of positive blood testing. No further study of this confounding effect was possible.

Conclusions

This study answers many questions left unanswered by previous studies,^{5-6 10} in particular by considering what some call an "at fault, not at fault" study¹¹ as a specific case-control study. However, in addition to the number of deaths linked to the responsibility of drivers, further work should include the share of all deaths attributable to the greater vulnerability of users under the influence of cannabis. This latter calculation was possible for drivers but is yet to be shown for other road users, namely passengers and pedestrians.

We thank the steering committee representatives of the French Home Office and Ministries of Defence, Justice, Transport, and Health. We also thank the members of the Scientific Committee (S Dally, C Dussault, T Harding, M Kaminski, E Lagarde, A Sasco); the French National Interministerial Road Safety Observatory (ONISR) and the French organisation TransPV that made their data available to us; the French Monitoring Centre for Drugs and Drug Addiction (OFDT) for its logistical support; and K Hodson, R Driscoll, and L Cant for their English mother tongue.

Contributors: See bmj.com.

Funding: The French Ministry of Health (DGS) funded this study, with additional funding from the National Institute for Health and Medical Research (INSERM) and the French National Institute for Transport and Safety Research (INRETS). The Ministry of Justice funded the screening process. The Home Office and the Ministry of Defence financed the data collection.

Competing interests: None declared.

- 1 Moskowitz H. Marijuana and driving. *Acc Anal Prev* 1985;17:323-45.
- 2 Berghaus G, Sheer N, Schmidt P. Effects of cannabis on psychomotor skills and driving performance, a meta-analysis of experimental studies. In: Kloeden CN, AJM, Road Accident Research Unit, the University of Adelaide, ed. *Proceedings of 13th International conference on alcohol, drugs and traffic safety*. Adelaide: 1995:403-9.
- 3 Ramaekers JG, Berghaus G, Van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Dependence* 2004; 73:109-19.

- 4 Robertson MD, Drummer OH. Responsibility analysis: a methodology to study the effect of drugs in driving. *Accid Anal Prev* 1994;26:243-7.
- 5 Dussault C, Brault M, Bouchard J, Lemire AM. The contribution of alcohol and other drugs among fatally injured drivers in Quebec: some preliminary results. *Alcohol, Drugs and Traffic Safety*. Quebec: SAAQ, 2002: 423-30.
- 6 Drummer OH, Gerastomoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accid Anal Prev* 2004;36:239-48.
- 7 Assailly J-P, Biecheler M-B. *Conduite automobile, drogues et risque routier* [Driving, drugs and road risk]. Arcueil: INRETS, 2002:87.
- 8 Everett SA, Lowry R, Cohen LR, Dellonger AM. Unsafe motor vehicle practices among substance-using college students. *Accid Anal Prev* 1999; 31:667-73.
- 9 Laumon B, Gadegebeku B, Martin JL, the SAM Group. *Stupéfiants et accidents mortels de la circulation routière (Projet SAM), Partie III: analyse épidémiologique* [Drugs and fatal road traffic accidents (SAM Project), Part III: epidemiological analysis]. Paris: OFDT, 2005.
- 10 Longo MC, Hunter CE, Lokan RJ, White JM, White MA. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability. Part II: The relationship between drug prevalence and drug concentration, and driver culpability. *Accid Anal Prev* 2000;32:623-32.
- 11 Terhune KW. An evaluation of responsibility analysis for assessing alcohol and drug crash effects. *Accid Anal Prev* 1983;15:237-46.
- 12 Institut national de la santé et de la recherche médicale (INSERM). *Cannabis: quels effets sur le comportement et la santé?* [Cannabis: What effects on behaviour and health?]. Paris: Editions INSERM, Expertise collective, 2001:165-99.
- 13 Davis GA, Gao Y. Statistical methods to support induced exposure analyses of traffic accident data. *Transport Res Rec* 1995;1401:43-9.

(Accepted 27 September 2005)

doi 10.1136/bmj.38648.617986.1F

Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study

JJ W Roche, R T Wenn, O Sahota, C G Moran

Abstract

Objectives To evaluate postoperative medical complications and the association between these complications and mortality at 30 days and one year after surgery for hip fracture and to examine the association between preoperative comorbidity and the risk of postoperative complications and mortality.

Design Prospective observational cohort study.

Setting University teaching hospital.

Participants 2448 consecutive patients admitted with an acute hip fracture over a four year period. We excluded 358 patients: all those aged < 60; those with periprosthetic fractures, pathological fractures, and fractures treated without surgery; and patients who died before surgery.

Interventions Routine care for hip fractures.

Main outcome measures Postoperative complications and mortality at 30 days and one year.

Results Mortality was 9.6% at 30 days and 33% at one year. The most common postoperative complications were chest infection (9%) and heart failure (5%). In patients who developed postoperative heart failure mortality was 65% at 30 days (hazard ratio 16.1, 95% confidence interval 12.2 to 21.3). Of these patients, 92% were dead by one year (11.3, 9.1 to 14.0). In patients who developed a postoperative chest infection mortality at 30 days was 43% (8.5, 6.6 to 11.1). Significant preoperative variables for increased

mortality at 30 days included the presence of three or more comorbidities (2.5, 1.6 to 3.9), respiratory disease (1.8, 1.3 to 2.5), and malignancy (1.5, 1.01 to 2.3).

Conclusions In elderly people with hip fracture, the presence of three or more comorbidities is the strongest preoperative risk factor. Chest infection and heart failure are the most common postoperative complications and lead to increased mortality. These groups offer a clear target for specialist medical assessment.

Introduction

Hip fractures related to osteoporosis constitute a major clinical and financial burden to the NHS. Excess mortality after hip fracture is 20% in the first year and is higher in older men.^{1 2} The high mortality, particularly in the first three months, is probably due to the combination of trauma, major surgery in elderly people with concurrent medical problems,¹ and a low physiological reserve. We investigated how demographic factors and important medical conditions influence postoperative outcomes following hip replacement.

Department of Trauma and Orthopaedics, University Hospital Nottingham, Nottingham, NG7 2UH

JJ W Roche
clinical fellow
R T Wenn
audit coordinator
C G Moran
professor

Department of Care of the Elderly, University Hospital Nottingham, Nottingham
O Sahota
consultant physician

Correspondence to:
C G Moran
anne.hay@qmc.nhs.uk

BMJ 2005;331:1374-6



This is the abridged version of an article that was posted on bmj.com on 18 November 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38643.663843.55>