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Santé et insécurité routière : Influence de la consommation de médicaments (Étude CESIR-A)

Health-related factors and road safety: Influence of medicine use (The CESIR-A study)

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Scientific productions

Articles

Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A and Lagarde E. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf* 2009;18(8):647-58.

Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B, Laumon B, Salmi LR and Lagarde E, on behalf of the CESIR research group. Prescribed medicines and the risk of road traffic crashes: results of a French registry-based study. **Revision submitted**; Plos Medicine.

Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M and Lagarde E, on behalf of the CESIR research group. Benzodiazepine-like hypnotics and the risk of road traffic crashes. **Submitted**; BMJ.

Communications

Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B, Laumon B, *et al*. Prescribed medicines and the risk of road traffic crashes: results of a French registry-based study. Safety 2010 world conference, London (UK), 21st-24th September 2010. (Poster)

Résumé

La prise de conscience de l'implication des médicaments dans la genèse des accidents de la route date d'une vingtaine d'années. Les médicaments psycho-actifs peuvent altérer les capacités de conduite par leur action sur le système nerveux (par exemple, un effet sédatif le lendemain d'une prise d'hypnotique). D'autres médicaments sont susceptibles d'affecter les fonctions psychomotrices par leur action sur les fonctions physiologiques (tel que les hypoglycémies liées à un traitement antidiabétique). L'étude CESIR-A a été mise en place pour contribuer à la connaissance du lien épidémiologique entre médicaments et accidents de la route.

L'étude utilise trois bases de données françaises : le Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIR-AM), les Procès Verbaux d'accidents (PV) et les Bulletins d'Analyse des Accidents Corporels de la circulation (BAAC). L'appariement de ces données a conduit à l'inclusion de 72,685 conducteurs impliqués dans un accident corporel sur la période juillet 2005-mai 2008. L'analyse a été réalisée grâce à deux méthodes: une analyse cas-témoin comparant les responsables aux non-responsables des accidents et une analyse dite en case-crossover. Les périodes d'exposition aux médicaments ont été estimées à partir des dates de délivrances de médicaments prescrits, puis remboursés par l'assurance maladie.

L'étude des médicaments regroupés selon les quatre niveaux de risque sur la conduite définis par l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) [du niveau 0 (pas de risque) au niveau 3 (risque élevé)], a montré que les utilisateurs de médicaments prescrits de niveau 2 et de niveau 3 ont un risque significativement plus élevé d'être responsables de leur accident (OR=1,31 [1,24-1,40] et OR=1,25 [1,12-1,40], respectivement). La fraction de risque attribuable à l'utilisation de ces médicaments était de 3,3% [2,7%-3,9%].

Le risque d'être responsable d'un accident était augmenté chez les utilisateurs de zolpidem (OR=1,28 [1,07-1,53]) mais pas chez les utilisateurs de zopiclone ou de benzodiazépines hypnotiques. Plus particulièrement, ce risque était augmenté chez les 139 conducteurs ayant eu plus d'un comprimé de zolpidem délivré par jour au cours des cinq mois précédant l'accident (OR=2,38 [1,61-3,52]). L'analyse case-crossover a mis en évidence un sur-risque d'accident de la route chez les utilisateurs de benzodiazépines hypnotiques seulement (OR=1,42 [1,09-1,85]). Les conducteurs exposés aux hypnotiques partagent les mêmes caractéristiques au regard du type d'accident, qui survenaient plus fréquemment sur autoroute.

Dans notre base de données, 196 conducteurs ont été exposés à la buprénorphine et/ou à la méthadone, le jour de leur accident. Cette population spécifique était jeune, essentiellement masculine, avec d'importantes co-consommations, notamment d'alcool de médicaments de niveau 3. Les conducteurs exposés à la buprénorphine et/ou à la méthadone présentaient un risque accru d'être responsables de leur accident (OR= 2,19 [1,51-3,16]).

Notre étude fournit des informations importantes sur la contribution des médicaments au risque d'accident de la route. D'après nos résultats, la classification de l'AFSSAPS semble appropriée concernant les médicaments de niveaux 2 et 3. Les sur-risques d'être responsable d'un accident chez les exposés au zolpidem ou aux traitements de substitution pourraient être liés, au moins en partie, au comportement à risque de ces conducteurs. L'amélioration du comportement des conducteurs représente un des défis pour la sécurité routière. L'objectif de la classification française et de la signalétique apposée sur les boîtes de médicaments est donc de fournir aux patients une information appropriée sur les effets des médicaments sur leur capacité de conduite.

Abstract

In recent decades, attention has been increasingly focused on the impact of disabilities and medicinal drug use on road safety. Psychoactive medicines may impair driving abilities due to their action on the central nervous system (e.g. sedation in the morning following administration of a hypnotic), while other medicines may affect psychomotor functions by their action on physiological functions (e.g hypoglycaemic seizures related to diabetic treatment). The CESIR-A project was set up to improve the epidemiological knowledge on medicines and the risk of road traffic crashes.

The study matched three French nationwide databases: the national healthcare insurance database, police reports, and the police national database of injurious crashes, leading to the inclusion of 72,685 drivers involved in an injurious road traffic crash from July 2005 to May 2008. Two methods were performed for data analysis: a case-control analysis in which cases where responsible drivers and controls non-responsible ones and a case-crossover analysis. Medicine exposures were estimated from prescription drug dispensations in the healthcare reimbursement database.

The study of medicines grouped according to the four levels of driving impairment risk of the French classification system [from 0 (no risk) to 3 (high risk)], showed that users of level 2 and level 3 prescribed medicines were at higher risk of being responsible for the crash (OR=1.31 [1.24-1.40] and OR=1.25 [1.12-1.40], respectively). The fraction of road traffic crashes attributable to levels 2 and 3 medicines was 3.3% [2.7%-3.9%].

Zolpidem use was associated with an increased risk of being responsible for a road traffic crash (OR=1.28 [1.07-1.53]) whereas use of zopiclone and benzodiazepine hypnotics use was not. Responsibility risk was only increased in the 139 drivers with dispensing of more than one pill of zolpidem a day during the five months before the crash (OR=2.38 [1.61-3.52]). Case-crossover analysis showed an increased risk of crash for benzodiazepine hypnotic users only (OR=1.42 [1.09-1.85]). Hypnotic users shared similar crash characteristics, with crashes more likely to occur on highways.

In our database, 196 drivers were exposed to buprenorphine and/or methadone on the day of crash. This specific population was young, essentially males, with important co-consumption of other substances, in particular alcohol and level 3 medicines. Injured drivers exposed to buprenorphine and/or methadone on the day of crash, had an increased risk of being responsible (OR=2.19 [1.51-3.16]). The case cross-over analysis did not demonstrate any association (OR=1.26 [0.93 - 1.70]).

Our study provides evidence of the contribution of medicines to the risk of road traffic crashes. According to our results, the French risk classification seems relevant regarding medicines classified as levels 2 and 3 of risk for road traffic crashes. The observed increased risks of being responsible for a crash for zolpidem and substitution maintenance treatment users may be linked to risky behaviors. Improving driver behaviour is one of the challenges for road safety. Providing patients with proper information on the potential effect of medicines on their driving abilities is the main objective of drug and risk classifications such as the French one.

“ While the individual man is an insoluble puzzle,
in the aggregate he becomes a mathematical certainty.
You can, for example, never foretell what any one man will do,
but you can say with precision what an average number
will be up to.”

Arthur Conan Doyle
Sherlock Holmes, The Sign of the Four

SUMMARY

INTRODUCTION

La lutte contre les accidents de la route constitue un enjeu majeur de santé publique, au regard de leurs conséquences en termes de mortalité et de morbidité. Réduire le nombre d'accidents de la route est une priorité des instances Européennes. Ainsi, le programme d'action en faveur de la sécurité routière 2003-2010 de la Commission des Communautés Européennes prévoit un catalogue de mesures comme le déploiement de nouvelles technologies de sécurité routière, l'amélioration de l'infrastructure routière et des actions visant à améliorer le comportement des usagers.[1] En effet, un certain nombre de facteurs liés à un risque accru d'accident de la route sont imputables à des comportements tels que consommation d'alcool, conduite en état de fatigue, utilisation de substances psychoactives et de médicaments.

En France, la consommation de médicaments, en particulier de médicaments psychoactifs, est élevée et se banalise.

Même si l'impact des facteurs liés à la santé sur l'insécurité routière est reconnu, cette thématique est encore relativement peu explorée sur le plan épidémiologique. Les données de la littérature rendent compte d'une relative abondance et d'une grande diversité des tests d'évaluation des capacités cognitives et motrices mais aussi de la pauvreté de la littérature épidémiologique disponible. Les informations relevant des seuls tests psychotechniques et physiologiques ou des tests de conduite réelle ou sur simulateur ne permettent pourtant pas d'évaluer l'impact réel en population. En outre, ces tests ne sont pas réalisés de façon systématique avant la mise sur le marché des médicaments.

Depuis la directive européenne du 26 octobre 1983, les effets des médicaments sur la capacité de conduite et l'utilisation de machines sont identifiés dans une rubrique spécifique du résumé des caractéristiques du produit. [2]

Dans le cadre du programme d'action défini par le Comité Interministériel de la Sécurité Routière (CISR), l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) a été chargée, en 2003, d'élaborer une classification, en quatre niveaux de risque (du niveau 0 [risque nul ou négligeable] au niveau 3 [risque majeur]), des médicaments susceptibles d'altérer les capacités de conduite, les niveaux 1 à 3 étant illustrés par des pictogrammes apposés sur le conditionnement des médicaments. Un groupe d'experts a ainsi évalué le niveau de risque des médicaments grâce à l'étude des données pharmacodynamiques, des données de pharmacovigilance, des données expérimentales et des données épidémiologiques disponibles.[3-5] Le constat d'un manque réel de données populationnelles a été dressé.

Ce travail de thèse s'inscrit donc dans ce contexte, avec pour objectif principal d'identifier les médicaments associés à un sur-risque d'accident de la route.

The fight against road traffic crashes is a major public health issue with regard to their consequences in terms of mortality and morbidity. Reducing the number of road accidents is a priority of European institutions. Thus, the Action Programme for Road Safety 2003-2010 of the European Communities Commission provided a list of actions such as deploying new technologies on road safety, improving road infrastructure and actions to improve the users' behaviour.[1] Indeed, a number of factors associated with an increased risk of road traffic crashes are attributable to behaviours such as alcohol consumption, driving while tired, use of psychoactive substances and medicines.

In France, consumption of medicines, particularly psychoactive medicines, is high and is becoming commonplace.

Although the impact of health-related factors on road safety is recognized, this issue is still relatively unexplored. Available literature data reflect the abundance and variety of tests to assess cognitive and motor skills but also the poverty of the epidemiological literature. Moreover, information from psychological and physiological testing, driving tests or simulator experiences, do not assess the impact in the actual driving population. In addition, these tests are not performed routinely before the marketing of medicines.

Since the European Directive of October 26th, 1983, the effects of medicines on driving ability and use of machines are identified in a specific section of the Summary of Product Characteristics.[2] In 1999, in France, this information was complemented with a unique triangular pictogram on medicines' packaging. In 2003, the French Health Products Safety Agency (Afssaps) was requested by the Interministerial Committee for Road Safety Board, to grad the pictogram system, setting up a classification in four risk levels of medicines that may affect driving abilities (level 0 [zero or negligible risk] to 3 [major risk]). Risk levels are illustrated by three colors and a written warning followed by a short informative message on the attitude patients should adopt when using these medicines. For this purpose, a multidisciplinary group of experts was appointed to rate all medicines regarding their effects on driving performances.[3-5] Faced to the lack of epidemiological data, the experts recommended that an epidemiological study be conducted to help assess the role of medicines in road safety and validate the classification system.

In this context, the main objective of this thesis is to identify medicines associated with an increased risk of road traffic crashes.

STATE OF KNOWLEDGE

The literature research presented in this chapter has resulted in the publication of an article entitled: a systematic review of epidemiological studies on the impact of medicines on the risk of road traffic crashes. [6] (Appendix 1)

Literature review by therapeutic classes

Anxiolytics and hypnotics

Anxiety and sleep disorders are frequently encountered disorders in today's society. Thus, France is a leader in terms of anxiolytic prescriptions, benzodiazepines being the most prescribed medicines. [7]

The substances' half-life determines the duration of its action. It represents the time after administration for its concentration to be decreased by half. Thus, the longer the half-life is, the more likely the drug is to have a residual effect after administration. Table 1 shows the main benzodiazepines and results of epidemiological studies on their effects on the risk of crash.

Table 1. Benzodiazepines and the risk of road traffic crashes

Substance	Half-life	Risk
Anxiolytics	All	2.9 [2.5-3.5] [8]; 5.6 [1.7-18.4] [9]; 2.18 [1.52-3.13] [10]
Bromazepam	Long	
Diazepam	Long	2.8 [2.2-3.6] [11]; 3.1 [1.4-6.5] [12]
Prazepam	Long	-
Clorazepate dipotassium	Long	-
Nordazepam	Long	-
Clobazam	Long	-
Ethyl loflazepate	Long	-
Oxazepam	Intermediate	1.0 [0.3-6.3] [12]
Lorazepam	Intermediate	2.4 [1.0-6.3] [12]
Alprazolam	Intermediate	-
Clotiazepam	Intermediate	-
Hypnotics	All	3.3 [2.1-4.7] [8]; 6.5 [1.9-22.4] [9]
Flunitrazepam	Long	4.0 [2.4-6.4] [13]
Nitrazepam	Long	2.7 [1.8-3.9] [13]
Flurazepam	Long	5.1 [2.3-11.6] [12]
Temazepam	Intermediate	-
Loprazolam	Intermediate	-
Lormetazepam	Intermediate	-
Estazolam	Intermediate	-
Triazolam	Short	3.2 [1.4-7.3] [12]

The impact of benzodiazepines on the risk of car crashes has been extensively assessed in several studies. [8-25] The strength of the associations and the consistency between studies indicate that benzodiazepines consumption is a risk factor for road traffic crashes. The effects of benzodiazepines on the risk of crash have been demonstrated in the elderly [16 22], but also among younger drivers. [9 10 12 13] The effects of treatment initiation have been explored. [9 12 13 16] A cohort study about the risk of hospitalisation for traffic crash injuries showed a diminished risk with elapsed time from the new prescription fill-date [9], probably reflecting tolerance to medicinal drug effects or decreasing doses or use over time. In a case-crossover study, a dose-response relationship between benzodiazepine consumption and crash risk was described. [10] Benzodiazepine hypnotics and anxiolytics have been studied separately, as well as long and short half-life benzodiazepines and individual drugs (Table 1).

Benzodiazepine-like hypnotics (zopiclone and zolpidem) have appeared on the market of medicines used in the treatment of insomnia in the late 80's. Zopiclone (Imovane ®) and zolpidem (Stilnox ®) are currently the most widely used hypnotics because of their shorter half-lives than those of benzodiazepines (3 to 6 hours and 1.5 to 2.4 hours, respectively). These drugs have not been extensively studied so far, in terms of their effects on driving abilities. A study conducted in the UK from 1992 to 1995, found an association between the risk of crash and the use of zopiclone (OR = 4.00 [1.31-12.2]). [10] A recent Norwegian study found a significant increased risk for users of zopiclone and zolpidem (SIR=2.3 [2.0-2.8] and SIR=2.2 [1.4-3.4], respectively); this risk was lower than for users of benzodiazepine hypnotics. [13]

Antidepressants

Psychomotor and cognitive deficits associated with depression make it difficult to identify the effect of treatment. Indeed, symptoms of depression (difficulty concentrating, anxiety, irritability, fatigue) are likely to modify the risk associated with driving. Taking antidepressants may improve the depressive state but also for some of them, alter the ability to drive. [26]

There are 4 classes of antidepressants: tricyclic antidepressants and related (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin reuptake inhibitors (SRIs) and other antidepressants. In terms of their clinical action, the classification is done according to their stimulant (psychotonic) or sedative effect. Thus, the MAOIs and SRIs do not exhibit sedative effects while some TCAs or other antidepressants (tetracyclic antidepressants) have a sedative effect. [26] Experimental studies have shown a deleterious effect on driving of amitriptyline [27 28] (TCA) and mirtazapine [29 30] (tetracyclic antidepressant). The most frequently used substances, paroxetine [29 31-33] and fluoxetine [34] (SRIs), appear to have a lower risk.

Two epidemiological studies conducted in the elderly have shown an association between use of TCAs and the risk of traffic crashes (RR=2.2 [1.3-3.5] [22] and OR=2.3 [1.1-4.8] [18]). In contrast, Barbone *et al*'s study, conducted in an English population of 410 306 people, aged of 18 and more, for 3 years, found no association, neither for TCAs nor for SRIs [10], suggesting that the risk is specific to the elderly. However, the most recent study has shown a risk for drivers following a prescription of sedative or non-sedative antidepressants (SIR=1.4 [1.2-1.6] and SIR=1.6 [1.5-1.7], respectively), the risk being higher among younger drivers. [35]

Antiepileptics

The antiepileptic medicines are intended to eliminate or reduce the frequency and/or severity of seizures, causes of traffic crashes. Indeed, the impact of epilepsy on the risk of road accidents has been demonstrated in several studies. [36-38]

Most antiepileptic medicines have central side effects that may impair driving abilities: drowsiness, confusion, dizziness, and visual disturbances. Four molecules are considered as "classic" antiepileptics. The first generation of these medicines is represented by phenobarbital and phenytoin, gradually supplanted by the second generation medicines (carbamazepine and valproate). The new antiepileptic medicines (third generation: Lamotrigine, Vigabatrin, Gabapentin, Topiramate, Tiagabine, Oxcarbazepine, Levetiracetam) have appeared on the market in the 90's. Finally, some benzodiazepines are used in the treatment of epilepsy for their anti-convulsing properties (clonazepam, clobazam, diazepam).

Experimental studies show that the side effects are more pronounced in patients receiving combination therapy and/or too high dosage. Among "classic" antiepileptics, phenobarbital seems to have the most deleterious effects on behaviour and cognition, while valproic acid would have a better safety profile compared to carbamazepine and phenytoin.[39] Available data on the third generation substances suggest a more favourable profile than older treatments, although differences between them remain to be explored.[40] [41] Patients on antiepileptic therapy, however, show psychometric scores lower than untreated patients. [42]

In a retrospective cohort study, Hansotia and Broste found that the lack of antiepileptic treatment was a risk factor for crashes among drivers who had a history of seizures. [43] In the case-control study by Krauss *et al*, having had their antiepileptic treatment reduced or switched significantly decreased the chances of patients with epilepsy having road traffic crashes due to seizures. [44]

Opioids

An opioid is a synthetic substance which effects are similar to those of opium. There are three types of opioid receptors: mu, kappa and delta receptors. Opioid medicines can be classified according to their pharmacological actions on these receptors: pure agonists (morphine, fentanyl) including weak agonists (methadone, codeine, dextropropoxyphene), partial agonists or mixed agonist-antagonist (buprenorphine) and antagonists (naloxone). Thus, some substances, such as buprenorphine, may be partial agonists for a subtype of opioid receptors and antagonist for another.

Opioid medicines are used in pain treatment and as substitution treatment in opioid dependence. The effects of opioids on psychomotor and cognitive functioning have been studied in several experimental studies. [45] Impairment by opioids tends to occur more often in healthy volunteers (who have little or no prior exposure to the drugs) than in those who have a history of opioid use (non-dependent and dependant users, chronic pain patients). [45 46]

Two epidemiological studies using prescription databases found a significant association between the use of opioid medicines and road traffic crashes. [8 18] Engeland *et al* found that the risk was increased in users of natural opium alkaloids such as codeine, morphine and oxycodone (SIR=2 [1.7-2.4]).[8] In the same database, further study examined separately codeine and tramadol. An association was found for codeine high consumers only but this risk may have been linked to co-prescription of other impairing medicines too. [47] In study by Leveille *et al*, opioid analgesic use was associated with an elevated crash risk in older drivers (OR=1.8 [1-3.4]).[18] A longitudinal study from a cohort of 13,548 French workers suggested that pain and pain treatment could be associated with the risk of crash. The authors noted, however, that severe pain may itself be associated with poorer driving performance.[48] On the other hand, a large retrospective cohort study of 16,262 older drivers conducted in Tennesse (USA) found no association for opioid analgesics. [22]

H1-antihistamines

H1-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. The allergic inflammation is mainly regulated through the H1-receptor. First generation H1-antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine, prometazine…) potentially cause central nervous system side effects (fatigue, drowsiness and performance impairment) as a result of their lipophilic structure. Indeed, these molecules are able to cross the blood brain barrier and act on H1-receptor sites in the brain. First generation H1-antihistamines are also used for their antiemetic effect, in the treatment of insomnia, and in some other conditions affecting the central nervous system. Second generation H1-antihistamines (cetirizine, loratadine…) are much more selective for peripheral H1-receptors

and are less sedative than first generation molecules. Finally, fexofenadine, desloratadine and levoceterizine were introduced as third generation H1-antihistamines

The cognitive tests and experimental studies made under conditions of real driving suggest that first generation H1-antihistamines should be avoided by drivers. The second generation can also affect the ability to drive, though in a very variable manner. [49-51] It seems that the third generation medicines do not impair driving abilities. [49 51]

A few studies explored the association between H1-antihistamines and car crashes. In the studies by Leveille *et al* [18] and by Ray *et al* [22], both conducted in the elderly, the association was not significant. Nevertheless, Howard *et al* showed that histaminergic consumption was associated with the risk of traffic crashes in professional drivers**.**[52] There is a lack of epidemiological data on the impact of the different generations of antihistamines.

Antipsychotics

The effect of antipsychotic treatment on the psychomotor performance and driving ability of schizophrenic patients has been subject of investigation. Patients with schizophrenia show worse results in psychometric tests compared to healthy controls.[53] Despite the fact that antipsychotics have been shown to impair driving performances in healthy subjects, there is good agreement suggesting that schizophrenic patients manifest improved performances while on these medications.[54] In clinical studies, conventional dopamine antagonist neuroleptics were associated with worse results regarding psychomotor and cognitive impairment compared to atypical neuroleptic medications. [53 55]

There is no epidemiological study about the effects of long term maintenance of antipsychotic drugs on driving performance in schizophrenic patients.

Lithium is an antipsychotic drug used in the treatment of bipolar disorders as mood stabilizer. In a nested case-control study, the risk of being involved in an injurious motor vehicle crash for elderly people who use lithium was found to be increased two-fold.[56] Recently, an increase of traffic crash risk was found in young female drivers on lithium. [57]

Antiparkinsonians

In Parkinson disease, patients suffer from muscle rigidity, tremor and slowing of physical movement which can alter driving ability.

There are two main classes of medicines used in Parkinson disease: anticholinergic agents and dopaminergic agents.

In a research letter, Ferreira *et al* reviewed several cases of sleep attacks at the wheel in patients taking antiparkinsonian dopaminergic drugs. [58] In a case-control study, dopamine agonists significantly increased the risk of sudden uncontrollable somnolence. [59]

Muscle relaxants

Carisoprodol, a muscle relaxing drug, has been considered in a pharmacoepidemiological study because of its central nervous system depressant potential. The standardised incidence ratio for being involved in a crash having been prescribed carisoprodol was 3.7 [2.9-4.8]. [11]

Antidiabetics

The risk of crashes for diabetic drivers is linked to degenerative complications and to hypoglycaemic seizures related to treatment. Inconsistent results have been published about the role of diabetes and its treatment in causing traffic crashes, probably because of the heterogeneity in treatment regimes. [36 60-62]

A responsibility study conducted in the elderly did not find any association between diabetes and at-fault crash involvement and no interaction with treatment type. [20 62] Traffic injury risk has been reported to be 2.6-fold higher in older diabetic drivers, especially those treated with insulin (OR=5.8 [1.2-28.7]) but not in those using oral hypoglycaemic agents. [61] Hemmelgarn *et al* found the rate ratios for current users of insulin monotherapy were 1.4 [1.0-2.0] and 1.3 [1.0-1.7] for sulfonylurea and metformin combined. The authors note the difficulty of distinguishing between medicinal drug effects and diabetes-related complications since treatment is strongly correlated with disease progression. [63]

Cardiovascular drugs

Cardiovascular diseases have been shown to be associated with the risk of road traffic crashes. [20 61]

Among the medicinal drugs considered in epidemiological studies, calcium channel blockers were not associated with an increased risk of crashes [8], and were associated with a reduced risk of at-fault crash involvement, as well as vasodilators.[20] In the latter study, anticoagulants and angiotensin-converting enzyme inhibitors were positively associated with being at-fault for a crash but the odds ratios were no longer significant after adjustment for concomitant diseases. [20] In a recent case-control study, the use of warfarin, an anticoagulant, was not associated with an elevated rate of injurious motor vehicle crash. [64]

Nonsteroidal anti-inflammatory drugs

Recently, Engeland *et al* raised the question of nonsteroidal anti-inflammatory drug (NSAID) effects in the central nervous system, as they found a significant association with the risk of traffic crash (OR=1.5 [1.3-1.9]).[8] This result could be an indicator of clinical disability in some arthritic conditions. McGwin *et al* found that NSAID association with an increased risk of at-fault involvement in crashes persisted after adjustment for arthritis which was also independently associated with crash risk in females. The authors note however that some NSAID users may be undiagnosed for musculoskeletal impairments. [20]

Methodological issues

In available epidemiological studies, several different research methods were used: case-control studies, exposed/non exposed studies, responsibility studies and case-crossover studies.

The sample populations were different, ranging from victims of road traffic crashes with personal injury (from crashes databases), victims hospitalized for road traffic crash injury (from hospital records) to fatally injured drivers.

Drug exposure assessment was heterogeneous, mostly depending on available retrospective data in national databases or on the molecule selection for biological testing.

In addition, the effects of medicines in a same therapeutic class may be heterogeneous and it would be recommended to consider each substance in the context of the disease treated, which in turn may affect the risk of crash. The concern of confounding by indication is difficult to address and consequently, it often remains unclear whether crashes occur as a result of medicine use or of the underlying disease.

Another issue relates to potential confounding due to the consumption of other substances such as alcohol or illicit drugs which are not always measured. Other factors such as driving conditions or number of miles driven should be included in risk modelling.

Conclusion

All of these factors make the comparison between studies difficult and partly explain the conflicting results with regard to certain therapeutic classes.

Our systematic review highlighted several fields where more epidemiological data are needed. There is a need for large studies, investigating the individual and combined role of substances in the risk of road traffic crashes. The differential effect of the older generations of medicinal drugs versus newer ones must be compared to adapt patient care. The impact on crash risk of dose changes, beginning or end of treatment, must be further investigated. As described above, some non-psychoactive medicinal drugs may alter driving abilities due to their action on physiological functions or regarding central side effects. The impact of these medicinal drugs on road traffic crash risk has hardly been assessed in epidemiological studies so far. Studies should also be designed to assess the relative roles of disease and medication in the risk of road traffic crashes. Quantifying the risk in patients who may be under-represented in the general driving population is also of interest as they may be at high risk due to the disease itself, and to the medicinal drugs used to treat the condition.

OBJECTIVES

The CESIR-A study (Combinaison d'Etudes sur la Santé et l'Insécurité Routière – Appariement de bases de données nationales) aims to assess the role of medicines as a risk factor for road traffic crashes.

This work is divided into several studies:

In the first one, we examined the relationship between the risk of road traffic crashes and prescribed medicines with a particular focus on the relevance of the French classification system. The fraction of crashes attributable to medicine use was estimated from the results of this study.

The aim of the second study was to evaluate the impact of hypnotics on the risk of crash and particularly to compare the effects of benzodiazepine hypnotics to the effects of the two benzodiazepine-like hypnotics: zopiclone and zolpidem.

In the third study, we were interested in opioid medicines used in addictive disorders.

The choice of the studied medicines is explained below ("The CESIR-A study" part, "Choice of the medicines to be studied" sub-heading and "Results" part)

THE CESIR-A STUDY

The methodology consists in matching reimbursement data of the national healthcare insurance database (SNIIR-AM) with data on injurious traffic crashes collected by the police (police reports [PV] and the police national database of injurious crashes obtained from reports on injury traffic crashes [BAAC]), through partnership with the national healthcare insurance (CNAM-TS) and the national institute for research on transport and safety (INRETS).

Data sources

Police reports (PV)

French police forces are supposed to fill in a police report for each injurious crash occurring in the country (about 70,000 reports are written each year). They are scanned and stored as image files by Agira-TransPV that centralizes all PV for insurance responsibility purposes. All available police reports in France were gathered over the study period, from July 2005 to May 2008.

For some of the individuals involved in these injurious road traffic crashes, the national healthcare number (national ID) is recorded in the police report and can later be matched with the medicine dispensing records of the healthcare insurance database.

Police national database of injurious crashes (BAAC)

Reports on injury traffic crashes (BAAC) are filled in by police forces using a standardized grid containing descriptive variables about crash characteristics and location, vehicles and users involved. All the BAAC information are coded and computerized in the police national database of injurious crashes. Theoretically, to each subject involved in an injurious traffic crash and identified in a PV, corresponds a BAAC record.

The variables of interest are listed below. They contribute in the project to run matching procedures, to determine a responsibility score and to describe the crash and subjects characteristics.

<u>Matching PV/BAAC variables:</u>

- PV number
- crash date
- crash location’s zip code
- date of birth of the individual involved
- gender of the individual involved

Variables used for responsibility determination:

- weather
- road administrative category
- road directions
- road conditions
- road curves
- intersection
- lighting
- maneuver before the crash
- number of vehicles involved
- number of pedestrians
- moving obstacle
- vehicle conditions
- responsibility as determined by police forces
- infractions (excepted alcohol and illicit drugs)

Descriptive variables:

They are listed in Appendix 2. It includes:

- year, month and day of week of crash
- vehicle type
- socio-economic category of subjects involved
- alcohol level

All drivers involved in a road traffic crash are supposed to be tested for the presence of alcohol using a breath test. If this test is positive ($\geq$ 0.5 g/L), the driver refuses to take the test or the severity of the crash makes the test impossible, then the blood alcohol concentration is measured. If the breath test is negative then the driver is registered as not being under the influence of alcohol. Missing data on alcohol impairment correspond to the following situations: the result of the blood measurement was unknown at the time of data entry in the database, the blood measurement was impossible (not enough blood for example), the breath test was not done by the police, the breath test was positive but the measurement of blood alcohol concentration was not performed, the breath test was negative but it was not coded in the database.

- injury severity

Police forces conduct additional investigations regarding injury severity from hospital records and categorize the people involved in one of the four groups: unhurt, slightly injured, seriously injured (hospitalized more than 24 hours) or killed (in the 30 days following the crash).

Healthcare insurance database

The national healthcare insurance database (Système national d'Informations Inter-Régimes de l'Assurance Maladie [SNIIR-AM]) covers the whole French population (64 million people in 2008) and includes data on reimbursed prescription medicines. A record is added to the database each time a prescribed medicine is dispensed to an outpatient at the pharmacy, including national ID, date of dispensing, the seven-digit code (CIP code) assigned to the medicine at the time of its marketing authorization and the number of boxes delivered. Data on long-term chronic diseases are also registered in this database, with the ICD-10 code (International Classification of Diseases code), start and end dates. In France, patients are fully reimbursed for health care expenses, including medicines, related to 30 recognized long-term chronic diseases. [65]

Data on reimbursed prescription medicines dispensed within six months before the crash, were obtained by linking included drivers to the national healthcare insurance database using their national ID, gender and date of birth.

Data collection

National ID extraction

Drivers involved in an injurious crash in France, from July 2005 to May 2008, were included through their national ID, gender and date of birth extracted from police reports.

The national ID is assigned to all individuals living in France when they start working or during their last year in high school or at the latest at 20 years old. Individuals who do not have a personal ID can be identified by the parent or wife/husband national ID, the claimant gender, the claimant date of birth, the combination of which forms a unique identifier.

An application, based on Optical Character Recognition (OCR), was developed for automatic extraction from the police report image files of the crash date and the driver's national ID, gender and date of birth. First, the file is saved as a text file. An application is then run to detect 13 or 15-digit codes which may correspond to a national ID. The last two numbers are the "control key" allowing the identification of false national IDs. If the control key is not present, a test is realized on the fourth and fifth numbers which should correspond to the month of birth. Finally, the date of birth and gender are searched within an interval of a hundred lines around the national ID.

The extraction procedure was validated on a subsample of 293 police reports for which all pages were printed and coded manually.

Subjects whose police reports did not contain their national ID could not be included. Drivers were censored at their first involvement in a road traffic crash in order to attenuate the impact of previous crashes on medicine exposure.

PV/BAAC matching procedures

A procedure was implemented to match each individual whose ID was extracted from police reports, with the corresponding record from the police national database of injurious crashes.

The following common variables were used: police report number, crash date, crash location's zip code, police forces who recorded the crash, date of birth and gender of the individual involved. Two records were considered matched if they were concordant for all six variables. If a pair was discordant for three or more variables, it was considered unmatched. For pairs with concordance for less than six variables and more than three variables, a probabilistic linkage method was developed. [66]

The principle of the probabilistic linkage method is to consider all possible pairs.
A weight is assigned to each common variable according to its reliability. Each variable has two probabilities associated with it:

- The probability that a variable agrees given that the pair is a matched pair (m) is linked to the error rate on this variable
- The probability that a variable agrees given that the pair is an unmatched pair (u) is linked to the number of values the variable can take.

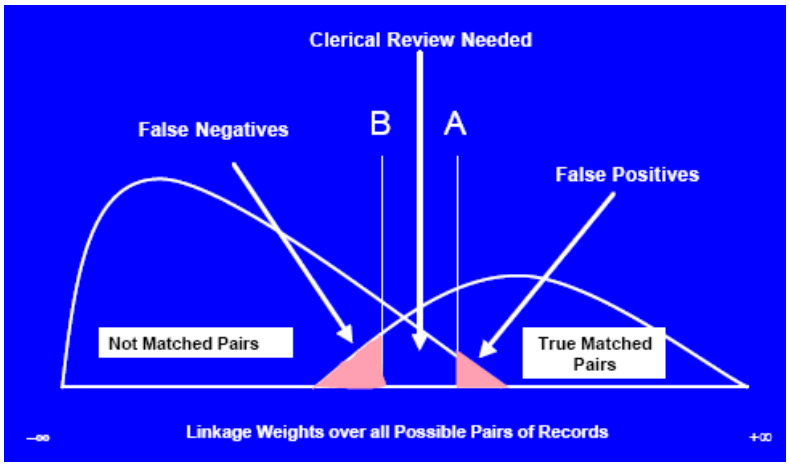
To determine the weights assigned to each variable, a sample of PV were matched manually to the corresponding BAAC.

The weight is computed as follows:

- If the pair agrees on the variable: $w = \log_2 (m/u)$
- If the pair disagrees on the variable: $w = \log_2 (1-m)/(1-u)$

The global score is the sum of each weight for all the common variables. It represents the degree of agreement between the two records. A threshold is selected to minimize the number of non-matches considered as matched pairs and the number of matches considered as non-matched pairs. All scores higher than the chosen threshold are considered matched. Below the threshold, pairs are unmatched. When a decision could not be made automatically, pairs are reviewed by hand. (Figure 1)

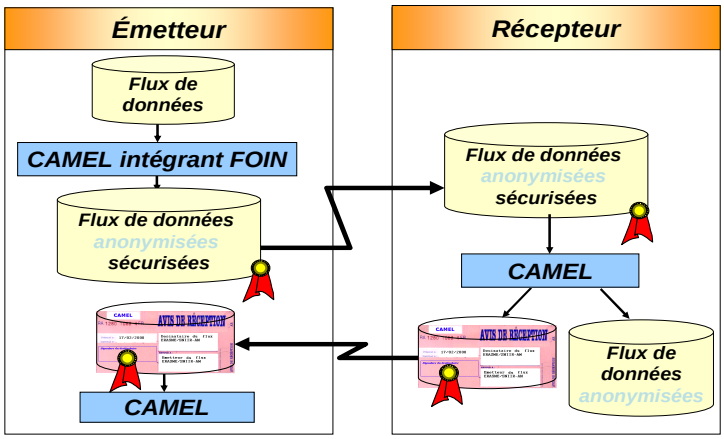
Figure 1. Distribution of weight for a typical matching process



Data security and anonymity

According to the French law on data privacy of January 6th, 1978, the methodology of the research must not allow the direct identification of subjects. That is why the French national healthcare insurance developed a system that guarantees strong occultation of such sensible information as national ID number which provides access to electronic nominative information. This system, called FOIN (nominative occultation function), combines an authenticity process and a double anonymisation, ensuring that no correspondence table can be built. [67] (Figure 2)

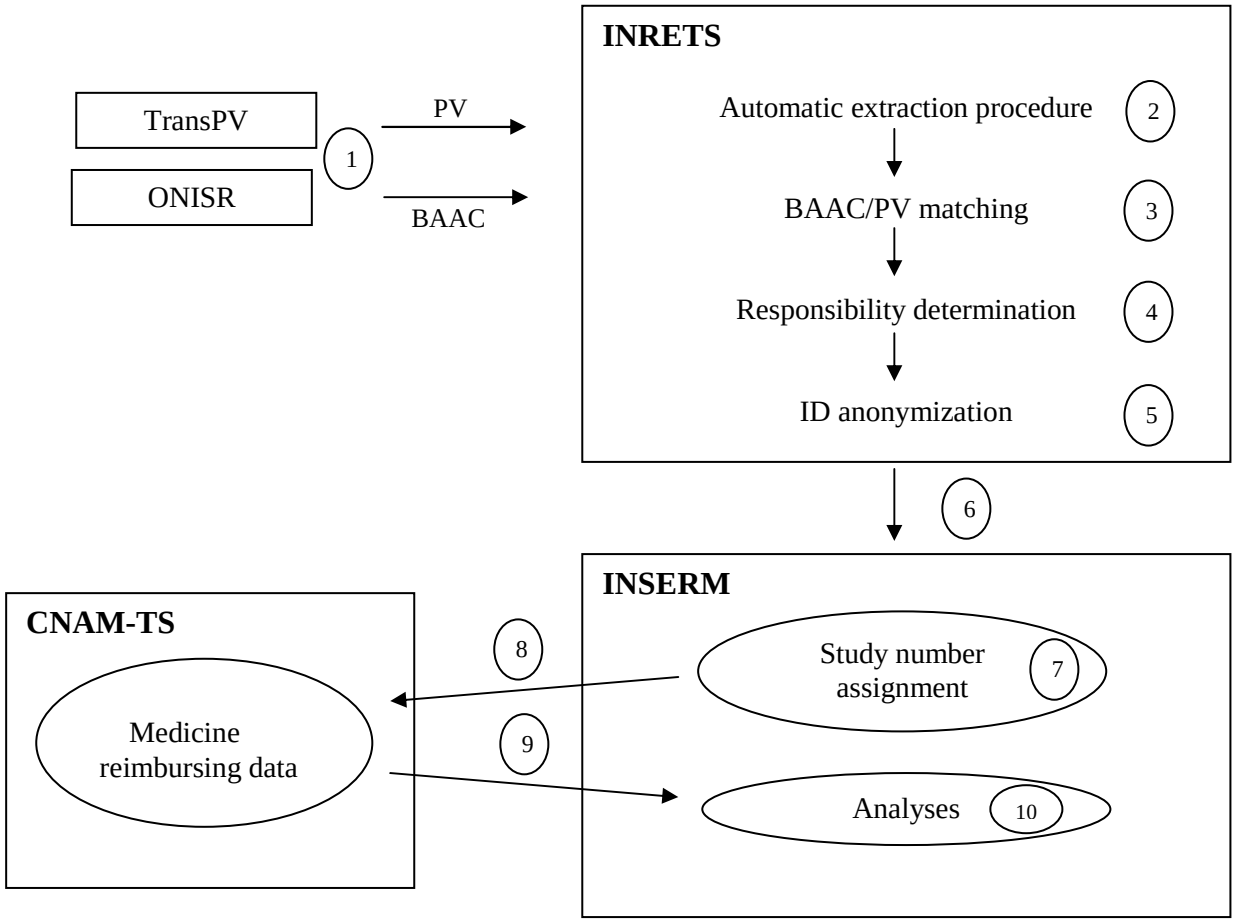
Figure 2. FOIN process (nominative occultation function)



Data exchanges

Figure 3 shows the circuit followed for data collection and exchanges between the different partners involved in the project.

Figure 3. Flowchart of data collection



Step 1: *PV and BAAC collection*

Each year, the INRETS is addressed all BAAC from the national interministerial road safety observatory (ONISR). All PV over the study period were gathered through a partnership with Agira-TransPV that centralizes all PV for insurance purposes.

Step 2: *Automatic extraction procedure*

The combination national ID/ gender/ date of birth of drivers involved is extracted from PV by an automatic OCR procedure which was developed especially for the study.

Step 3: *BAAC/PV matching*

BAAC and PV are matched using a probabilistic linkage method.

Step 4: *Responsibility determination*

The INRETS computes responsibility levels for each driver involved in an injurious traffic crash, by a standardized method using BAAC data.

Step 5: *ID anonymization*

The personal information anonymization function of the healthcare national insurance system (FOIN) is used in order to secure exchanges between the different partners.

Step 6: *Data exchange from the INRETS to the INSERM*

Anonymized IDs and a number of BAAC variables, describing crash characteristics and users involved, are encrypted and transmitted to the INSERM.

Step 7: *Study number assignment*

A study number is assigned to each subject.

Step 8: *Data exchange from the INSERM to the CNAM-TS*

The couples anonymized IDs - study number and crash dates are forwarded to the CNAM-TS after data encryption.

Step 9: M*edicine reimbursing data*

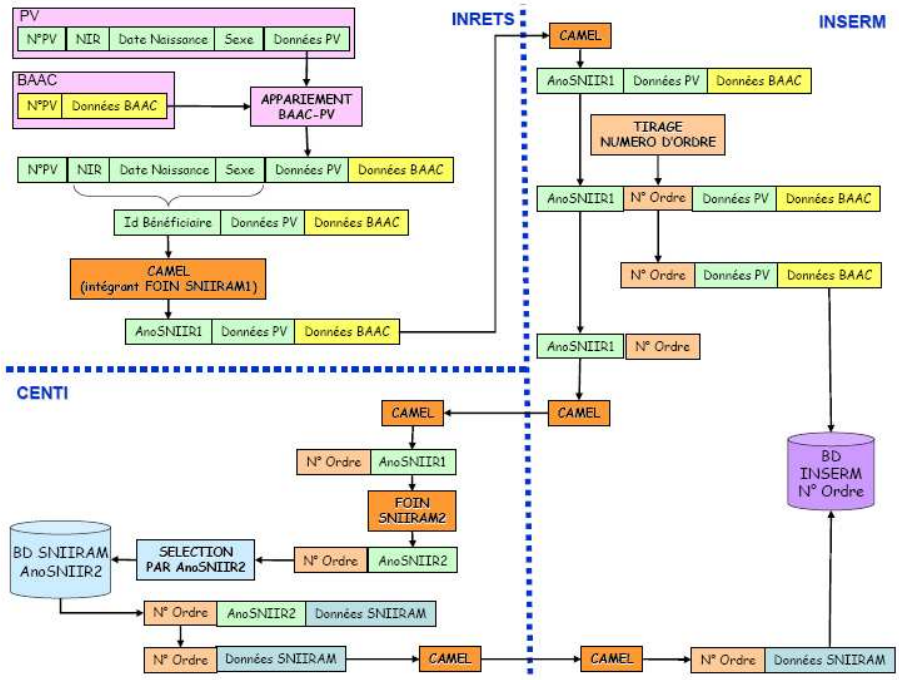
The CNAM-TS extracts reimbursed medicines data 6 months before and 2 months after the crash, by means of the anonymized ID. Data are encrypted and sent back to the INSERM.

Step 10: *Analyses*

All data are merged for analysis.

The flow, processing and matching of files are detailed in Figure 4 below. Those anonymization procedures are required because the consent of participants can not be obtained. It is thus necessary to make their identification impossible. This study was approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [CNIL]).

Figure 4. Anonymization procedures



Medicines and exposure periods

The Anatomical Therapeutic Chemical (ATC) classification

This classification was developed by the World Health Organization (WHO). In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified in groups at five different levels. As an example:

N	Nervous system
N05	Psycholeptics
N05C	Hypnotics and sedatives
N05CF	Benzodiazepine related drugs
N05CF01	Zopiclone

The EPPM survey

The EPPM survey (Enquête Permanente sur la Prescription Médicale) is a survey on medicine prescription in France. This survey is conducted among 800 practitioners, representative of French physicians. Three times a year, over a seven-day period, all prescriptions are collected and information about prescribed medicines and treatment duration prescribed is recorded in a database. [68] The database is structured as follows:

Medicine (CIP code / ATC class)
- Packaging 1
  - prescribed duration 1 ➔ number of prescriptions
  - prescribed duration 2 ➔ number of prescriptions
- Packaging 2
  - prescribed duration 1 ➔ number of prescriptions
  - prescribed duration 2 ➔ number of prescriptions

We collected prescription data over the June 2005 - May 2008 period, data was thus available for twelve trimesters. We computed the median value of treatment duration for each ATC class (4^{th} level), weighted by the total number of prescriptions of this duration over the twelve trimesters. In France, the duration of a treatment dispensed at the pharmacy cannot usually exceed 30 days (with a very small number of exceptions such as contraceptive pills), so the maximum duration was 30 days.

Day-by-day exposures were estimated using the median value computed as described above. Exposure was considered starting on the day following the dispensing day.

When we conducted further analysis in specific ATC classes, exposure duration was estimated more precisely for these classes. This is described in Methods parts, Medicines and exposure periods sections of each chapter.

Analyses

Descriptive analysis

We compared included with non-included subjects, regarding age, gender, injury severity, vehicle type, crash location, type of police forces who filled in the police report, alcohol level and responsibility status. This analysis was performed by logistic regression.

Responsibility analysis

The study database only includes drivers involved in a crash, and therefore no external reference group. The general principle of the analysis is to use drivers non responsible for their crash as the reference group.

In the present study, responsibility status was determined using the "SAM method" presented below, which is derived from a method initially developed by Robertson and Drummer.

Responsibility determination

- Robertson and Drummer method

A method was developed by Robertson and Drummer to determine the culpability or responsibility of a driver in a crash. [69]

Eight mitigating categories (i.e. likely to reduce driver responsibility) are identified from the police report:

- condition of road
- condition of vehicle
- driving conditions
- type of accident
- witness observations
- traffic rule obedience
- difficulty of task involved
- level of fatigue

A score is assigned to each driver for each of these factors from 1 (favourable to driving) to 4 (not favourable to driving). The higher the sum of the scores is, the more the conditions are unfavourable to driving, and thus the more likely the driver will be considered as non-responsible for his crash. The scoring guidelines are available in Appendix 3.

In our study, if medicines are contributing to crash causation, it would be expected that they would be overrepresented in the responsible group.

- SAM method

In the present study, responsibility levels in the crash were determined by a method adapted from Robertson and Drummer. This automatic method uses available variables from

the police national database of injurious crashes. Witness observations and level of fatigue are not recorded in this database so the score is computed over the other six categories. The algorithm for the determination of scores is presented in Appendix 4.

- If the score is between 8 and 15, the driver is fully responsible
- If the score is more than 15, the driver is non responsible

This method has previously been validated by the INRETS in the SAM (Stupéfiants et Accidents Mortels) study on cannabis intoxication and fatal road crashes in France. [70]

In this study, this automatic assessment of responsibility was compared to expert evaluation, in a common sample. Agreement between the two methods has been shown to be satisfactory (kappa=0.71).

Advantages / drawbacks

In a classical case-control study, controls would have not been involved in a crash, but would come from the driving population. In such studies, controls can be randomly selected from moving traffic or at petrol stations; the selection is therefore done on a voluntary basis which may lead to a selection bias. Another way is to select controls from the source of case data (heath insurance data, hospital admission…); however, one can not know if these controls actually drive.

The main interest of the responsibility analysis is that both cases and controls are selected from the same driving population and that controls are actually drivers. The main underlying assumption is that non responsible drivers are representative of the driving population. The comparison of non responsible drivers with the driving population has been validated in the SAM study. [70]

The Robertson and Drummer's method has been used in previous studies.[15] [19] The method has been indirectly validated for alcohol use, which has been found to be overrepresented in responsible drivers, with a dose-effect relationship, in accordance with the known effects of alcohol on driving. [69]

In our study, the assessment of responsibility is carried out without considering alcohol and drug intoxication or others factors that may relate to medicine use such as sex and age. However, the responsibility status, determined by police forces, is taken into account in the responsibility algorithm. Police forces may often consider drivers under the influence of alcohol as responsible for their crash and in this way, alcohol level may influence responsibility score.

Another drawback is that the method does not capture the risk of being unable to avoid a crash without being responsible (for example, braking in time to avoid a vehicle crossing against the light).

Statistical analysis

As in a classical case-control study, the principle of responsibility analysis is to compare exposure probabilities on the day of crash between responsible drivers (cases) and non-responsible drivers (controls). Statistical analyses were thus conducted using logistic regression.

Case-crossover analysis

Definition, study population and assumptions

In 1991, Maclure proposed a case-crossover study as a new statistical method to measure the association between transient exposures and acute outcomes.[71] In this design, subjects serve as their own matched controls and only individuals who had the outcome of interest are included. Comparisons are made at different time points in the same subject: the exposure during a period immediately before the outcome (e.g. a crash, case period) is compared with the exposure during an earlier period (control period). The control period is used to estimate the exposure rate at the time when the subjects did not have the outcome of interest. Only subjects with discordant exposure between the two time windows contribute to information. Therefore, this method is adapted to exposures varying over time as medicine use can be. Exposure history was available in our study over the six months before the crash.

The case-crossover design has been used in some pharmacoepidemiological studies estimating medicines effects on the risk of road traffic crashes. [10 22 72] Each subject being his own control, confounding due to fixed characteristics is therefore eliminated, including genetics, personality, education, lifestyle and chronic diseases. This overcomes the problem of confounding by chronic indication, a common cause of bias in pharmacoepidemiolgy. However, acute diseases or fluctuations in diseases may still be confounders.

The case period is defined as the time window that immediately precedes the outcome event and is arbitrarily chosen by the researchers, depending upon how the risk factor is hypothesized to work. In our study, we defined the case period as the day of crash. The control window is of the same width as the case window.

From the estimation of exposure periods to studied medicines, we determined the exposure status (exposed or non-exposed) in both case and control windows. In order to take into account the distribution of exposure periods and the uncertainty on actual exposure, we

interposed a “wash-out” period between the case and control windows. Indeed, any exposure arising in the control period which would also arise in the case period would reduce the number of discordant exposures between the two periods and as a consequence would reduce statistical power. Moreover, if the exposure effects are cumulative or persistent, the proximity of the periods may impinge upon the assumption of conditional independence of exposures.

The choice of the length of the wash-out period is crucial. Indeed, the overall prevalence of exposure should be stable over time. Any change that may cause a difference in frequency of medicine prescription between the two periods would introduce a time trend bias. In the same way, any within-subject characteristics that may vary across the period would bias the results. Therefore, the wash-out period should be long enough to avoid carryover effects and short enough to avoid time trend.
The choice of the length of wash-out periods for each studied medicines is presented in the Methods section of each chapter.

Statistical analysis

This is achieved by analyzing the data as a matched case-control study. In a case-crossover study, the number of strata equals the number of subjects in the dataset. The Mantel-Haenszel method can be used to estimate the odds ratio as is usually done in a pair-matched case-control study, which is algebraically equivalent to the McNemar estimate. Case-crossover designs are typically analyzed using conditional logistic regression models.

In SAS, matched analyses are carried out using the PHREG procedure.

All analyses were performed using the SAS® statistical software package, version 9.0 (SAS Institute Inc, Cary, NC, USA).

Choice of the medicines to be studied

One of the challenges of the study was related to the problem of multiple comparisons as many statistical inferences could be erroneously considered simultaneously. Even if our database is large, the statistical power is far from sufficient for the over 1,000 molecules that were prescribed in the study period to be tested individually. A strategy was clearly needed to address the issue of multiple-testing.

To overcome the issue of multiple statistical testing and to answer one of the study objectives, the first approach was to group medicines according to their level of risk defined by the French classification system. This method allowed studying all medicines classified in four groups (from level 0 to level 3).

In order to be able to study a large number of ATC classes (4^{th} level), we screened the hundred classes the most frequently used. The frequency was computed over the six months before crashes, in number of days, using exposure periods as defined above. We performed a responsibility analysis on these hundred classes. We applied a Bonferroni correction for statistical level significance: $\alpha = 0.05/100 = 0.0005$. The classes significantly associated with the risk of being responsible for a crash were or will be studied individually.

STUDY POPULATION

Results of the inclusion procedures

National ID extraction

Because national ID extraction procedure was automatic and was performed on a very large number of police reports (210,818), it was not possible to determine the exact proportion of drivers with or without a national ID. This is why a validation study was performed manually on 293 police reports that showed that the national ID was recorded for 140 of the 455 drivers involved (28%)

The automatic OCR software extracted 110 of the 140 national IDs. Therefore, the extraction rate was 79%. The reasons explaining why a driver's ID was not extracted could be the failure of the OCR procedure (e.g. ID not legible enough), the ID was written manually and could not be recognized by the software, or there was a typing error.

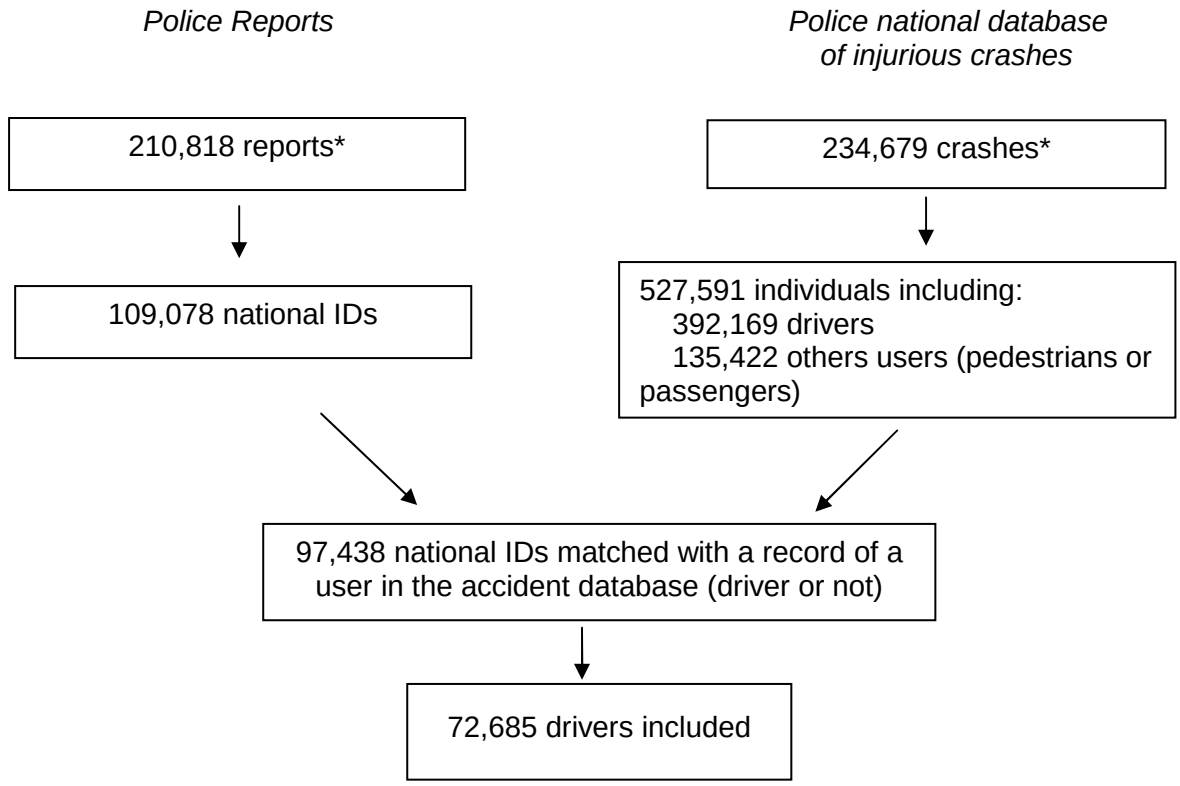
We extracted 109,078 national ID/gender/date of birth from 210,218 police reports available from July 2005 to May 2008, corresponding to any individual involved in an injurious road traffic crash.

PV/BAAC matching

Ninety percent of the extracted national ID/gender/date of birth were matched with a corresponding record in the police national database of injurious crashes (72.8% agreed on all variables, 14.0% were matched by the probabilistic linkage method and 3.1% manually). The linkage did not succeed for 10% of the individuals, mainly because the ID corresponded either to a driver involved in the crash but not entered in the police national database or to an individual not involved in the crash (eg: a witness, the owner of a vehicle involved). When the linkage succeeded, it provided data on the status of the individual involved (driver, pedestrian, passenger).

The procedure finally led to the inclusion of 72,685 drivers (Figure 5). In the police national database of injurious crashes, 392,169 drivers were registered in the study period. Consequently, we estimated the inclusion rate at 18.5% (72,685 / 392,169).

Figure 5. Flowchart of included drivers



* The discrepancy between the number of police reports and the number of records in the police national database of injurious crashes is explained by the fact that a small proportion of unavailable reports were being used for on-going further legal investigations.

Description of the study population

Drivers involved in injurious road traffic crashes are described in Table 2. They are mostly men (68.5%). Age classes are equally distributed between 18 and 54 years old. Classes of less than 18 and above 54 years old are less represented. Cars represent about 60% of the vehicle involved, scooters and motorbikes account for approximately 30% when grouped together. Finally, 1.9% of the drivers were killed in their crash. The proportions of slightly injured and seriously injured drivers were almost the same (36%).

Table 2. Driver characteristics

	N	%
	72,685	
Gender		
Men	49,770	68.5
Women	22,915	31.5
Age		
< 18	3,055	4.2
18-24	14,814	20.4
35-34	16,666	22.9
35-44	15,488	21.3
45-54	11,796	16.2
55-64	5,990	8.2
65-74	2,837	3.9
≥ 75	2,039	2.8
Socio-economic category		
Higher managerial and professional occupations	2,784	3.8
Intermediate occupations	24,984	34.4
Workers	11,887	16.4
Retired	6,449	8.9
Unemployed	3,021	4.2
Other/missing	16,014	22.0
Student	7,546	10.4
Vehicle type		
Light vehicle	42,792	58.9
Bicycle	3,867	5.3
Scooter	10,099	13.9
Motorbike	10,458	14.4
Commercial vehicle	2,550	3.5
Heavy goods vehicle	1,342	1.9
Other	1,577	2.2
Injury severity		
Unhurt	19,093	26.3
Slightly injured	26,327	36.2
Seriously injured	25,864	35.6
Killed	1,401	1.9

Comparative analysis of included drivers versus non-included drivers

Several reasons may explain the non-inclusion of drivers: the police reports did not contain the driver's national ID, the extraction procedure failed or the linkage with the corresponding record in the police national database of injurious crashes did not succeed.

We compared included with non-included subjects, regarding age, gender, injury severity, vehicle type, crash location, type of police forces who filled in the police report, alcohol level and responsibility status.

Injury severity was the main factor explaining inclusion by means of the national ID (OR=3.43 [3.29-3.58] for seriously injured drivers and OR=2.67 [2.57-2.77] for slightly injured drivers), thus explaining higher rates of inclusion for bicycle and scooter drivers, drivers involved in non-urban accidents and drivers who had consumed alcohol, all of whom are more seriously injured. Law enforcement officers from the National Gendarmerie (most frequently in charge of non-urban areas) are more likely to ask for the national ID of the drivers involved than officers from the National Police (most frequently in charge of urban areas) (OR=2.24 [2.16-2.32]). The inclusion rate was slightly lower for responsible drivers than for non-responsible drivers (0.91 [0.88-0.94]). (Table 3)

Table 3. Odds ratios for inclusion of drivers by means of the national ID

	N	% included	OR [99.9% CI] *	OR [99.9% CI] †
Drivers	392,169	18.5		
Vehicle				
Light vehicle	246,212	17.4	Reference	Reference
Bicycle	14,442	26.8	1.74 [1.63-1.85]	1.24 [1.16-1.33]
Scooter	29,798	23.3	1.45 [1.38-1.52]	1.09 [1.03-1.16]
Motorbike	19,460	17.7	1.03 [0.96-1.09]	0.81 [0.76-0.87]
Commercial vehicle	16,916	15.1	0.84 [0.79-0.91]	0.93 [0.86-1.00]
Heavy goods vehicle	13,471	14.9	0.83 [0.77-0.91]	0.85 [0.78-0.93]
Other	51,870	21.3	1.29 [1.24-1.34]	0.95 [0.90-0.99]

Table 3. (continued)

	N	% included	OR [99.9% CI] *	OR [99.9% CI] †
Age				
55-64	33,324	17.6	Reference	Reference
missing	1,247	20.9	1.24 [0.98-1.57]	0.64 [0.50-0.82]
<18	30,936	22.6	1.37 [1.28-1.46]	0.90 [0.84-0.97]
18-24	72,688	18.1	1.04 [0.98-1.10]	0.94 [0.88-1.00]
25-34	92,994	17.8	1.02 [0.96-1.07]	1.01 [0.96-1.07]
35-44	76,559	18.5	1.06 [1.01-1.13]	1.06 [1.00-1.13]
45-54	58,402	18.6	1.07 [1.01-1.14]	1.07 [1.01-1.14]
65-74	16,387	18.7	1.08 [1.00-1.17]	1.00 [0.91-1.08]
> 75	9,632	18.8	1.08 [0.98-1.20]	0.92 [0.83-1.02]
Gender				
Men	288,515	17.8	Reference	Reference
Women	103,654	20.7	1.21 [1.17-1.25]	1.20 [1.16-1.24]
Injury severity				
Unhurt	185,689	10.3	Reference	Reference
Killed	9,729	14.4	1.47 [1.33-1.62]	0.96 [0.86-1.07]
Seriously injured	77,087	33.6	4.41 [4.25-4.57]	3.43 [3.29-3.58]
Slightly injured	119,664	22.0	2.46 [2.38-2.55]	2.67 [2.57-2.77]
Location				
Urban	265,925	15.3	Reference	Reference
Non-urban	126,244	25.3	1.88 [1.83-1.93]	1.14 [1.10-1.18]
Police forces				
Police	281,780	14.1	Reference	Reference
Gendarmerie	110,389	29.9	2.60 [2.52-2.67]	2.24 [2.16-2.32]
Responsibility				
Not responsible	206,290	18.3	Reference	Reference
Responsible	185,579	18.8	1.04 [1.01-1.06]	0.91 [0.88-0.94]
Alcohol				
Negative breath test	301,711	18.5	Reference	Reference
Missing	59,135	16.7	0.89 [0.85-0.92]	0.97 [0.93-1.01]
0	10,181	23.7	1.38 [1.27-1.49]	1.03 [0.95-1.12]
0.1-0.5	3,627	17.3	0.93 [0.80-1.07]	0.97 [0.84-1.13]
0.5-0.8	3,443	16.5	0.87 [0.75-1.02]	0.88 [0.75-1.03]
0.8-1.2	3,963	19.8	1.09 [0.96-1.25]	0.92 [0.80-1.06]
1.2-2.0	5,326	26.1	1.56 [1.41-1.73]	0.91 [0.82-1.02]
> 2	4,783	27.6	1.68 [1.51-1.88]	0.98 [0.88-1.10]

* Crude Odds Ratios

† Odds Ratios adjusted for age, gender, injury severity, vehicle type, crash location, police forces who filled in the police report, alcohol level and responsibility status

RESULTS

The first study was interested in estimating the relationship between the risk of road traffic crashes and prescribed medicines with a particular focus on the relevance of the French classification system (Chapter 1).

Among the hundred most frequently used therapeutic classes screened (4th level of the ATC classification), seven classes were significantly associated with the risk of being responsible for a crash, after adjustment for crash and individual variables, with all p-value less than 0.0005. (Table 4)

The effects of benzodiazepines on the risk of crash are well documented in scientific literature. Because they have shorter half-lives than benzodiazepines, zolpidem and zopiclone were presented as alternatives for the treatment of insomnia and were supposed to present fewer or no residual effects in the morning following administration. This is the reason why we were interested in studying these medicines (Chapter 2).

The result found for medicines used in opioid dependence deserved further investigation as it is a therapeutic class which has not received much attention regarding the risk of crash so far. A more detailed analysis is thus presented in Chapter 3.

Table 4. Odds ratios for responsible road traffic crashes

	OR [95% CI]	**p**
Psycholeptics (N05)		
Anxiolytics, benzodiazepines derivatives (N05BA)	1.49 [1.36-1.63]	<0.0001
Hypnotics and sedatives, benzodiazepine related drugs (N05CF)	1.29 [1.13-1.47]	0.0002
Psychoanaleptics (N06)		
Antidepressants, selective serotonin reuptake inhibitors (N06AB)	1.44 [1.30-1.79]	<0.0001
Antidepressants, other antidepressants (N06AX)	1.61 [1.38-1.87]	<0.0001
Other nervous system drugs (N07)		
Drugs used in addictive disorders, opioid dependence (N07BC)	1.88 [1.45-2.44]	<0.0001
Antiepileptics (N03)		
Carboxamide deririvatives (N03AF)	2.06 [1.41-2.99]	0.0002
Fatty acid derivatives (N03AG)	2.50 [1.75-3.57]	<0.0001

Model computed for 62,766 drivers without missing values for the adjustment variables
Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity

CHAPTER 1: THE FRENCH CLASSIFICATION SYSTEM AND THE RISK OF ROAD TRAFFIC CRASHES

Introduction

Within the European Union, it is mandatory for a pharmaceutical company to provide data regarding the effects of a medicinal drug on the ability to drive and to use machinery prior its commercialization. It is this information which is used to write the Summary of Product Characteristics and the package insert.[2] In Europe, there are several classification and labeling systems regarding medicines and driving. Some of the member states, such as France (since 1999), have been complementing the information with a unique triangular pictogram on medicine packaging. More than 3,000 medicines (a third of the 9,000 medicines marketed in France) were labeled with this pictogram between 1999 and 2005. The risk being unequal between medicines, this labeling system was considered as not enough informative and it was decided to adopt a grading system, following a request from the French governmental committee for road safety to the Afssaps. A working group, formed in majority with experts from the pharmacovigilance, marketing authorization and narcotics and psychotropics commissions elaborated this classification in four levels of risk. The grading method was developed in order to be reproducible and considered all available data: pharmacodynamic effects, individual sensitivity, conditions of use of each medicine, pharmacovigilance data, experimental and accidentological data. [3-5]

Level 0: Medicinal products with no pharmacodynamic effect likely to alter the ability to drive, in the present state of knowledge. (6,282 medicines)

Level 1: Medicinal products which do not generally question the ability to drive but require patient information. (1,190 medicines)

Level 2: Medicinal products which could affect the ability to drive and require medical advice before use. (1,601 medicines)

Level 3: Medicinal products which affect the ability to drive during their use. (194 medicines)

For the last three levels, a graded pictogram is printed on medicine packs. Risk levels are illustrated by three colors and a written warning followed by a short informative message on the attitude patients should adopt when using these medicines. This driving warning system was gradually set up over the 2005-2008 period.

Quantitatively, the Afssaps'risk gradation is distributed as follows:

Table 5. Afssaps'risk gradation

Therapeutic class (ATC)	Level 1	Level 2	Level 3
Digestive tract and metabolism (A)	80	196	1
Cardiovascular system (C)	348	28	0
Genito-urinary system (G)	80	21	0
Anti-infectives for systemic use (J)	82	159	0
Antineoplastics and immunomodulating agents (L)	39	120	0
Musculoskeletal system (M)	153	43	14
Nervous system (N)	90	902	157
Respiratory system (R)	128	75	1
Ophtalmology (S)	120	29	14

The Afssaps noted that this classification is liable to change due to new data, in particular data generated from epidemiological studies which are very few on this subject. That is why the Afssaps is contributing to the CESIR-A study.

Objectives

The aim of this first study was to estimate the association between medicine use and the risk of injurious road traffic crashes, as well as the fraction of crashes attributable to medicine use in France with a particular focus on the relevance of the classification system implemented since 2005.

Methods

Responsibility analysis

The associations between responsibility and age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level and injury severity were initially investigated using bivariate analysis: associated variables were included in the multivariate model when their p-value was less than 20% (Chi-squared test). This was the case for all variables except the year of crash which was forced into the model because prescription patterns may have change between the 2005-2006 and 2007-2008 periods. Further analyses adjusted for the presence of long-term chronic diseases. We tested the interactions between exposure and each of the adjustment variables.

Attributable fraction

The population attributable fraction can be interpreted as the proportion of cases that would be prevented following elimination of the exposure, assuming the exposure is causal.

When adjusted odds ratios are used, attributable fractions are estimated from the prevalence of exposure in cases, using the following formula: p * [(OR-1)/OR] where p is the proportion of cases exposed to the risk factor and OR the adjusted odds ratio. [73]

Estimation of the confidence intervals was computed using the bootstrap method. The method relies on resampling by reconstruction of the sample population with replacement. The logistic regression model is run in each sample, leading to an attributable fraction estimate in each sample. Confidence intervals are estimated from the 2.5^{th} and the 97.5^{th} percentiles of the distribution.[74 75]

In the present study, we performed 500 simulations which is a fair compromise between the high number of simulations to obtain precise estimates and the computing limitations due to the high number of subjects in the database.

Case-crossover analysis

In France, the duration of a treatment dispensed at the pharmacy cannot usually exceed 30 days (almost without exception, i.e. contraceptive pills), so the duration of the wash-out period was 30 days.

Results

Twenty seven percent (n=19,777) of the drivers included in the study were exposed to at least one prescribed medicine on the crash day. There were 13,167 drivers (18%) exposed to at least one prescribed medicine of level 1, 2 or 3. The detail is provided in Table 6.

Table 6. Number of exposed drivers on the crash day by level of risk

Number of medicines	Exposed drivers
Level 0 medicines	15,715 (21.6%)*
1	6,917
2	3,757
3	2,161
4	1,233
>4	1,647
maximum level 0	6,610 †
Level 1 medicines	7,415 (10.2%)*
1	5,681
2	1,361
3	315
4	49
>4	9
maximum level 1	4,432 †
Level 2 medicines	8,268 (11.4%)*
1	5,102
2	2,029
3	745
4	253
>4	139
maximum level 2	6,753 †
Level 3 medicines	1,982 (2.7%)*
1	1,724
2	234
3	23
4	1
maximum level 3	1,982 †

* exposed to at least one medicine of the risk level considered

† only considering exposure to medicine of the highest level of risk

Table 7 shows the main pharmacotherapeutic classes used on the crash day among level 2 and 3 medicines by ATC class (3rd level of the ATC system).

Table 7. Level 2 and level 3 pharmacotherapeutic classes used on the crash day.

ATC class	Level 2 medicines	Level 3 medicines
Total	13,147	2,265
Alimentary tract and metabolism (A)	1,056	-
Insulins and analogues (A10A)	370	-
Blood glucose- lowering drugs, excl. insulins (A10B)	668	-
Cardiovascular system (C)	196	-
Antiadrenergic agents, centrally acting (C02A)	195	-
Musculoskeletal system (M)	277	-
Muscle relaxants, centrally acting (M03B)	248	-
Nervous system (N)	10,870	2,265
Opioids (N02A)	1,935	2
Antimigraine preparations (N02C)	337	-
Antiepileptics (N03A)	1,053	-
Anti-Parkinsonian drugs (N04)	175	-
Antipsychotics (N05A)	804	8
Anxiolytics (N05B)	2,843	471
Benzodiazepine derivatives (N05BA)	2,362	471
Antidepressants (N06A)	3,122	-
Selective serotonin reuptake inhibitors(N06AB)	2,188	-
Hypnotics and sedatives (N05C)	-	1,784
Benzodiazepine derivatives (N05CD)	-	295
Benzodiazepine related drugs (N05CF)	-	1,196
Hypnotics and sedatives in combination, excl. barbiturates (N05CX)	-	293
Drugs used in addictive diseases (N07B)	443	-
Drugs used in alcohol dependence (N07BB)	69	-
Drugs used in opioid dependence (N07BC)	374	-
Antihistamines for systemic use (R)	327	-
Phenothiazine derivatives (R06AD)	216	-

Some drivers may have been exposed to several substances from the same pharmacological subgroup, explaining the difference with the number of exposed drivers presented in Table 6.

When adjusted for variables found to be associated with responsibility in the crash (age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity) and for medicines of other levels, the use of at least one medicine of level 2 or level 3 was associated with the risk of being responsible for a crash (OR=1.31

[1.24-1.40] and OR=1.25 [1.12-1.40]). The use of level 0 medicines was associated with a decreased risk of being responsible for a crash (OR=0.92 [0.88-0.97]). The risk of being responsible for a crash was not significant for the risk level 1 (Table 8). The fractions of road traffic crashes attributable to levels 2 and 3 medicine use were 3.0% [2.4%-3.5%] and 0.7% [0.4%-0.9%] respectively. The global fraction attributable to both level 2 and 3 medicines (considering exposure to level 2 and/or level 3 medicines on the crash day) was 3.3% [2.7%-3.9%]. The associations remained significant after adjustment for long-term chronic diseases (OR=0.92 [0.88-0.97] for level 0, OR=1.30 [1.22-1.38] for level 2 and OR=1.24 [1.11-1.39] for level 3). There was no interaction of exposure to medicines with alcohol consumption (p=0.84 for level 2 and p=0.23 for level 3). The information on alcohol level was missing for 9,919 subjects (13.6%). Excluding these subjects from the univariate analysis led to no significant change in estimated odds ratios. We did not find any interaction between the use of level 2 or level 3 medicines and the adjustment variables.

Table 8. Odds ratios for responsible road traffic crashes in users of prescribed medicines.

	Exposed drivers	**OR [95% CI]** †	**Exposed drivers** ‡	**OR [95% CI]** §	**OR [95% CI]** ‖
Level 0	15,715	0.92 [0.88-0.95]***	13,702	0.92 [0.88-0.97]*	0.92 [0.88-0.97]**
Level 1	7,415	0.96 [0.92-1.01]	6,478	0.96 [0.90-1.02]	0.95 [0.89-1.01]
Level 2	8,268	1.24 [1.19-1.30]***	7,102	1.31 [1.24-1.40]***	1.30 [1.22-1.38]***
Level 3	1,982	1.56 [1.42-1.71]***	1,679	1.25 [1.12-1.40]***	1.24 [1.11-1.39]**

Reference group = drivers not exposed to medicines of the risk level considered

† Crude Odds Ratios

‡ Model computed for 62,766 drivers without missing values for the adjustment variables

§ Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity and other level medicines

‖ Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity, long-term chronic diseases and other level medicines

* p<0.01, ** p<0.001, *** p<0.0001

Among level 2 medicines, the risk of being responsible for a crash was significant for medicines used in diabetes (A10), antiepileptics (N03), psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07). The odds ratio for psycholeptics belonging to level 3 medicines corresponded to the odds ratio estimated for all level 3 medicines (Table 9).

Table 9. Odds ratios for responsible road traffic crashes in users of prescribed medicines by ATC classes.

	Exposed drivers [†]	OR [95% CI] [‡]
Level 2		
Drugs used in diabetes (A10)	795	1.20 [1.03-1.40]*
Antihypertensives (C02)	172	1.07 [0.78-1.47]
Muscle relaxants (M03)	219	0.82 [0.62-1.09]
Analgesics (N02) [§]	1,845	1.04 [0.94-1.15]
Antiepileptics (N03)	755	1.41 [1.21-1.65]***
Anti-Parkinson drugs (N04)	125	1.15 [0.79-1.68]
Psycholeptics (N05) [‖]	2566	1.27 [1.15-1.40]***
Psychoanaleptics (N06) [††]	2572	1.31 [1.19-1.44]***
Other nervous system drugs (N07) [¶]	369	1.46 [1.16-1.84]**
Antihistamines for systemic use (R06)	267	1.05 [0.81-1.35]

Reference group = drivers not exposed to the medicine considered

[†] Model computed for 62,766 drivers without missing values for the adjustment variables

[‡] Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity, long-term chronic diseases and other medicines

[§] Including opioids (N=1585), other analgesics and antipyretics (N=22) and antimigraine preparations (N=281)

[‖] Including antipsychotics (N=558) and anxiolytics (N=2250)

[††] Including antidepressants (N=2509), psychostimulants (N=56) and anti-dementia drugs (N=33)

[¶] Including drugs used in alcohol dependence (N=51), drugs used in opioid dependence (N=295), antivertigo preparations (N=7) and other nervous system drugs (N=16)

* p<0.05, ** p<0.001, *** p<0.0001

The risk of being responsible for a crash gradually increased from 1.14 [1.06-1.22] for users of one medicine of level 2 or 3 to 1.88 [1.58-2.25] for users of more than 3 medicines of level 2 or 3 (Table 10).

Table 10. Odds ratios for responsible road traffic crashes by number of level 2 and/or level 3 medicines used.

Number of level 2 / level 3 medicines	Exposed drivers	OR_a [95% CI] †
0	55,264	Reference
1	4,259	1.14 [1.06-1.22]*
2	1,829	1.30 [1.17-1.43]**
3	817	1.86 [1.59-2.16]**
>3	597	1.88 [1.58-2.25]**

† Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level and injury severity

* p<0.001, ** p<0.0001

Results from the case-crossover analysis showed a statistically significant association between the use of level 3 medicines and the risk of road traffic crash. There was no association with level 0, level 1 and level 2 medicines (Table 11).

Table 11. Case crossover analysis - Odds ratios for road traffic crashes in users of prescribed medicines.

	Exposed drivers†	OR [95% CI] ‡
Level 0	4,047	1.02 [0.98-1.07]
Level 1	2,249	1.02 [0.96-1.08]
Level 2	3,131	1.00 [0.95-1.05]
Level 3	896	1.15 [1.05-1.27]*

† drivers exposed in the case period and not exposed in the control period

‡ only considering exposure to medicine of the highest level of risk

* p<0.01

Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B, Laumon B, Salmi LR and Lagarde E, on behalf of the CESIR research group. Prescribed medicines and the risk of road traffic crashes: results of a French registry-based study. Revision submitted; Plos Medicine. (Appendix 5)

CHAPTER 2: BENZODIAZEPINE-LIKE HYPNOTICS AND THE RISK OF ROAD TRAFFIC CRASHES

Introduction

Barbiturates were the first medicines used in the treatment of sleep disturbances. Unfortunately, because of their secondary effects (severe sedation during daytime, tolerance, high abuse potential), their use was abandoned and benzodiazepines became the first-choice pharmacological treatment for the relief of sleep disturbances.

Benzodiazepines are commonly prescribed as hypnotics for the treatment of insomnia. The clinical effects (i.e. sedation) should occur during a limited time (a few hours after bedtime administration) in order to avoid any residual effect the next day. The use of benzodiazepines in the treatment of insomnia has been declining over the last decades while at the same time, the prescriptions of the non-benzodiazepine hypnotics, zolpidem and zopiclone have been increasing substantially. In Europe, zolpidem was introduced into clinical practice in 1988, zopiclone in 1985. In the United States, zolpidem was approved by the Food and Drug Administration in 1992. In the US, zopiclone is not commercially available although its active stereoisomer, eszopiclone is sold under the name Lunesta® since 2005. These rapidly acting hypnotics have been developed to avoid next-day sedation. Indeed, zolpidem and zopiclone are benzodiazepine-like hypnotics with short elimination half-lives (2.5 and 5 hours respectively). The latter molecules are chemically unrelated to benzodiazepines, despite sharing with them sedative, hypnotic, anticonvulsant, myorelaxant and amnestic effects. These effects are linked to a specific agonist activity at sites on the GABA-A receptor complex. Zolpidem is an imidazopyridine, binding preferably to the alpha-1 subunit of the receptor which is believed to mediate the sedative and hypnotic properties. This selectivity for GABA-A receptors containing alpha-1 subunits may partially explain zolpidem narrower spectrum of pharmacological effects relative to benzodiazepines (less tolerance and lack of anticonvulsant and anxiolytic properties when used at hypnotic doses). Zopiclone belongs to the cyclopyrrolone class and is less selective than zolpidem in binding to the GABA receptor subunits. [76 77]

Several pharmacoepidemiological studies have shown that patients using benzodiazepine hypnotics are at increased risk of road traffic crashes. The duration of the sedative effect partly depends on drug kinetics: long half-life benzodiazepines have been shown to be associated with an increased risk of road traffic crashes whereas, in the same study, short half-life benzodiazepines have not. [16] However, hypnotics with a short half-life can have residual effects, depending on individual responses to the drug and on the actual conditions of use. [77] Despite their importance in the sleep medicine market, there are few epidemiological studies of their effects in the scientific literature. A case-crossover study conducted in the UK showed that the use of zopiclone was associated with an increased risk of road traffic crashes (OR=4.00 [1.31-12.2]). [10] A recent Norwegian study found an increased risk of traffic crashes in drivers who had received a prescription for zopiclone as compared with non-users (SIR=2.3 [2.0-2.8]). [13] Two literature reviews on residual effects of

hypnotics recommended that users of zopiclone should be advised not to drive whereas the use of zolpidem was considered safer. [77] [78] However, zolpidem has recently been also found to be associated with an increased risk of road traffic crashes (SIR=2.2 [1.4-3.4]). [13]

Objectives

The aim of our study was to provide further insights into the impact of zopiclone, zolpidem and benzodiazepine hypnotics on the risk of road traffic crashes, using a large database extracted from national population-based registries.

Methods

Medicines and exposure periods

Zopiclone and zolpidem

In France, zopiclone is available as 3.75 mg and 7.5 mg pills while zolpidem is only dispensed as 10 mg divisible pills. Exposure duration was estimated from the number of drug boxes dispensed and the number of pills in each box. For elderly people (>65 years old) taking zolpidem, it is recommended to reduce the dose to 5 mg so the duration of the estimated exposure period was doubled for this population. [79]

Benzodiazepine hypnotics

Treatment duration for each benzodiazepine hypnotic was estimated using median values from the EPPM survey on medicine prescription in France.

Concomitant exposure

We have previously shown that users of level 2 and 3 medicines were at higher risk of being responsible for the crash. [80] Consequently, analyses were adjusted for the use of other medicines grouped according to the French classification system. The exposure duration was estimated as described above for benzodiazepines.

Descriptive analysis

The frequencies of exposures to zopiclone, zolpidem or benzodiazepine hypnotics were compared according to individual and crash characteristics in a bivariate analysis, using Chi-squared tests. Multivariate analysis was performed by logistic regression.

Prescription patterns

We explored the number of dispensations in the six months before the crash to see if there were any differences between zolpidem and zopiclone.

Responsibility analysis

The model included terms for age, gender, socioeconomic category, day of week and time of crash, vehicle type, injury severity, blood alcohol level, concomitant treatments and chronic long-term disorders.

Case-crossover analysis

In France, no more than 30 day's worth of treatment with benzodiazepines may be dispensed by pharmacies, so the duration of the wash-out period was 30 days.
The duration of the wash-out period for zopiclone and zolpidem was determined by the 95th percentile of the exposure period distribution. This was computed from the estimation of exposure distribution described above (number of pills*number of boxes) in all subjects exposed to these medicines. This led to a wash-out period of 56 days for the two medicines. (Appendix 6)

Results

Table 12 shows that exposures were more frequent among women, drivers aged more than 45 years and retired or unemployed drivers. Proportions of exposed drivers were also higher among those under the influence of alcohol. Hypnotic exposures were more likely among drivers involved in single-vehicle crashes, occurring on highways and, in the case of benzodiazepines, occurring in the morning.

Table 12. Exposure to zopiclone, zolpidem and benzodiazepine hypnotics on the crash day according to drivers and crashes characteristics

	N	Exposed to zopiclone	p† (p)‡	Exposed to zolpidem	p† (p)‡	Exposed to BZD	p† (p)‡
		n (%)		n (%)		n (%)	
	72,685	455 (0.6)		685 (0.9)		289 (0.4)	
Gender			<0.0001 (0.0026)		<0.0001 (<0.0001)		<0.0001 (<0.0001)
Men	49,770	267 (0.5)		375 (0.8)		161 (0.3)	
Women	22,915	188 (0.8)		310 (1.4)		128 (0.6)	
Age			<0.0001 (<0.0001)		<0.0001 (<0.0001)		<0.0001 (<0.0001)
< 18	3,055	2 (0.1)		0 (0.0)		0 (0.0)	
18-24	14,814	19 (0.1)		18 (0.1)		14 (0.1)	
35-34	16,666	56 (0.3)		84 (0.5)		27 (0.2)	
35-44	15,488	104 (0.7)		122 (0.8)		73 (0.5)	
45-54	11,796	136 (1.2)		159 (1.4)		97 (0.8)	
55-64	5,990	71 (1.2)		130 (2.2)		48 (0.8)	
65-74	2,837	36 (1.3)		108 (3.8)		13 (0.5)	
≥ 75	2,039	31 (1.5)		64 (3.1)		17 (0.8)	
Socio-economic category			<0.0001 (0.0144)		<0.0001 (<0.0001)		<0.0001 (<0.0001)
Higher managerial and professional occupations	2,784	16 (0.6)		19 (0.7)		8 (0.3)	
Intermediate occupations	24,984	125 (0.5)		175 (0.7)		70 (0.3)	
Workers	11,887	40 (0.3)		61 (0.5)		33 (0.3)	
Retired	6,449	94 (1.5)		200 (3.1)		52 (0.8)	
Unemployed	3,021	34 (1.1)		49 (1.6)		20 (0.7)	
Other/missing	16,014	124 (0.8)		165 (1.0)		95 (0.6)	
Student	7,546	22 (0.3)		16 (0.2)		11 (0.2)	
Injury severity			0.0953 (0.0180)		0.0251 (0.0073)		0.1839 (0.1428)
Unhurt	19,093	96 (0.5)		157 (0.8)		61 (0.3)	
Slightly injured	26,327	176 (0.7)		258 (1.0)		113 (0.4)	
Seriously injured	25,864	173 (0.7)		248 (1.0)		107 (0.4)	
Killed	1,401	10 (0.7)		22 (1.6)		8 (0.6)	
Alcohol			<0.0001 (<0.0001)		<0.0001 (<0.0001)		0.0002 (<0.0001)
< 0.5	58,700	318 (0.5)		528 (0.9)		213 (0.4)	
0.5-1.2	1,354	15 (1.1)		23 (1.7)		10 (0.7)	
1.2-2.0	1,392	24 (1.7)		27 (1.9)		14 (1.0)	
> 2	1,320	21 (1.6)		22 (1.7)		8 (0.6)	

Table 12. (continued)

	N	Exposed to zopiclone	p† (p)‡	Exposed to zolpidem	p† (p)‡	Exposed to BZD	p† (p)‡
		n (%)		n (%)		n (%)	
Time of day			0.1441 (0.6426)		0.0005 (0.8779)		0.0033 (0.0188)
04.00 - 08.59	11,001	56 (0.5)		85 (0.8)		36 (0.3)	
09.00 - 11.59	9,804	77 (0.8)		121 (1.2)		59 (0.6)	
12.00 - 17.59	28,895	178 (0.6)		297 (1.0)		120 (0.4)	
18.00 - 22.59	18,696	120 (0.6)		147 (0.8)		63 (0.3)	
23.00 - 03.59	4,289	24 (0.6)		35 (0.8)		11 (0.3)	
Accident type			0.0265 (0.1320)		0.0143 (0.0315)		0.0118 (0.0474)
1 vehicle							
Highway	1,303	8 (0.6)		19 (1.5)		12 (0.9)	
Secondary road	7,896	65 (0.8)		92 (1.2)		42 (0.5)	
Urban	4,941	39 (0.8)		61 (1.2)		20 (0.4)	
≥ 2 vehicles							
Highway	3,827	20 (0.5)		35 (0.9)		14 (0.4)	
Secondary road							
Intersection	6,313	28 (0.4)		48 (0.8)		16 (0.3)	
No intersection	23,129	142 (0.6)		193 (0.8)		80 (0.4)	
Urban							
Intersection	11,973	59 (0.5)		114 (1.0)		48 (0.4)	
No intersection	11,879	84 (0.7)		112 (0.9)		52 (0.4)	

Reference group=not exposed to the medicine considered

† Bivariate analysis

‡ Multivariate analysis, model computed for 61,567 drivers without missing values

Exposure to zolpidem was associated with an increased risk of being responsible for a crash (OR=1.28 [1.07-1.53]), whereas exposure to zopiclone was slightly associated with a decreased risk (OR=0.78 [0.64-1.00]) and there was no association for benzodiazepine hypnotics (OR=1.24 [0.95-1.63]) (Table 13). We did not find any interaction between the use of the medicines of interest and the adjustment variables.

Table 13. Odds ratios for responsible road traffic crashes in users of zopiclone, zolpidem and benzodiazepines

	Exposed drivers	OR [95% CI] †	Exposed drivers ‡	OR [95% CI] §
Zopiclone	455	1.17 [0.97-1.41]	378	0.78 [0.64-1.00]*
Zolpidem	685	1.57 [1.35-1.83]***	600	1.28 [1.07-1.53]**
BZD hypnotics	289	1.60 [1.26-2.02]***	245	1.24 [0.95-1.63]

Reference group = drivers not exposed to medicines considered

† Crude odds ratios

‡ Model computed for 62,766 drivers without missing values for the adjustment variables

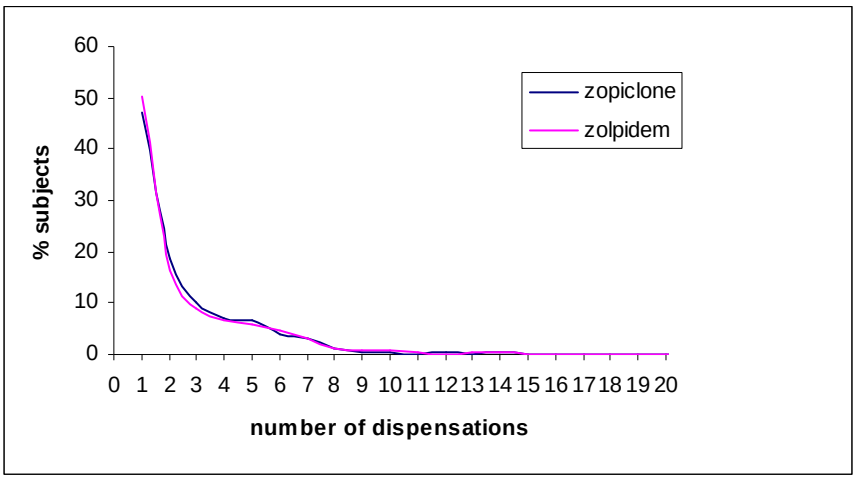
§ Odds ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, vehicle type, alcohol level, injury severity, concomitant exposure and long-term chronic diseases

* p<0.05, ** p<0.01, *** p<0.0001

Further analysis showed that, out of the 600 drivers exposed to zolpidem on the crash day, the responsibility risk was only increased in the 139 drivers exposed to zolpidem on the day of crash and who had dispensing data corresponding to more than one pill a day during the five months period preceding the crash. The corresponding odds ratio was 2.38 [1.61-3.52] versus 1.07 [0.88-1.31] for the remaining 461 patients with a lower level of consumption.

Dispensation patterns were not different between zolpidem and zopiclone. About half of the subjects exposed in the six month period before the crash, had only one dispensation. (Figure 5)

Figure 5. Dispensation patterns among all zopiclone and zolpidem users



Results from the case-crossover analysis showed a statistically significant association between the risk of road traffic crash and the use of benzodiazepine hypnotics (OR=1.42 [1.09-1.85]) and no association for zopiclone or zolpidem (Table 14).

Table 14. Case-crossover analysis - Odds ratios for road traffic crashes

	Exposed drivers[†]	**OR [95% CI]**
Zopiclone	243	1.17 [0.97-1.41]
Zolpidem	313	1.05 [0.90-1.24]
BZD hypnotics	135	1.42 [1.09-1.85]*

[†] drivers exposed in the case period and not exposed in the control period

* $p<0.01$

Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M and Lagarde E, on behalf of the CESIR research group. Benzodiazepine-like hypnotics and the risk of road traffic crashes. Submitted; BMJ. (Appendix 7)

CHAPTER 3: MEDICINES USED IN OPIOID DEPENDENCE AND THE RISK OF ROAD TRAFFIC CRASHES

Introduction

Opioids are used in different clinical indications: in pain treatment (codeine, dextropropoxyphene,…) and in opioid dependence (methadone and buprenorphine). Their effects on psychomotor and cognitive functioning have been shown to depend on the particular opioid and dose involved, the population studied, and the length of opioid use.

The agents for substitution therapy of opioid dependence have some opioid properties but they also prevent the emergence of withdrawal symptoms and reduce craving.
Methadone is indicated in the treatment of major pharmacodependence on opioids, and in particular on heroine. When they consume opioids, drug addicts seek euphoric effects using short half-life products with a high plasma concentration peak. Methadone has a long half-life and a small plasma concentration peak, decreasing craving and avoiding the euphoria sensation. [81] Moreover, because of its full agonist action, methadone has a full opioid effect and consequently this treatment is able to suppress concomitant heroin use. This later property also induce severe withdrawal syndrome because methadone produce/maintain dependence on opioids. [82]
Buprenorphine is a partial agonist and exerts weaker opioid effects which may be less satisfying to patients. However, this action appears to make buprenorphine safer in overdose. Other benefits may in particular include an easier withdrawal phase. [82]

Substitution treatments, buprenorphine and methadone, obtained a marketing authorization in France in 1995. [83] Dispensation rules are different between methadone and buprenorphine. The first prescription of methadone must be filled in by a medicine doctor in a specialized care center for drug addicts or in a healthcare center. Consequently, the first dispensation is made in the pharmacy of these centers and not in community pharmacies. This is not the case for buprenorphine. Both medicines must be prescribed on a specific form for controlled subtances.[84]

Medicines used as substitution maintenance therapy are prescribed in relatively stable doses over a long period of time (usually more than six months). [85]
It seems that some opioids impair psychomotor and cognitive functioning in healthy volunteers who have no history of opioid abuse. [45] [46] Particularly, clinical doses of buprenorphine have been reported to impair reaction time, muscle coordination, attention and short-term memory in opioid-naïve healthy volunteers. [86] [87] Likewise, single oral dose of methadone increased reaction time and impaired ocular coordination. [88] [89]
The effects on driving skills of long-term use of opioids, for the treatment of pain or opioid dependence, have been reviewed by Fishbain *et al* in 2003. [90] The majority of the studies indicated that opioids appear not to impair driving-related skills in opioid-dependent patients. Similarly, two studies showed no differences in traffic-relevant performances between patients maintained on buprenorphine or methadone and healthy controls. [91] [92]

Available epidemiological studies on the effects of opioids on the risk of road traffic crash assessed the impact of medicines used as analgesics, especially codeine. The crash risk has been found to be increased by two-fold in two studies using prescription databases. [8 18] Other studies used blood and/or urine samples to detect the presence of opioids in drivers involved in a crash.[15 21 25] Only one of these studies found an association between opiates and the risk of crash (OR=8.2 [2.5-27.3]).[25] In such designs, no distinction can be made between licit and illicit use.

Some epidemiological studies are available on methadone maintenance and road traffic crashes or traffic violations.[90] They were conducted in the United States in the 70's. A study comparing 798 methadone maintained patients to 579 controls showed no differences neither in convictions for motor vehicle violations, nor in road traffic crashes rates. The rate of road traffic crashes in these patients was not different from the rate for New York State. [93] In 1977, Maddux *et al* showed that methadone maintenance was not associated with road traffic crashes in Texas. [94] Another study did not evidence any differences in crashes and driving convictions rates between 448 patients in a methadone treatment program and 182 controls. [95] These studies are old and there is no data on the impact of buprenorphine.

In France, no epidemiological data are available since buprenorphine and methadone obtained their marketing authorizations in 1995 only.

Objectives

The objective of the present study was to provide further data in order to improve current knowledge on the risk of road traffic crashes among users of substitution maintenance treatments.

Methods

Medicines and exposure periods

Methadone and buprenorphine

French legislation imposes a strict framework for the prescription and dispensation of these medicines. Methadone is prescribed on a special form, for no more than 14 days, non renewable. Buprenorphine is also prescribed on a special form, for a maximum of 28 days, non renewable. Usually, pharmacists are allowed to dispense 7 day's worth of treatment with methadone or buprenorphine except if the practitioner mentioned "to dispense at once". [84]

The exposure period was estimated from the most frequently observed delay between two dispensations as measured in our database. This delay proved to be 7 days for the two medicines, which corresponds to the legislation. (Appendix 8)

Concomitant exposure

We previously showed that users of level 2 and 3 medicines were at higher risk of being responsible for the crash.[80] Consequently, analyses were adjusted for the use of other medicines grouped according to the French classification system.

Descriptive analysis

The frequencies of exposures to methadone or buprenorphine were compared according to individual and crash characteristics in a univariate analysis, using Chi-squared tests or Yates' correction when expected frequencies were less than 5 and more than 3. Multivariate analysis was performed by logistic regression.

Responsibility analysis

The model included terms for age, gender, socioeconomic category, time of crash, season, region of France where the crash occurred (North or South of France), location, vehicle type, injury severity, blood alcohol level, concomitant treatments and chronic long-term disorders.

Case-crossover analysis

The duration of the wash-out period for methadone and buprenorphine was determined by the 95th percentile of the observed durations between two dispensations for each subject. The wash-out period was 35 days for buprenorphine and 22 days for methadone. (Appendix 8)

Results

Exposures were higher among men, young drivers and uneducated drivers. Proportions of exposed drivers were also higher among those under the influence of alcohol and using other medicines of in the level 3 group according to the French classification. (Table 15)

Table 15. Exposure to buprenorphine or methadone on the crash day according to drivers and crashes characteristics

	N	Exposed n (%)	p[†]	p[‡]
	72,685	196 (0.3)		
Gender			<0.0001	0.0007
Men	49,770	167 (0.3)		
Women	22,915	29 (0.1)		
Age			<0.0001	<0.0001
< 29	25,026	73 (0.3)		
29-38	15,701	88 (0.6)		
39-48	14,700	33 (0.2)		
≥ 49	17,258	2 (0.01)		
Socio-economic category			<0.0001	<0.0001
Professional driver	2,283	8 (0.4)		
Independent occupations	2,438	2 (0.1)		
Higher and other intermediate occupations	22,659	33 (0.1)		
Workers and farmers	12,273	73 (0.6)		
Unemployed and retired	9,470	29 (0.3)		
Other/missing	16,014	48 (0.3)		
Student	7,546	3 (0.04)		
Injury severity			<0.0001	0.1191
Unhurt	19,093	40 (0.2)		
Slightly injured	26,327	61 (0.2)		
Seriously injured	25,864	81 (0.3)		
Killed	1,401	14 (1.0)		
Alcohol			<0.0001	0.0216
< 0.5	58,700	126 (0.2)		
0.5-1.2	1,354	10 (0.7)		
1.2-2.0	1,392	12 (0.9)		
> 2	1,320	11 (0.8)		
Level 2 medicines			<0.0001	0.9618
Non exposed	64,613	196 (0.3)		
Exposed	8,072	0 (0.0)		

Table 15. (continued)

	N	Exposed n (%)	p†	p‡
Level 3 medicines			<0.0001	<0.0001
Non exposed	70,703	147 (0.2)		
Exposed	1,982	49 (2.5)		
Day of week			0.4878	0.1208
Week	53,885	152 (0.3)		
Saturday	10,565	23 (0.2)		
Sunday	8,235	21 (0.3)		
Time of day			0.0011	0.5555
05.00 - 10.59	16,580	33 (0.2)		
11.00 - 13.59	11,430	29 (0.3)		
14.00 - 19.59	32,740	78 (0.2)		
20.00 - 22.59	6,936	31 (0.4)		
23.00 - 01.59	3,154	17 (0.5)		
02.00 - 04.59	1,845	8 (0.4)		
Region			0.0009	0.0002
North	35,167	118 (0.3)		
South	37,518	78 (0.2)		
Accident type			0.0002	0.1817
1 vehicle				
Highway/secondary road	9,199	45 (0.5)		
Urban	4,941	18 (0.4)		
≥ *2 vehicles*				
Highway	3,827	6 (0.2)		
Secondary road				
Intersection	6,313	9 (0.1)		
No intersection	23,129	49 (0.2)		
Urban				
Intersection	11,973	32 (0.3)		
No intersection	11,879	36 (0.3)		

Reference group=not exposed to the medicine considered

† Bivariate analysis

‡ Multivariate analysis, model computed for 61,567 drivers without missing values

Forty nine drivers (25% of the 196 buprenorphine and/or methadone users) were exposed to one or more other nervous system medicines on the day of crash, compared to only 2.7% of non-exposed drivers (1,933/72,489). These other medicines used concomitantly to substitution maintenance treatments are listed in Table 16.

Table 16. Level 3 medicines used concomitantly on the day of crash

Medicine (ATC class)	Exposed drivers*
Fentanyl (N02AB03)	1
Pipotiazine (N05AC04)	1
Diazepam (N05BA01)	10
Oxazepam (N05BA04)	10
Potassium clorazepate (N05BA05)	6
Flunitrazepam (N05CD03)	6
Lormetazepam (N05CD06)	3
Zopiclone (N05CF01)	7
Zolpidem (N05CF02)	8
Hypnotics and sedatives in combination, excl. barbiturates (N05CX)	3
Meprobamate, combinations (N05CX01)	4

* Some drivers were exposed to several other nervous system medicines

Adjusted responsibility analysis showed a two-fold increased risk associated to the use of substitution maintenance therapy (Table 17).

Table 17. Odds ratios for responsible road traffic crashes in users of buprenorphine and/or methadone

	Exposed drivers	OR [95% CI] †	Exposed drivers ‡	OR [95% CI] §
Buprenorphine	133	2.87 [1.97-4.19]***	111	2.16 [1.39-3.36]**
Methadone	61	2.33 [1.31-3.96]*	50	1.93 [1.03-3.62]*
Buprenorphine and/or methadone	196	2.78 [2.04-3.80]***	159	2.19 [1.51-3.16]***

Reference group = drivers not exposed to medicines considered

† Crude odds ratios

‡ Model computed for 62,766 drivers without missing values for the adjustment variables

§ Odds ratios adjusted for age, gender, socioeconomic category, region, location, time of day, month, vehicle type, alcohol level, injury severity, concomitant exposure and long-term chronic diseases

* $p<0.05$, ** $p<0.001$, *** $p<0.0001$

The case-crossover analysis found no association between exposure to buprenorphine and/or methadone and the risk of road traffic crash (Table 18).

Table 18. Case-crossover analysis - Odds ratios for road traffic crashes

	Exposed drivers[†]	**OR [95% CI]**
Buprenorphine and/or methadone	97	1.26 [0.93-1.70]

[†] drivers exposed in the case period and not exposed in the control period

DISCUSSION

The process of national ID extraction and matching led to the inclusion of 72,685 drivers involved in an injurious road traffic crash, giving unprecedented statistical power for a study on the impact of medicines on the risk of road traffic crashes. However, due to the inclusion procedures, selection biases may have arisen.

Police reports are supposed to be filled in by police forces for each road traffic crash with personal injury and the information is computerized in the police national database of injurious crashes. It is recognized that these data are incomplete. Indeed, some police reports are not sent to TransPV. Conversely, some scanned police reports are not coded in the national database of injurious crashes. Usually, the ratio PV/BAAC is around 91% and this is the figure we obtained in our study (210,818/231,979).

In our study, for 10% of the individuals identified in police reports, the corresponding BAAC record was not found, meaning that in some cases, the BAAC was partially filled in (the crash can be found but not the individual involved) or not filled in at all.
Secondly, police forces tend to report the most severe crashes. An analysis of selection biases in police forces records showed that there is an under-reporting of victims of single-vehicle crashes and of cyclists. Seriously injured victims are less under-reported. However, the appreciation of injury severity by police forces often exaggerates the victim's condition. [96]
Regarding this information, the inclusion rate of 18.5% we estimated from the number of drivers registered over the study period in the police national database of injurious crashes may be over-estimated since the real number of road traffic crash victims is unknown.

The national ID is present in police reports in only 28% of drivers and the automatic OCR software allowed the extraction of 79% of them.
The comparison between drivers included by means of their national ID and non-included drivers showed that injury severity is associated with the probability of being part of the study. Indeed, these victims are more likely to be admitted to hospital so their healthcare number is more frequently noted in the police report.

Thus, as a consequence of selection biases in police records and as a result of our inclusion procedure, our sample slightly over- represents drivers injured in severe crashes.

Medicine exposure was ascertained from computerized records of reimbursed prescriptions filled at the pharmacy. These data were not subject to underreporting, a major problem encountered when medicine exposure data is self-reported. Other studies using patient-derived data and the same dispensation database showed that the healthcare insurance data are reliable indicators of actual exposure for chronically used medicines, less for episodically used medicines. [97] Dispensing dates were considered in this study as a surrogate for actual consumption. We did not know if the medicines were actually ingested. Non-compliance, which we were not able to check, would therefore result in exposure

misclassification. We assumed that the exposure period started on the day after dispensing, as dispensing on the day of crash may have been a consequence of the crash. Exposure to self-medication drugs can not be estimated from the healthcare insurance database. However, less than 15% of units sold in France correspond to non-reimbursable medicines and most of these products have no or negligible influence on the ability to drive. Finally, medicines prescribed in the hospital are not available in the Health Insurance registry. However, most of the patients receiving such a prescription may have been exposed while hospitalized and consequently would not have drive under the influence of these medicines.

Underlying health conditions may influence the risk of crash for a driver. The relative roles of the disease itself and medicines used to treat this disease are difficult to disentangle.
In the healthcare insurance database, data on chronic long-term diseases were available with start and end dates. We were thus able to determine if drivers suffered at crash time from one the 30 diseases from the ALD30 list. This factor was taken into account in responsibility analyses which were adjusted for the presence of long-term diseases.
Moreover, by its particular design, the case-crossover analysis allows the adjustment for chronic characteristics, including chronic diseases that may not be listed as ALD. The choice of sufficiently short wash-out periods may avoid the influence of fluctuations in some disorders.
However, the effect of acute diseases can not be assessed by these two methods. As a consequence, it seems important to understand the mechanisms of action of medicines and of the disease itself that may have an impact on driving abilities in order to interpret the results found in the present study.

Data on alcohol status at the time of crash was available for approximately 86% of the drivers. It should be noted that the presence of alcohol may not be tested in drivers involved in slight injurious crashes; this variable may thus be underestimated. Moreover, drivers who had a negative breath test were not tested for precise blood alcohol concentration which is supposed to be less than 0.5g/L. Information about illicit drug use was not available in any database.

The design of this study overcomes many of the difficulties of selecting an appropriate control group. The two analyses used in this study are complementary and are both useful to interpret the potential impact of a medicine on the risk of road traffic crash.
Responsibility analysis is a real strength of the study as it allows for the comparison of cases and controls that share the same characteristic of being drivers. The reliability of the method used in our study has been previously validated and discussed (see “Methods” section, “Responsibility analysis” sub-heading). The strong dose-effect relationship found in our study between alcohol level and responsibility is a further indirect validation of the method.
The case-crossover design is appropriate for transient exposures. An individual taking a medicine throughout the study period would have the same exposure at the time of crash as in

the previous control period. Thus, a case-crossover study is likely to underestimate the risk associated with chronic treatments. However, the responsibility analysis is able to capture this risk. This latter method is more likely to estimate a risk associated to global driver behaviors and characteristics.

In a first step, we were interested in the assessment of the reliability of the French classification system. We evidenced an increased risk of being responsible for a crash for users of prescribed medicines defined as presenting a risk of level 2 or level 3 according to the French classification. The fraction of road traffic crashes attributable to levels 2 and 3 medicine use was 3.3% [2.7%-3.9%]. The within-person case-crossover analysis showed that drivers were more likely to be exposed to level 3 medicines on the day of crash than on a control day, 30 days earlier (OR=1.15 [1.05-1.27]).

In the responsibility analysis, after adjustment for crash and individual variables, the risk of being responsible for the crash was lowered for level 3 medicines, the association remaining significant (from 1.56 [1.42-1.71] to 1.25 [1.12-1.40]). The crude risk measured for level 3 medicines was thus partly related to these variables and particularly to a co-consumption of alcohol and level 2 medicines. In the case of level 2 medicines, the adjustment did not have such an important effect (from 1.24 [1.19-1.30] to 1.31 [1.24-1.40]). We showed that the more the number of medicine of level 2 and/or level 3 used is important, the higher the risk is. The protective effect of level 0 medicines could be explained by the treatment of acute medical conditions that may lead to an increased risk of being responsible for the crash. Indeed, a number of specific physical and/or psychological conditions are likely to influence driving ability.

The fraction of road traffic crashes attributable to level 2 medicines was higher than the fraction attributable to level 3 medicines (3.0% [2.4%-3.5%] and 0.7% [0.4%-0.9%] respectively). This is explained by the consumption rates of level 2 medicines which are much higher than consumption rates of level 3 medicines. Indeed, while medicines found in level 3 only belong to the psycholeptic class, level 2 includes several therapeutic classes and some of them are highly prescribed.

Various medicines are classified in level 2. The effect we found for psycholeptics and psychoanaleptics is concordant with others studies. The results on drugs used in diabetes, antiepileptics and other nervous system drugs are of interest and deserve further investigation. For some of the ATC classes in this level, the association in the responsibility analysis was not significant; however, the number of exposed drivers to antihypertensives, muscle relaxants, anti-Parkinson drugs and antihistamines for systemic use, was small. Despite of a relatively large number of subjects exposed to analgesics, we found no association with the risk of being responsible for a crash.

Of note, we were surprised to find no interaction between alcohol levels reported by police forces and medicines, while alcohol is known to potentiate medicine effects.

The respective role of disease and the medicines used to treat it is difficult to detangle. After adjustment for the presence of a long-term chronic disease, results from the responsibility analysis did not suggest an important confounding effect of the underlying conditions, the odds ratio estimates remaining slightly the same. In the case-crossover method, each subject is his own control and confounding due to individual factors is therefore eliminated, particularly fixed characteristics such as chronic diseases. Only benzodiazepine hypnotics proved to be however associated with the risk of crash in the case-crossover analysis.

The use of level 3 medicines was found to be associated with an increased risk of road traffic crashes both in the responsibility analysis and in the case-crossover analysis. Hypnotics and sedatives, mainly representing level 3 medicines, can be used on an acute basis which may explain why their impact on road traffic crashes are detected with the case-crossover analysis. However, we found no effect of level 2 medicines in the case-crossover analysis. The effect of chronic exposure can not be assessed by a case-crossover design. Indeed, an individual using a medicine throughout the study period would be exposed on the crash date and on the control day. Our results on level 2 medicines are therefore likely to be related to the impact of chronic medicine consumption, i.e. mainly drugs used in diabetes, opioids, antiepileptics, anxiolytics and antidepressants.

Results from the preliminary study showed that benzodiazepine derivative drugs used as hypnotics are associated with the risk of being responsible for a crash (OR=1.29 [1.13-1.47]) and in the first study, we found an increased risk for level 3 medicines mainly represented by hypnotics and sedatives. Consequently, we decided to further study the impact of benzodiazepine-like hypnotics (zolpidem and zopiclone), on the risk of road traffic crashes.

Zolpidem users were at increased risk of being responsible for their crash, and more particularly the small sample of those with a high consumption level in the past 5 months. In fact, the association found was totally explained by the risk of this small sample of high level zolpidem users. No such association was found for zopiclone or benzodiazepine hypnotic users. The case-crossover analysis showed that the risk of crash was increased in users of benzodiazepine hypnotics.

Exposure to benzodiazepine hypnotics were higher in drivers involved in single vehicle crashes, on highways and in the morning, suggestive of crashes due to sleepiness. [98] These medicines may thus have carry-over effects in the morning. Such a pattern was not observed for zopiclone and zolpidem, reinforcing the idea that these medicines do not have residual effects in the morning.

The presence of insomnia, for which hypnotics are prescribed, and its severity is not recorded in any database so there may be potential confounding by indication. However, the effects of insomnia should be the same for all drugs used for insomnia, and should not influence differences between drugs used for the same indication, unless there is channeling of more severe cases to one medicine or another.

The use of benzodiazepine hypnotics was not associated with the risk of being responsible for a crash, but an association with the risk of being involved in a crash was found in the case-crossover analysis (OR=1.42 [1.09-1.85]). These results suggest a residual effect of these medicines following an acute exposure. The latter result is consistent with the large case crossover study done in the UK in 1992-1995 which measured an odds ratio of 1.62 [1.24-2.12] for all benzodiazepines. However, a strong association was also found with zopiclone consumption in the same study.[10] Despite a longer half-life than zolpidem, zopiclone did not increase the risk of being responsible for a crash whereas zolpidem did. A review article on residual effects of hypnotics on driving abilities concluded that zopiclone had no advantage over benzodiazepines whereas driving after zolpidem intake was considered safer. [78] However, the magnitude of impairment may depend on various factors including dosage and time after administration. Zolpidem has been shown to have a potential for abuse and inappropriate use (high doses, daytime consumption, stimulant action). [99] The high risk we found for users who had more than one pill of zolpidem a day dispensed over the five months before the crash led us to think that the difference observed between zolpidem and zopiclone relies on their usage pattern. A study of forged prescriptions in France conducted between 2001 and 2004 showed that 10.2% of the suspected prescription concerned zolpidem while only 4.1% concerned zopiclone. [100] Moreover, in our database, dispensation patterns appeared to be slightly the same of zopiclone and zolpidem, supporting the idea that there may be a difference in actual use of these medicines. In the case-crossover analysis, we found no association between zolpidem and the risk of road traffic crashes. This suggests that the prescription is not immediately followed by a risk of road traffic crash, strengthening the hypothesis that the risk is linked to overall driver behaviors, perhaps to episodic inappropriate use that could not be capture in this study because exposure periods were estimated from dispensing data. Zopiclone may be used more appropriately.

Results showed that the risk of being responsible for a crash was significantly increased in users of medicines used in opioid dependence. We thus conducted more in-depth analysis into effects of buprenorphine and methadone on the risk of crash.

Injured drivers exposed to buprenorphine and/or methadone on the day of crash, had an increased risk of being responsible (OR= 2.19 [1.51-3.16]). The case cross-over analysis did not demonstrate any association (OR= 1.26 [0.93 - 1.70]).

The healthcare insurance database contains data on reimbursed medicines which are dispensed in community pharmacies. The first prescription of methadone must be filled in by a medicine doctor in a specialized care center for drug addicts or in a healthcare center. Consequently, using the healthcare insurance database, our study misses the first prescription of methadone. Buprenorphine treatment may be initiated in specialized centers but also and mostly in community pharmacies. Moreover, some patients will never have any dispensation in community pharmacies and will be followed in these centers during their whole treatment course. While this loss information is unlikely to have biased association measures, it has consequences in exposure prevalence estimates which are therefore underestimated.

Substitution maintenance treatments may be sold on the street. The provision of takeaway doses of methadone results in problems of diversion of the medicine for illicit use by those not in treatment. [82] Buprenorphine is much more easily accessible than methadone due to less restrictive policies. Patients may consult several practitioners to acquire more prescriptions to divert buprenorphine from its therapeutic use, for themselves or for dealing purposes. Misuses and accidents have been reported (intravenous drug use, fatal overdoses…). [101] Our study analyses dispensed medicines following a prescription and is not able to differentiate the situations described above. The part of substitution maintenance prescriptions that may be used for other purposes than therapeutic use is difficult to assess. However, it has been shown that buprenorphine is one of the medicines the most frequently reported in suspicious prescriptions (8.8% of the suspect prescriptions between 2001 and 2004). [100] In addition, the healthcare insurance estimated that in 2005-2006, 25% of buprenorphine dispensations were done for the benefit of 5% of the patients, leading to a real concern about contraband networks. [101]

Other medicines may be diverted from their therapeutic use by patients under substitution maintenance therapy. Codeine could be used by opiate addicts to reduce withdrawal symptoms or to substitute for other opioid dependence. Néocodion® is a codeine preparation, available without prescription, and known to be misused by opiate addicts.[102 103] Néocodion® sales decreased since methadone and buprenorphine were authorized as substitution treatments.[84] In a survey among a French network of community pharmacies, investigating codeine use and misuse, Néocodion® has been shown to be used by subjects presenting demographic characteristics comparable to those of drug addicts looking for opiate maintenance, most of these users were known as drug addicts in the pharmacy.[103] Another study evidenced that substitution treatments were used concomitantly to Néocodion® and, in 2002, the percentage of concomitant consumption of methadone or buprenorphine was 21%.[102]

Because several medicines containing codeine are available without a prescription, the healthcare insurance database did not allow us to take into account these consumptions. We note that, in our study, buprenorphine and/or methadone users did not concomitantly use any prescribed opioid analgesic level 2 medicines on the day of their crash.

We were able to adjust for exposure to prescribed benzodiazepines. In our study, 25% of the buprenorphine and/or methadone users were estimated to be exposed to another nervous system medicine on the day of crash; most of these medicines were benzodiazepines and/or benzodiazepine-related medicines (diazepam, oxazepam, flunitrazepam, potassium clorazepate, zolpidem, zopiclone). A literature review concluded that during substitution treatment, about 30% of patients are affected by dependence on alcohol and benzodiazepines.[104] Data on alcohol level was available in the national police database of injurious crashes. Seventeen percent of drivers under maintenance substitution treatment had a blood alcohol concentration above the legal limit as opposed to 5.6% among drivers not under such treatment.

Consumption of illicit products is commonplace in maintained patients. Heroin was reported to be used in 22% to 59% of the patients during their treatment. [105] Other drugs such as cannabis, cocaine, amphetamines are also frequently reported. [106] The information about illicit drugs is theoretically reported in the national police database of injurious crashes when known. In France, the detection of drugs is mandatory in fatal road crashes only. Consequently, this information is missing in 95% of drivers involved. This variable was thus unworkable.

The descriptive analysis showed that drivers exposed to buprenorphine and/or methadone on the day of crash were more frequently men and young drivers. The demographic characteristics of these drivers are those found in other studies. [102 103]

The risk of being responsible for a crash was increased by two-fold in drivers under maintenance substitution treatment. Results were similar for buprenorphine and methadone. These treatments are often used in long-term therapies which may partly explain why no association was found by the case-crossover analysis.

All the elements described above led us to think that this study highlights the risk of a particular population more than the risk associated with particular medicine consumption. Indeed, these drivers tend to use other substances concomitantly to their treatment (alcohol, illicit drugs, other medicines prescribed or not) and may even divert buprenorphine and methadone from their therapeutic use. Moreover, experimental studies show that opioid-dependant patients are not impaired in driving performances. The risk estimated in the responsibility analysis may be related to risky behaviors more than to the treatment itself.

The case-crossover method could be useful to investigate the impact of switching from methadone to buprenorphine or conversely. However, we only identified 17 switches from one to another medicine over the six months before the crash. The statistical power was too low to study the changes in treatment.

CONCLUSION

According to our results, the French classification system seems relevant regarding medicines classified into levels 2 and 3 of risk for road traffic crashes. Even if the risk for levels 2 and 3 is similar, we believe that it is useful to differentiate these two levels. For level 2 medicines, the effect depends on pharmacodynamics and on individual susceptibility; the patient should therefore seek medical advice. For level 3 medicines, the pharmacodynamic effect is predominant, so all users are advised not to drive. The effects of level 1 medicines may be so dependent on individual susceptibility that an effect on driving abilities might be a rare event. The relevance of this level should therefore be questioned.

The study of benzodiazepine-like hypnotics (zolpidem and zopiclone) provides further insights on the impact of these medicines on traffic safety. While driving is considered safe the morning following bedtime administration of zolpidem, we observed an increased risk of traffic crash among zolpidem users. Their road traffic crash risk should be further investigated in search of potential abuse and risky driving behaviors.

In the last step, we highlighted the risk associated to particular drivers, those who are under maintenance substitution therapy. This study is the first epidemiological study on the risk of road traffic crash in maintained patients with either buprenorphine or methadone.

There is compelling evidence from the CESIR-A study that use of medicines represent an important avoidable, significant and overall moderate risk factor for road traffic crashes.

According to the limitations mentioned in the discussion part, and particularly regarding the uncertainties on current exposures at the time of crash, another study conducted in parallel with our study, in injured drivers attending emergency rooms, will bring some useful elements, comparing medicines cited in self-reports, medicines registered in the healthcare insurance database and the presence of certain substances in blood samples. The results of this study are however not available at this time.

The CESIR-A database is a useful research tool and is the largest ever built on the subject. One of the challenges was to adopt a strategy in order to address the problem of multiple statistical tests. Our strategy did not allow us to study all the molecules individually. Consequently, we are working with the biostatistic team of the U897 INSERM research center in assessing the applicability of existing statistical procedures, particularly shrinkage methods, in order to build a global model taking into account all individual molecules and a large number of interactions. Further work will also be conducted on the risk of crash associated with antidepressant and antiepileptic use. A specific analysis will be performed among pedestrians. The methodology of data collection will be reproduced over the 2009-2012 period. The aim is to set up a surveillance system to investigate the impact of newly marketed medicines and to evaluate the effect of the French warning system.

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APPENDIXES

APPENDIX 1

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THE IMPACT OF MEDICINAL DRUGS ON TRAFFIC SAFETY: A SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL STUDIES

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Key points:

- Taking benzodiazepines has been identified as a risk for road traffic crashes in several epidemiological studies. However, data are missing for other medicinal drugs.
- Main methodological issues are confounding by indication and grouping of drugs with different properties.
- Exposure assessment methods are heterogeneous, partly explaining the inconsistent literature results.

ABSTRACT

Purpose: To evaluate the quality of epidemiological research into effects of medicinal drugs on traffic safety and the current knowledge in this area.

Data sources: The bibliographic search was done in Medline electronic database using the keywords: ((accident* or crash*) and traffic and drug*) leading to 1141 references. Additional references were retrieved from the Safetylit website and the reference lists of selected studies. Original articles published in English or French, between April 1st, 1979 and July 31st, 2008, were considered for inclusion. We excluded descriptive studies, studies limited to alcohol or illicit drug involvement, and investigations of injuries other than from traffic crashes. Studies based on laboratory tests, driving simulators or on-the-road driving tests were also excluded. Eligible studies had to evaluate the causal relationship between the use of medicinal drugs and the risk of traffic crashes. Study quality was assessed by two independent experts, according to a grid adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Results: 22 studies of variable methodological quality were included. Definition of drug exposure varied across studies and depended on the data sources. Potential confounding due to the interaction between the effects of the medicinal drug and disease-related symptoms was often not controlled. The risk of motor-vehicle crashes related to benzodiazepines has been amply studied and demonstrated. Results for other medicinal drugs remain controversial.

Conclusion: There is a need for large studies, investigating the role of individual substances in the risk of road traffic crashes.

INTRODUCTION

Traffic crashes are a common cause of death in many countries. Among the numerous risk factors (eg, speed, alcohol, talking on cell phones, road infrastructures), the effect of medicinal drugs has not received sufficient attention. Assessment of effects of medicinal drugs on driving ability by laboratory tests, driving simulators or on-the-road driving tests provides helpful insights on potential impact, but only partially assesses the impact in "real life" conditions where driver behaviour, health status, and road traffic environment interact. Reports on the state of knowledge about drugs and driving were published in 1999 [1] and 2003 [2], showing an increase concern about the role medicinal drug use may play in road traffic crashes. In 2003, a European Safety Action program was set up to encourage research on the effects of medicinal drugs, in order to establish a European classification regarding road safety [3]. Two literature reviews, focusing on a few medicinal drugs (benzodiazepines, opioids, antihistamines and antidepressants), concluded that benzodiazepines represent a major traffic safety problem but remained cautious about other medicinal drugs [4 5]. The aim of this article is to review available epidemiological studies, their results and methodological issues, in order to make recommendations for further research.

METHODS

Search strategy

The bibliographic search was done in Medline electronic database using the keywords: ((accident* or crash*) and traffic and drug*). We updated the search using the Safetylit website which provides an updated literature on injury prevention with a special section on "alcohol and other drugs". The reference lists of papers considered for inclusion were scanned for any further potentially eligible studies. Original articles published in English or French, between April 1st 1979 (oldest article we included) and July 31st, 2008 (end of inclusion period), were considered for inclusion. We excluded descriptive studies, studies limited to involvement of alcohol or illicit drugs, and studies of injury risk other than in traffic crashes. Studies based on laboratory tests, driving simulators or on-the-road driving tests were also excluded. Eligible studies were those that evaluated the causal relationship between the use of medicinal drugs and the risk of traffic crashes.

Quality assessment

A reading grid was adapted from the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) [6] and from the quality assessment checklists published by Salmi [7] (see Appendix 1). Criteria covered methods of selecting participants,

data collection regarding outcomes, exposures and potential confounders, statistical methods and reported results, as well as discussion content.

Participant selection was evaluated according to the relevance of eligibility and exclusion criteria to reflect a general population of drivers, the choice of sources, the independence of selection from the event or the drug exposure, and the comparability of the reference group. We considered the way medicinal drug exposure was assessed. In studies on medicinal drug consumption and crash risk, several potential confounders should be measured and controlled in analyses. Apart from subjects' age and gender, interaction between disease-related symptoms and the effects of the medicinal drug used to treat the disease, which can both modulate the risk of crash, should be addressed. Other important variables to be measured are the number of kilometres driven in each group and the consumption of alcohol or other drugs. We assessed the relevance of statistical methods and results presentation and discussion. Two authors (EL and LO) reviewed the selected studies independently according to the grid criteria. Disagreements were referred to a third reviewer (LRS) and resolved by discussion.

RESULTS

Bibliographic search retrieved 1141 references from which 16 eligible studies were selected on the basis of their title and abstract. An additional six studies were found either from a Safetylit website search or from the reference lists of the initial 16 studies. This process led us to select 22 epidemiological studies of the impact of medicinal drugs on the risk of traffic crashes [8-29]. Their methodology and main results are presented in Table 1.

Quality of available research

Two sources for the outcome variable (the crash) are described in these studies. In eight studies, case selection was based on emergency admission to hospital for injuries related to the crash [16 18 20 21 23 26-28]. Accident record databases represented the most frequent source for identification of subjects involved in traffic crashes [8-15 17 19 22 25 29]. Drummer *et al* [11] focused on fatal crashes while two other studies only considered non-fatally injured drivers [18 27].

Case-control was the most frequent design [10 13 15-17 20 23-25 27]. Two strategies were used to select an appropriate control group, composed of drivers who have not been involved in a crash. The first method consisted of random selection from moving traffic or at petrol stations [16 20]. Selection was therefore done on a voluntary basis, which can lead to a selection bias. In the second method, control subjects were selected from the source of case data, such as health insurance records [17], driver licence records [10 13 15 19 25], general practitioner records [23] or hospital admissions [27]. Depending on the characteristics of the source population,

extrapolation to the general driver population must be done with caution, especially if there is no indication that these controls actually drive.

Among selected epidemiological studies, five were responsibility studies [11 18 19 24 26] which can be viewed as a particular case-control study. The main principle is that if a medicinal drug contributes to crash causation, it would be over-represented in drivers whose responsibility in the crash was demonstrated compared to non-responsible drivers. Responsibility analysis, based on police records, must be objective and independent of data related to medicinal drug consumption. A standardized method to determine the level of driver responsibility was described by Robertson and Drummer [30] and applied in studies by Drummer *et al* [11] and Longo *et al* [18]. The responsibility determination criteria were not described precisely in the other three studies [19 24 26].

Barbone *et al* [8] and Ray *et al* [22] used a case-crossover design, where the exposure risk to a given medicinal drug in a period immediately before the crash was compared with the exposure risk in an earlier period. Each subject was his own control and confounding due to all fixed characteristics was therefore eliminated, including genetics, personality, education, lifestyle and chronic diseases. This design, appropriate to study the effects of episodic exposure on the risk of acute events [31], is not adapted to chronic exposure.

Exposed/non-exposed studies have also been conducted, in which users and non-users are followed up for subsequent road traffic crashes [9 12 14 21 22 28 29]. Unlike case-crossover designs, these studies ensure independence of subject selection from outcome and can address chronic consumption. This is not always true in case-control studies.

Available data about medicinal drug prescription (eg, dose, treatment duration) depended on national records. The link between prescription and actual consumption is estimated in various ways. Exposure periods can be estimated according to the date of dispensation and the number of defined daily doses (DDDs) dispensed [9 12 25 29] or according to the prescribed duration of treatment when known [8 15]. Sensitivity to definition of consumption period has been tested, comparing the results obtained for a presumed exposure of seven days with fourteen days, starting the day after dispensing [9 12 14]. Incident use was defined as exposure after a non-use period to assess the effect of treatment initiation [9 14 15 21 25 28 29], as opposed to chronic consumption defined by repeated exposure [10 13 28].

Drug exposure assessment was performed by the analysis of urine or blood samples in six studies [11 16 18 20 24 27]. This method measures actual use and offers the advantage of accounting for non-prescribed medicinal drugs. The main limits are the small number of substances tested and the time period between crash and sampling which may be critical for some medicinal drugs.

McGwin *et al* [19] collected medicinal drug exposure data during a telephone interview, leading to possible bias due to self-reporting. Indeed, Honkanen *et al* [16] showed that only half of the patients in whom benzodiazepines were detected by serum analysis reported having taken these medicinal drugs.

Another issue relates to the grouping of drugs according to therapeutic class, often for reasons of statistical power. As an example, all benzodiazepines were assessed as a single class of exposure [8 11 17-20 22 27], whereas, in this class, drugs can have different pharmacokinetic properties: benzodiazepines with longer half-lives are probably more likely to be associated with an associated risk of road traffic crash [15].

Concomitant consumption of non-medicinal psychoactive substances was sometimes controlled in the analysis: illicit drugs in two studies [11 18], alcohol in five studies [11 18 20 21 24]. The frequency of driving was measured and accounted for in statistical models in only two studies [17 19]. A few studies considered the potential interaction with medical conditions [10 13 15 17 19 25]. McGwin *et al* [19] estimated the risk for angiotensin-converting enzyme inhibitors and anticoagulants adjusted for the conditions for which they are prescribed, and the same strategy was used for nonsteroidal anti-inflammatory drugs and arthritis. In the study of the effect of warfarin, adjustment was made for cardiovascular events and strokes [10]. Other studies adjusted for a summary chronic disease score based on selected prescription medications used in the management of chronic conditions [13 15 17 25].

The effects of medicinal drugs on road safety

Benzodiazepines

The impact of benzodiazepines on the risk of car crashes has been extensively considered in several studies [8 11 12 14-24 26-28]. The strength of the associations and the consistency between studies indicate that benzodiazepines are a cause of car crash risk, although part of the effect could result from the indication of benzodiazepines (sleep problems). The effects of benzodiazepines on the risk of crash have been demonstrated in the elderly [15 22], but also among younger drivers [8 14 21 28]. The effects of treatment initiation have been explored [14 15 21 28]. A cohort study about the risk of hospitalisation for traffic crash injuries showed a diminished risk with elapsed time from the new prescription fill-date [21], probably reflecting tolerance to medicinal drug effects or decreasing doses or use over time. In the case-crossover study, a dose-response relationship between benzodiazepine consumption and crash risk was described [8]. Benzodiazepine hypnotics and anxiolytics have been studied separately [8 12 21], as well as long and short half-life benzodiazepines [15] and individual drugs (eg, zopiclone, zolpidem, diazepam, lorazepam) [14 28]. Four studies did not find any significant relationship. Two of them lacked sufficient statistical power [11 17], and in the third information was obtained

via self-report [19]. In the last study, the authors note that the assay used to detect blood benzodiazepines measures certain benzodiazepines poorly, especially triazolam [24].

Antidepressants

Two studies conducted in older drivers found a significant association between the risk of being involved in a car crash and the consumption of tricyclic antidepressants (relative risk=2.2 [1.3-3.5] [22] and odds ratio=2.3 [1.1-4.8] [17]). Bramness *et al* found an increased risk for drivers who had received a prescription for any antidepressant, slightly higher for young drivers (18-34 years old), but without adjusting for the use of other narcotics and without being able to distinguish between the effects of the medicinal drugs and depression [29]. Two other studies showed no association, probably because of insufficient statistical power [19 20]. However, despite a study population of 410 306 people aged at least 18 years, Barbone *et al* [8] found no relationship with the risk of traffic crash, for selective serotonin-receptor inhibitors or for tricyclic antidepressants, suggesting the risk to be specific to older drivers.

Lithium

In a nested case-control study, the risk of being involved in an injurious motor vehicle crash for elderly people who use lithium was found to be increased two-fold. Carbamazepine, another common mood stabiliser, also used in epilepsy, was not associated with the risk of traffic crashes [13].

Opioids

Engeland *et al* [12] found that the risk of road traffic crashes was increased in users of natural opium alkaloids such as codeine, morphine and oxycodone (SIR=2 [1.7-2.4]), and that the risk was higher in the 18-54 age group. In the case-control study by Leveille *et al* [17], opioid analgesic use was also associated with an elevated crash risk in older drivers (OR=1.8 [1-3.4]). Mura *et al* [27] also found the association significant, but no distinction was made between licit and illicit use of opiates as only biological samples were used for their detection. No significant association was found by three studies which may have lacked statistical power [11 20 23], and by Ray *et al* [22]. A longitudinal study from a cohort of 13 548 French workers suggested that pain and pain treatment could be associated with the risk of crash. The authors noted, however, that severe pain is more likely to be treated and may itself be associated with poorer driving performance [32].

H1 antihistamines

A few studies explored the association between H1 antihistamines and car crashes. Skegg *et al* identified only 3 antihistamine users (5.3%) among a small sample of 57 cases [23]. In the studies by Leveille *et al* [17] and by Ray *et al* [22], both conducted in the elderly, the association was not significant. Nevertheless, Howard *et al* [33] showed that histaminergic consumption was associated with the risk of traffic crashes in professional drivers**.** There is a lack of

epidemiological data on impact of the different generations of antihistamines which have different ability to cross the blood-brain barrier and induce sedation.

Diabetic treatment

The risk of crashes for diabetic drivers is linked to degenerative complications and to hypoglycaemic seizures related to treatment. Inconsistent results have been published about the role of diabetes and its treatment in causing traffic crashes, probably because of the heterogeneity in treatment regimes [34-37]. A responsibility study conducted in the elderly did not find any association between diabetes and at-fault crash involvement and no interaction with treatment type [19 36]. Traffic injury risk has been reported to be 2.6-fold higher in older diabetic drivers, especially those treated with insulin (OR=5.8 [1.2-28.7]) but not in those using oral hypoglycaemic agents [35]. Hemmelgarn *et al* [25] found the rate ratios for current users of insulin monotherapy were 1.4 [1.0-2.0] and 1.3 [1.0-1.7] for sulfonylurea and metformin combined. The authors note the difficulty of distinguishing between medicinal drug effects and diabetes-related complications since treatment is strongly correlated with disease progression.

Cardiovascular drugs

Among the medicinal drugs considered in epidemiological studies, calcium channel blockers were not associated with an increased risk of crashes [12], and were associated with a reduced risk of at-fault crash involvement, as well as vasodilators [19]. In the latter study, anticoagulants and angiotensin-converting enzyme inhibitors were positively associated with being at-fault for a crash but the odds ratios were no longer significant after adjustment for concomitant diseases [19]. In a recent case-control study, the use of warfarin, an anticoagulant, was not associated with an elevated rate of injurious motor vehicle crash [10].

Carbamates

Carisoprodol, a muscle relaxing drug, has been considered in a pharmacoepidemiological study because of its central nervous system depressant potential. The standardised incidence ratio for being involved in a crash having been prescribed carisoprodol was 3.7 [2.9-4.8] [9].

Nonsteroidal anti-inflammatory drugs

Recently, Engeland *et al* [12] raised the question of nonsteroidal anti-inflammatory drug (NSAID) effects in the central nervous system, as they found a significant association with the risk of traffic crash (OR=1.5 [1.3-1.9]). This result could be an indicator of clinical disability in some arthritic conditions. McGwin *et al* found that NSAID association with an increased risk of at-fault involvement in crashes persisted after adjustment for arthritis which was also independently associated with crash risk in females. The authors note however that some NSAID users may be undiagnosed for musculoskeletal impairments [19].

Discussion

The 22 studies included in this systematic review were of variable methodological quality. Several different research methods were used, leading to difficulties to compare them. The sample populations were different, ranging from victims of road traffic crashes with personal injury, victims hospitalized for road traffic crash injury to fatally injured drivers. Drug exposure assessment was heterogeneous, mostly depending on available retrospective data or on the molecule selection for biological testing.

Another identified issue was related to potential confounding. Particularly, alcohol or illicit drugs interact with medicinal drugs in impairing driving abilities and were not always taken into account. Driving conditions such as day of week, time of the day, road environment are important factors too, so is the number of miles driven. These latter factors were rarely assessed and included in risk modelling. Finally, the main issue of confounding by indication is addressed in a few studies only. Consequently, it often remains unclear whether crashes occur as a result of medicinal drug consumption or of the underlying disease, a concern highlighted in a literature review on benzodiazepines and driving [38].

This systematic review highlights several fields where more epidemiological data are needed. There is a need for large studies, investigating the individual and combined role of substances in the risk of road traffic crashes. The differential effect of the older generations of medicinal drugs versus newer ones must be compared to adapt patient care. The impact on crash risk of dose changes, beginning or end of treatment, must be further investigated. As described above, some non-psychoactive medicinal drugs may alter driving abilities due to their action on physiological functions or regarding central side effects. The impact of these medicinal drugs on road traffic crash risk has hardly been assessed in epidemiological studies so far. Other studies should also be designed to assess the relative roles of disease and medication in the risk of road traffic crashes. Quantifying the risk in patients who may be under-represented in the general driving population is also of interest as they may be at high risk due to the disease itself, and to the medicinal drugs used to treat the condition (eg Parkinson's disease and dopamine agonists [39]).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Engeland *et al*, 2007 [12] Norway	Cohort Apr 2004- Sept 2005	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry <u>Exposed</u>: - 7 or 14 days starting the day after dispensing - number of DDDs dispensed <u>Unexposed</u>: - unexposed or not previously exposed to the drug or to any prescribed drug	Age Gender Other prescribed drugs	natural opium alkaloids BZD tranquilizers BZD hypnotics NSAIDs	SIR=2.0 [1.7-2.4] SIR=2.9 [2.5-3.5] SIR=3.3 [2.1-4.7] SIR=1.5 [1.3-1.9]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Gustavsen *et al*, 2008 [14] Norway	Cohort Jan 2004- Sept 2006	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - 7 or 14 days starting the day after dispensing - incident use: washout period=180 days - concurrent use allowed or not Unexposed: - to the drug or to other prescribed psychoactive drugs	Age Gender Other prescribed drugs	zopiclone + zolpidem nitrazepam flunitrazepam	SIR=2.3 [2.0-2.7] SIR=2.7 [1.8-3.9] SIR=4.0 [2.4-6.4]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Bramness *et al*, 2007 [9] Norway	Cohort Apr 2004- Sept 2005	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - prevalent use: exposure within 7 days starting the day after dispensing - incident use: washout period=180 days - concurrent use allowed or not - DDD Unexposed: - within the study period - within the washout period	Age Gender Other prescribed drugs	carisoprodol diazepam salbutamol	SIR=3.7 [2.9-4.8] SIR=2.8 [2.2-3.6] SIR=1.1 [0.6-1.8]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Bramness *et al*, 2008 [29] Norway	Cohort Apr 2004- Sept 2006	3.1 millions 18-69 years old	Registry Crash with personal injury	Registry Exposed: - prevalent use: any exposure within study - incident use: washout period=180 days - DDD Unexposed: - within the study period - within the washout period	Age Gender	Cyclic, sedating antidepressants Newer, nonsedating antidepressants	SIR=1.4 [1.2-1.6] SIR=1.6 [1.5-1.7]	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Neutel et al, 1995 [21] Saskatchewan, Canada	Cohort 1979-1986	323,658 > 20 years old	Registry Hospitalization for crash injury	Registry Exposed: - incident use: washout period=6 months Unexposed: Absence of a prescription in the 6 months before simulated index prescription	Age Gender History of alcohol abuse Other prescribed drugs	BZD hypnotics BZD anxiolytics	OR=6.5 [1.9-22.4] OR=5.6 [1.7-18.4]	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Neutel, 1998 [28] Saskatchewan, Canada	Cohort 1979-1986	323,658 > 20 years old	Registry Hospitalization for crash injury	Registry Exposed: - incident use: washout period=6 months - repeat users: 3 prescriptions within 5 months Unexposed: Absence of a prescription in the 6 months before simulated index prescription	Age Gender Other prescribed drugs	BZDs Triazolam Flurazepam Oxazepam Lorazepam Diazepam	OR=3.1 [1.5-6.2] OR=3.2 [1.4-7.3] OR=5.1 [2.3-11.6] OR=1.0 [0.3-3.7] OR=2.4 [1.0-6.3] OR=3.1 [1.4-6.5]	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Ray *et al*, 1992 [22] Tennessee, USA	Cohort + Case-crossover 1984-1988	16,262 65-84 years old	Registry Crash with personal injury	Registry -current use (dose and duration) - indeterminate use - former use - non use	Age Gender Race Residence Year Use of medical care Non-psychoactive drugs	BZDs cyclic antidepressants antihistamines opioid analgesics	RR=1.5 [1.2-1.9] RR=2.2 [1.3-3.5] RR=1.2 [0.6-2.4] RR=1.1 [0.5-2.4]	Good
Barbone *et al*, 1998 [8] Tayside Region, UK	Case-crossover 1992-1995	410,306 ≥ 18 years old	Registry 19 386 drivers involved in a first road-traffic crash	Registry Exposure assessment: dose and duration	All fixed characteristics Crash characteristics	tricyclic antidepressants selective serotonin-reuptake inhibitors BZDs zopiclone	OR=0.93 [0.72-1.21] OR=0.85 [0.55-1.33] OR=1.62 [1.24-2.12] OR=4.00 [1.31-12.2]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Leveille *et al*, 1994 [17] Puget Sound, USA	Case-control 1987-1988	234 cases 447 controls ≥ 65 years old	Registry Cases: treatment for motor vehicle crash within 7 days of crash Controls: no crash injury during one year	Registry Exposure assessment: - probability quotient (quantity/days) - current use: within 60 days - past use: within 2-6 months - number of psychoactive prescribed drugs within 6 month	Age Gender Residence Chronic disease score and medical history Driving habits Race Marital status Education Diabetic receiving treatment	BZDs antidepressants opioids antihistamines	OR=0.9 [0.4-2.0] OR=2.3 [1.1-4.8] OR=1.8 [1.0-3.4] OR=0.7 [0.3-1.7]	Outstanding
Etminan *et al*, 2004 [13] Quebec	Case-control nested within a cohort Jun 1990-May 1993	5579 cases 13,300 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: - any use the year before - number of prescriptions - current use: within 60 days	Age Gender Residence Previous crash Other prescribed drugs Chronic disease score	Lithium carbamazepine	Rate Ratio=2.08 [1.11-3.90] Rate Ratio=0.83 [0.48-1.44]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Delaney *et al*, 2006 [10] Quebec	Case-control nested within a cohort Jun 1990-May 1993	5579 cases 12,911 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: - any use in the 30 days before - any use in one year - frequent use: ≥ 5 prescriptions	Age Gender Residence Previous crash Chronic disease score Other prescribed drugs CV events and strokes	warfarin	Rate Ratio= 0.74 [0.55-1.05]	Good
Hemmelgarn *et al*, 1997 [15] Quebec	Case-control nested within a cohort Jun 1990-May 1993	5579 cases 55,790 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: duration of treatment New use: washout period=3 days	Age Gender Residence Previous crash Other prescribed drugs Chronic disease score	long half-life BZDs short half-life BZDs	Rate Ratio= 1.45 [1.04-2.03] Rate Ratio= 1.04 [0.81-1.34]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Hemmelgarn *et al*, 2006 [25] Quebec	Case-control nested within a cohort Jun 1990-May 1993	5579 cases 13,300 controls 67-84 years old	Registry Cases: drivers in crashes with at least one personal injury Controls: random sample of the cohort	Registry Exposure assessment: - use during the one-year time window preceding - current exposure: use during the 30 days before - DDD and dose response	Age Gender Residence Previous crash Chronic disease score Other prescribed drugs	Insulin alone oral hypoglycaemics alone Insulin + oral hypoglycaemics Sulfonylureas Metformin Sulfonylureas + metformin Sulfonylureas + metformin (high dose)	Rate Ratio= 1.4 [1.0-2.0] Rate Ratio= 1.0 [0.9-1.2] Rate Ratio= 1.0 [0.5-2.0] Rate Ratio= 1.0 [0.8-1.1] Rate Ratio= 1.0 [0.7-1.6] Rate Ratio= 1.3 [1.0-1.7] Rate Ratio= 1.4 [1.0-2.0]	Good

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Skegg *et al*, 1979 [23] Oxford, UK	Case-control Mar 1974-Feb 1976	57 cases 1425 controls	Registry Cases: hospital admissions or deaths for injuries due to crash Controls: randomly selected from the same practice	Registry Exposure assessment: Medicinal drugs dispensed in the 3 month before	Age Gender Residence	sedatives and tranquilizers minor tranquilizers	RR=5.2 [2.2-12.6] RR=4.9 [1.8-13.0]	Average
Movig *et al*, 2004 [20] Netherlands	Case-control May 2000-Aug 2001	110 cases 816 controls	ER Cases: injured car or van drivers Controls: randomly selected from moving traffic	Urine/blood samples	Age Gender Blood alcohol concentration Other prescribed drugs Season Time of day	BZDs opiates	OR=5.05 [1.82-14.04] OR=2.35 [0.87-6.32]	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Honkanen *et al*, 1980 [16] Helsinki, Finland	Case-control 1977 (16 weeks)	201 cases 325 controls	ER Cases: injured drivers in ER within 6 hours Controls: randomly selected in petrol stations	Blood samples + interview	Day of week Hour of day Location	diazepam	found more commonly in patients than in controls p=0.03	Average
BZDand driving collaborative group, 1993 [24] France	Responsibility May 1989-July 1990	3147 subjects 2852 complete files > 16 years old	Hospital centres Injured drivers examined less than 6h after the crash	Blood samples	Age Gender Alcohol	BZDs	No association	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Mura *et al*, 2003 [27] France	Case-control Jun 2000-Sept 2001	900 cases 900 controls	ER Cases: involved in a non-fatal road crash Controls: having a driving licence and attended for any non-traumatic reason	Blood and urine (or sweat) samples	Age Gender	Opiates (licit and illicit) BZDs	OR=8.2 [2.5-27.3] OR=1.7 [1.2-2.4]	Average
Jick *et al*, 1981 [26] Seattle, USA	Responsibility Jan 1977-Dec 1978	244 people with an automobile crash 15-64 years old	Registry Hospitalization for injurious car crash	Registry Exposure assessment: At least one prescription within 3 months	Age Gender	Sedating drugs	No association	Poor
Longo *et al*, 2000 [18] South Australia	Responsibility Apr 1995-Aug 1995 Dec 1995- Aug 1996	2500 non-fatally injured drivers	Hospital crash and emergency unit Non fatal road crashes victims who survive >30 days	Blood samples	Alcohol and illicit drugs	Benzodiazepines	Significant increase in culpability	Average

Study	Design and period	Population/ Sample	Outcome variable (sources, definition)	Drug exposure (sources, assessment)	Adjustment/ Stratification/ Controlled variables	Main studied agent(s)	Results	Overall quality
Drummer *et al*, 2004 [11] 3 states of Victoria, Australia	Responsibility 1990-1999	3398	Registry Fatally-injured drivers	Forensic toxicology	Age Gender Alcohol and illicit drugs Type of crash Location Year	BZDs Opiates (licit and illicit) Other psychoactive medicinal drugs	OR=1.27 [0.5-3.3] OR=1.41 [0.7-2.9] OR=3.78 [1.3-11]	Good
McGwin *et al*, 2000 [19] Alabama, US	Responsibility + Case-control 1996	901 drivers ≥ 65 years old	Registry Responsibility: subjects involved in at least one automobile crash Case-control: comparison with drivers not involved in crashes	Questionnaire	Age Gender Other prescribed drugs Annual mileage Associated diseases	BZDs antidepressants NSAIDs ACE inhibitors anticoagulants calcium channel blockers vasodilators oral hypoglycaemics insulin	OR=5.2 [0.9-30.0] OR=0.3 [0.1-1.0] OR=1.7 [1.0-2.6] OR=1.6 [1.0-2.7] OR=2.6 [1.0-7.3] OR=0.5 [0.2-0.9] OR=0.3 [0.1-1.0] OR=1.3 [0.7-2.4] OR=0.9 [0.4-1.8]	Average

DDD=defined daily dose, BZD=benzodiazepine, SIR=standardized incidence ratio, OR=odds ratio, RR=relative risk

Table 1: Epidemiological studies of traffic crash risk and medicinal drug consumption: methodology and main results

Appendix 1: Reading grid

Criteria	Y	I	N	NA	DNK	Comment
Study design						
Objectives are clearly stated	☐	☐	☐	☐	☐	
Key elements of study design are provided	☐	☐	☐	☐	☐	
Location and dates are specified	☐	☐	☐	☐	☐	
Participants						
Cohort study						
Eligibility criteria are defined and appropriate	☐	☐	☐	☐	☐	
Exclusion criteria are defined and appropriate	☐	☐	☐	☐	☐	
Sources are described and appropriate	☐	☐	☐	☐	☐	
Selection method is described and appropriate	☐	☐	☐	☐	☐	
Selection is independent from risk of collision	☐	☐	☐	☐	☐	
Follow-up period is defined and long enough	☐	☐	☐	☐	☐	
Compared exposures are described	☐	☐	☐	☐	☐	
Reference group is appropriate	☐	☐	☐	☐	☐	
Selection procedures are identical in all exposure groups	☐	☐	☐	☐	☐	
Case-control study						
Eligibility criteria are defined and appropriate	☐	☐	☐	☐	☐	
Exclusion criteria are defined and appropriate	☐	☐	☐	☐	☐	
Sources are described and appropriate	☐	☐	☐	☐	☐	
Selection is independent of drug exposure	☐	☐	☐	☐	☐	
Definition of cases is appropriate	☐	☐	☐	☐	☐	
Controls are selected from same population as cases	☐	☐	☐	☐	☐	
Control group is appropriate	☐	☐	☐	☐	☐	
Selection procedures are identical in cases and controls	☐	☐	☐	☐	☐	
Matching is appropriate	☐	☐	☐	☐	☐	
Variables						
Drug exposure						
Data sources are described and appropriate	☐	☐	☐	☐	☐	
Choice of studied drugs is justified	☐	☐	☐	☐	☐	
Drug exposure assessment method is described and justified	☐	☐	☐	☐	☐	
Case/control status is masked when assessing exposure	☐	☐	☐	☐	☐	

Collision data

Data sources are described and appropriate	☐	☐	☐	☐	☐
Collision characteristics are accounted for	☐	☐	☐	☐	☐

Accounting for potential confounders

Age	☐	☐	☐	☐	☐
Gender	☐	☐	☐	☐	☐
Associated diseases	☐	☐	☐	☐	☐
Number of kilometres/miles driven	☐	☐	☐	☐	☐
Alcohol and other drugs	☐	☐	☐	☐	☐

Statistical methods

Sample size calculation	☐	☐	☐	☐	☐
Appropriate estimates and models	☐	☐	☐	☐	☐
Control for confounding	☐	☐	☐	☐	☐
Sensitivity analysis	☐	☐	☐	☐	☐

Results

Number of subjects reported	☐	☐	☐	☐	☐
Number of refusals reported	☐	☐	☐	☐	☐
Description of all groups	☐	☐	☐	☐	☐
Reported confidence intervals or p	☐	☐	☐	☐	☐

Discussion

Key results/study objective	☐	☐	☐	☐	☐
Limitations and possible biases discussed	☐	☐	☐	☐	☐

(Y=Yes, I=Incomplete, N=No, NA= Not Applicable, DNK=Do Not Know)

Conclusion	
Quality	
Outstanding	☐
Good	☐
Average	☐
Poor	☐

Discussion

APPENDIX 2
Standardized reports on injurious road traffic crashes - Bulletins d'Analyse des Accidents Corporels (BAAC)

1 - CARACTERISTIQUES

	Colonnes	***longueur***	***Intitulé***	***remarques***	Caractère de la variable
1	1-2	2	10		
2	3-9	7	Code Unité	cadré à gauche	
3	10-14	5	Numéro P.V.		
4	15-16	2	Numéro de feuillet		
x5	17	1	Organisme	1 - Gendarmerie 2 - Préfecture de Police de Paris 3 - C.R.S. 4 - P.A.F. 5 – Sécurité publique	
x6	**18-19**	**2**	**Jour**		
x7	**20-21**	**2**	**Mois**		
x8	**22-23**	**2**	**An**		
9	24	1	Filler[3]	A blanc	
x10	**25-26**	**2**	**Heure**		
x11	**27-28**	**2**	**Minute**		
x12	**29**	**1**	**Lumière**	**1 - plein jour** **2 - crépuscule ou aube** **3 - nuit sans éclairage public** **Nuit avec éclairage public** **4 - non allumé** **5 – allumé**	
x13	**30 à 32**	**3**	**Département**	**Code INSEE cadré à gauche**	
X14	**33 à 35**	**3**	**Commune**	**Code INSEE**	
x15	**36**	**1**	**Localisation [4]**	**1 - hors agglomération** **2 - en agglomération**	
x16	**37**	**1**	**Intersection**	**0 – non renseigné** **1 - hors intersection** **<u>En intersection ou à proximité immédiate</u>** **2 - en X** **3 - en T** **4 - en Y** **5 - à plus de 4 branches** **6 - giratoire** **7 - place** **8 - passage à niveau** **9 – autre**	

[3] Suppression de type de jour.
[4] La variable « localisation » passe de 9 à 2 modalités.

	Colonnes	*longueur*	*Intitulé*	*remarques*	Caractère de la variable
x17	**38**	**1**	**Conditions atmosphériques**	**1 – normale** **2 - pluie légère** **3 - pluie forte** **4 - neige - grêle** **5 - brouillard - fumée** **6 - vent fort - tempête** **7 - temps éblouissant** **8 - temps couvert** **9 – autre**	
x18	**39**	**1**	**Type de collision**	**Véhicule contre véhicule** **1 – frontale** **2 – par l'arrière** **3 – par le côté** **Accident impliquant au moins 3 véhicules** **4 – collisions en chaîne** **5 – collisions multiples** **Autre collision** **6 – Autre collision** **7 – Sans collision**	
19	**40 à 63**	**24**	**Adresse postale du lieu acc**		
20	64	1	Filler	A blanc	
21	**65 à 79**	**15**	**Coordonnées GPS**[5]		
22	80	1	Identifiant BAAC 2002[6]	1 – pour les BAAC 2002 issu d'un transcodage de BAAC 93. 2 – pour tous les BAAC version 2002	

2 - LIEUX

	colonnes	*longueur*	*Intitulé*	*remarques*	Caractère de la variable
1	1-2	2	**20** ou **21**		
2	3-9	7	Code Unité		
3	10-14	5	Numéro P.V.		
4	15-16	2	Numéro de feuillet		
5	17	1	Organisme	1 – Gendarmerie 2 - Préfecture de Police de Paris 3 - C.R.S. 4 - P.A.F. 5 – Sécurité publique	
6	18	1	Code route		

[5] Voir annexe sur la codification du GPS.
[6] Dans la version 1993, ce caractère était laissé à blanc.

	colonnes	*longueur*	*Intitulé*	*remarques*	Caractère de la variable
x **7**	**19**	**1**	**Catégorie**	**1 – Autoroute** **2 - Route Nationale** **3 - Route Départementale** **4 - Voie Communale** **5 - Hors réseau public** **6 - Parc de stationnement ouvert à la circulation publique** **9 – autre**	
8	20-24	5	numéro de voie	(= numéro route)	
9	25	1	2 : bis, 3 : ter	indice numérique	
10	26	1	Lettre : indice de la voie	indice alpha	
x11	**27**	**1**	**Régime de circulation**	**0 - non renseigné ou sans objet** **1 - à sens unique** **2 - bidirectionnelle** **3 - à chaussées séparées** **4 - avec voie(s) à affectation variable**	
x12	**28-29**	**2**	**Nombre total de voies de circulation**		
13	**30**	1	Filler	à blanc[7]	
x14	**31**	**1**	**Voie spéciale : Existence**	**0 - non renseigné ou sans objet** **1 - piste cyclable** **2 - bande cyclable** **3 - voie réservée**	
X15	**32**	**1**	**Profil en long**	**0 – non renseigné** **1 – plat** **2 - pente** **3 - sommet** **4 - bas de côte**	
16	33-36	4	N° borne - PR	Point kilométrique - point repère	
17	37-40	4	Distance - PR (m)	Point kilométrique - point repère	
X18	**41**	**1**	**Tracé en plan**	**0 - non renseigné** **1 - partie rectiligne** **2 - en courbe à gauche** **3 - en courbe à droite** **4 - en S**	
19	42	1	Filler	à blanc[8]	
20	**43-45**	**3**	**Largeur Terre-plein central**	**(en décimètres)**	
21	**46-48**	**3**	**Largeur route hors TPC**	**(en décimètres)**	

[7] Suppression du « marquage chaussée »
[8] Suppression de « état de la route »

	colonnes	*longueur*	*Intitulé*	*remarques*	Caractère de la variable
x22	**49**	**1**	**Etat de la surface**	**0 – non renseigné** **1 - normale** **2 - mouillée** **3 - flaques** **4 - inondée** **5 - enneigée** **6 - boue** **7 - verglacée** **8 - corps gras - huile** **9 – autre**	
x23	**50**	**1**	**Aménagement infrastructure**	**0 – non renseigné ou sans objet** **1 - souterrain - tunnel** **2 - pont - autopont** **3 - bretelle d'échangeur** **4 - voie ferrée** **5 - carrefour aménagé** **6 - zone piétonne** **7 - zone péage**	
24	**51**	**1**	**Situation de l'accident**	**0 – non renseigné** **1 - sur chaussée** **2 - sur BAU** **3 - sur accotement** **4 - sur trottoir** **5 - sur voie cyclable**	
25	52-53	2	Filler	à blanc[9]	
26	54-55	2	Filler	à blanc[10]	
27	**56-57**	**2**	**Proximité d'une école**	**00 – Non renseigné** **03 – à proximité d'une école** **99 – Non à proximité[11]**	
28	58-59	2	Filler	à blanc[12]	
29	60-80	21	Filler	à blanc	

3 - VEHICULES

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
1	1-2	2	3x		
2	3-9	7	Code Unité		
3	10-14	5	Numéro P.V.		
4	15-16	2	Numéro de feuillet		
5	17	1	Organisme	1 - Gendarmerie 2 - Préfecture de Police de Paris 3 - C.R.S. 4 - P.A.F. 5 – Sécurité publique	
6	18	1	Lettre conventionnelle		

[9] Suppression de « signalisation 1 »
[10] Suppression de « signalisation 2 »
[11] Remplacement de « environnement 1 » par « point école »
[12] Suppression de « environnement 2 »

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
7	19	1	Code route		
8	**20**	**1**	**véhicule ou conducteur en fuite**	**0 – sans objet** **1 - véhicule en fuite** **2 – conducteur en fuite[13]**	
9	**21**	**1**	**Sens de circulation**	**0 - non renseigné ou sans objet** **1 - PK ou PR croissants** **2 - PK ou PR décroissants**	
10	**22-23**	**2**	**Catégorie administrative**	**01 – bicyclette** **02 - cyclomoteur** **03 - voiturette ou tricycle à moteur** **04 - scooter immatriculé** **05 - motocyclette** **06 - side-car** **07 - VL seul** **08 - VL + caravane** **09 - VL + remorque** **10 - VU seul 1,5T <= PTAC <= 3,5T** **11 - VU (10) + caravane** **12 - VU (10) + remorque** **13 - PL seul 3,5T <PTCA <= 7,5T** **14 - PL seul > 7,5T** **15 - PL > 3,5T + remorque** **16 - tracteur routier seul** **17 - tracteur routier + semi-remorque** **18 - transport en commun** **19 - tramway** **20 - engin spécial** **21 - tracteur agricole** **99 - autre véhicule**	
11	**24-26**	**3**	**département ou pays immatriculation**	**Code INSEE cadré à gauche pour les départements,** **Code du pays cadré à gauche pour les immatriculations étrangères.**	
12	**27-28**	**2**	**Date première mise en circulation mois**		
13	**29-30**	**2**	**Date première mise en circulation année**		
14	31-32	2	Filler	à blanc[14]	
15	33-34	2	Filler	à blanc[15]	
16	35-42	8	Filler	à blanc[16]	

[13] Ajout de la modalité « conducteur en fuite », on pourra ainsi décrire un véhicule sans son conducteur.
[14] Suppression de « date du dernier contrôle technique »
[15] Idem
[16] Le « type de véhicule » passe de 8 à 15 caractères, il est repoussé en fin d'enregistrement

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
17	**43**	**1**	**Appartenant à**	**0 - non renseigné** **1 – conducteur** **2 - véhicule volé** **3 - propriétaire consentant** **4 - administration** **5 – entreprise**	
18	**44**	**1**	**Véhicules spéciaux**	**0 – non renseigné ou sans objet** **1 – taxi** **2 - ambulance** **3 - pompiers** **4 - police - gendarmerie** **5 - transports scolaires** **6 - matières dangereuses** **9 – autres**	
19	**45**	**1**	**Facteur lié au véhicule**	**0 – non renseigné ou sans objet** **1 - défectuosité mécanique** **2 - éclairage - signalisation** **3 - pneu usé** **4 - éclatement de pneu** **5 - chargement** **6 - déplacement du véhicule** **7 – incendie du véhicule** **9 – autre**	
20	46	1	filler	à blanc[17]	
21	**47**	**1**	**Assurance**	**0 – non renseigné** **1 – oui** **2 - non** **3 – non présentation**	

[17] Suppression de « chargement du véhicule »

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
22	**48-49**	**2**	**Obstacle fixe heurté**	**01 - véhicule en stationnement** **02 - arbre** **03 - glissière métallique** **04 - glissière béton** **05 - autre glissière** **06 - bâtiment, mur, pile de pont** **07 - support signalis. vertic. ou PAU** **08 - poteau** **09 - mobilier urbain** **10 - parapet** **11 - îlot, refuge, borne haute** **12 - bordure de trottoir** **13 - fossé, talus ou paroi rocheuse** **14 - autre obstacle fixe sur chaussée** **15 - autre obstacle fixe sur trottoir ou accotement** **16 - sortie de chaussée sans obstacle** **00 – sans objet**	
23	**50**	**1**	**Obstacle mobile heurté**	**0 – non renseigné ou sans objet** **1 – piéton** **2 - véhicule** **4 – véhicule sur rail** **5 - animal domestique** **6 – animal sauvage[18]** **9 - tout autre obstacle mobile**	
24	**51**	**1**	**Point de choc initial**	**0 – non renseigné** **1 – avant** **2 - avant droit** **3 - avant gauche** **4 - arrière** **5 - arrière droit** **6 - arrière gauche** **7 - côté droit** **8 - côté gauche** **9 - chocs multiples**	

[18] Dédoublement de la modalité « animal » en « animal sauvage » et « animal domestique »

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
25	**52-53**	**2**	**Manœuvre principale avant l'accident**	**00 – non renseigné** **<u>Circulant :</u>** **01 - sans changement de direction** **02 - même sens, même file** **03 - entre deux files** **04 - en marche arrière** **05 - à contresens** **06 - en franchissant le TPC** **07 - dans couloir bus dans même sens** **08 - dans couloir bus en contre sens** **09 - en insertion** **10 - en faisant 1/2 tour sur chaussée** **<u>Changement de file :</u>** **11 et 12 - à gauche et à droite** **<u>Déporté :</u>** **13 et 14 - à gauche et à droite** **<u>Tournant :</u>** **15 et 16 - à gauche et à droite** **<u>Dépassant :</u>** **17 et 18 - à gauche et à droite** **<u>Divers :</u>** **19 - traversant la chaussée** **20 - manœuvre de stationnement** **21 - manœuvre d'évitement** **22 - ouverture de porte** **23 - arrêté (hors stationnement)** **24 – en stationnement (avec occupants)**	
26	**54-56**	**3**	**Nombre d'occupants dans le T.C.**	**conducteur compris; pour les transports en commun seulement (sinon : 000)**	
27	57	1	Filler	espace séparateur (blanc)	
28	58-59	2	Filler	à blanc	
29	60	1	Filler	à blanc	
30	**61-75**	**15**	**Type de véhicule**	**Code CNIT**	
31	76-80	8	filler		

4 - USAGERS

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
1	1-2	2	4x		
2	3-9	7	Code Unité		
3	10-14	5	Numéro P.V.		

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
4	15-16	2	Numéro de feuillet		
5	17	1	Organisme	1 - Gendarmerie 2 - Préfecture de Police de Paris 3 - C.R.S. 4 - P.A.F. 5 – Sécurité publique	
6	18	1	Lettre conventionnelle		
7	19	1	Place dans le véhicule	0 – sans objet (piéton) 1 à 9	
8	20	1	Responsabilité présumée	1 responsable présumé sinon 0	
9	**21**	**1**	**Catégorie**	**1 - conducteur** **2 - passager** **3 – piéton** **4 – piéton en roller ou en trottinette**	
10	**22**	**1**	**Gravité des blessures**	**1 – indemne** **2 - tué** **3 - blessé grave** **4 - blessé léger**	
11	23-24	2	Filler	à blanc[19]	
12	25-26	2	Filler	à blanc[20]	
13	27-28	2	Filler	à blanc[21]	
14	**29**	**1**	**Catégorie socio professionnel**	**1 – conducteur professionnel** **2 – agriculteur** **3 – artisan, commerçant, prof. ind.** **4 – cad. sup., prof. lib., chef d'entr.** **5 – cadre moyen, employé** **6 –ouvrier** **7 – retraité** **8 – chômeur** **9 – autre** **A – étudiant**	
15	**30**	**1**	**Sexe**	**1 – masculin** **2 – féminin**	
16	31-33	3	Filler	à blanc[22]	
17	**34-36**	**3**	**Résidence : département ou pays**	**Code INSEE cadré à gauche pour les départements** **Code du pays cadré à gauche pour les étrangers.**	
18	**37-38**	**2**	**Mois Naissance**		
19	**39-42**	**4**	**année Naissance**		

[19] Suppression de « AIS »
[20] Idem
[21] Idem
[22] Suppression de « Nationalité »

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
20	**43**	**1**	**Facteur lié à l'usager**	**0 – non renseigné ou sans objet** **1 - malaise – fatigue** **2 - médicament - drogue** **3 - infirmité** **4 - attention perturbée** **5 – ivresse apparente**	
21	**44**	**1**	**Alcoolémie (conducteur et piéton)**	**0 – sans objet (passagers)** **1 – impossible** **2 - refusé** **3 – prise de sang** **4 - éthylomètre** **5 - résultat non connu** **6 - dépistage négatif**	
22	**45-47**	**3**	**Taux d'alcoolémie[23]**	**Si cette rubrique n'est pas rempli, elle codé à blanc. Ceci permettra de distinguer un non remplissage d'un code '0' : pas d'alcoolémie.**	
23	**48**	**1**	**Permis de conduire[24]**	**0 – non renseigné ou sans objet** **1 – valide** **2 - périmé** **3 - suspendu** **4 – conduite en auto-école** **5 - catégorie non valable** **6 - défaut de permis** **7 – conduite accompagnée**	
24	**49-50**	**2**	**mois Date d'obtention**		
25	**51-52**	**2**	**Année Date d'obtention**		
26	**53**	**1**	**Trajet**	**0 – non renseigné** **1 - domicile / travail** **2 - domicile / école** **3 - courses / achats** **4 - utilisation professionnelle** **5 - promenade / loisirs** **9 – autre**	
27	**54-58**	**5**	**1ère infraction[25]**	**CODE « NATINF »**	
28	**59-63**	**5**	**2ème infraction**	**CODE « NATINF »**	
29	**64**	**1**	**Equipements de sécurité : existence**	**1 - ceinture** **2 - casque** **3 - dispositif enfant** **4 - équipement réfléchissant** **9 - autre équipement de sécurité**	
30	**65**	**1**	**Equipements de sécurité : utilisation**	**1 - oui** **2 - non** **3 - non déterminable**	

[23] Le taux doit dorénavant être rempli même pour des alcoolémies en dessous de 0.5g/l

[24] La modalité 'apprentissage de la conduite' est dédoublée en 'conduite en auto-école' et 'conduite accompagnée'

[25] Le référentiel des infractions passe sous le format « NATINF » codé sur 5 caractères au lieu de 3 auparavant.

	colonnes	*longueur*	*intitulé*	*remarques*	Caractère de la variable
31	**66**	**1**	**Manœuvre du piéton - localisation**	**0 – non renseigné ou sans objet** **<u>sur chaussée</u>** **1 - à plus de 50 m du pass.piéton** **2 - à moins de 50 m du pass.piéton** **<u>sur passage piéton</u>** **3 - sans signalisation lumineuse** **4 - avec signalisation lumineuse** **<u>divers</u>** **5 - sur trottoir** **6 - sur accotement ou B.A.U.** **7 - sur refuge** **8 - sur contre-allée**	
32	**67**	**1**	**Manœuvre du piéton – Action**	**0 – non renseigné ou sans objet** **<u>Se déplaçant</u>** **1 - sens véhicule heurtant** **2 - sens inverse véhicule heurtant** **<u>divers</u>** **3 - traversant** **4 - masqué** **5 - jouant - courant** **6 - avec un animal** **9 - autre** **0 - non renseigné**	
33	**68**	**1**	**Piéton**	**0 – non renseigné ou sans objet** **1 - seul** **2 - accompagné** **3 - en groupe**	
34	69	1	filler	espace séparateur (blanc)	
35	70-72	3	Filler	A blanc	
36	**73**	**1**	**Drogue par dépistage**	**0 – non renseigné ou sans objet** **1 – non fait** **2 – impossible** **3 – refusé** **4 – positif pour au moins un produit** **5 – négatif pour tous produits**	
37	**74**	**1**	**Drogue par prise de sang**	**0 – non renseigné ou sans objet** **1 – non fait** **2 – impossible** **3 – refusé** **4 – positif pour au moins un produit** **5 – négatif pour tous produits** **6 – résultat inconnu**	
38	75-80	4	Filler	espace séparateur (blanc)	

APPENDIX 3

Scoring guidelines for responsibility assignment - Robertson and Drummer

	Mitigating category	*Score*
1.	**Condition of road**	
	*Sealed road**	
	Two or more lands and smooth	1
	Divided road	1
	Two or more lanes and rough	2
	Unmarked, thin and smooth	2
	Unmarked, thin and rough	3
	Unsealed road	
	Smooth	2
	Rough and/or corrugated	3
2.	**Condition of vehicle**	
	Roadworthy	1
	Unroadworthy (contribution to accident unclear)	2
	Unroadworthy (contributing to accident)	4
3.	**Driving conditions**	
	Day	
	Clear and/or cloudy	1
	* Fog and/or mist, clear and windy (>40 kph)	2
	* Visibility good and road wet	2
	Showers and/or rain	3
	Night	
	† ‡Clear	1
	‡ Cloudy	2
	Fog/mist/showers/rain/ice/wind	3
4.	**Type of accident**	
	Single-vehicle	
	No influence from other vehicles	1
	Influence from other vehicles	3
	Multi-vehicles	
	Striking vehicle attempting to avoid	2
	Striking vehicle not attempting to avoid	1
	Struck vehicle in the wrong	1
	Struck vehicle in the right	3
5.	**Witness observations**	
	No apparent reason	1
	Reckless	
	Swerving	1
	Irregular driving	1
	Negligent	
	Witnessed road infringement	1
	Lack of road sense	1
	Vehicle fault	3
	Driver not to blame	4
6.	**Road law obedience**	
	Was driver obeying road laws ?	
	Yes	3
	No	1

Mitigating category	*Score*
7. Difficulty of task involved	
Straight road or sweeping band	1
§ Accross lanes in	
Heavy traffic	2
Light traffic	1
Winding road/sharp bend/U-turn	2
Overtaking	2
Avoiding unexpected traffic	3
8. Level of fatigue	
Onlyif mentioned in police reports	2

* Add 1 if road has been newly resurfaced
† If in heavy traffic, add 1 point
‡ If not lighted, add 1 point
§ Scores 1, if under the guidance of traffic signals

APPENDIX 4

Scoring guidelines for responsibility assignment - SAM study

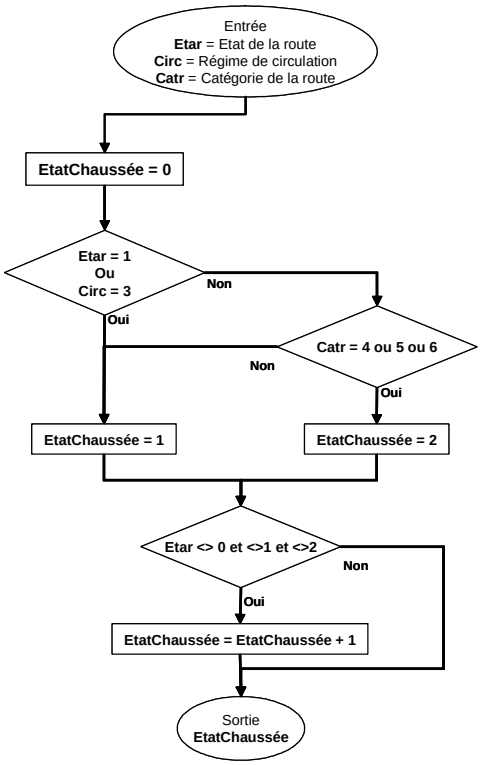

Figure 1 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié à la route.

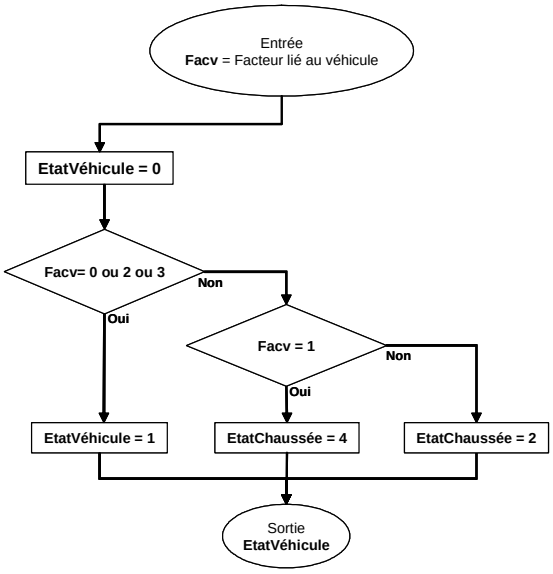

Figure 2 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié au véhicule.

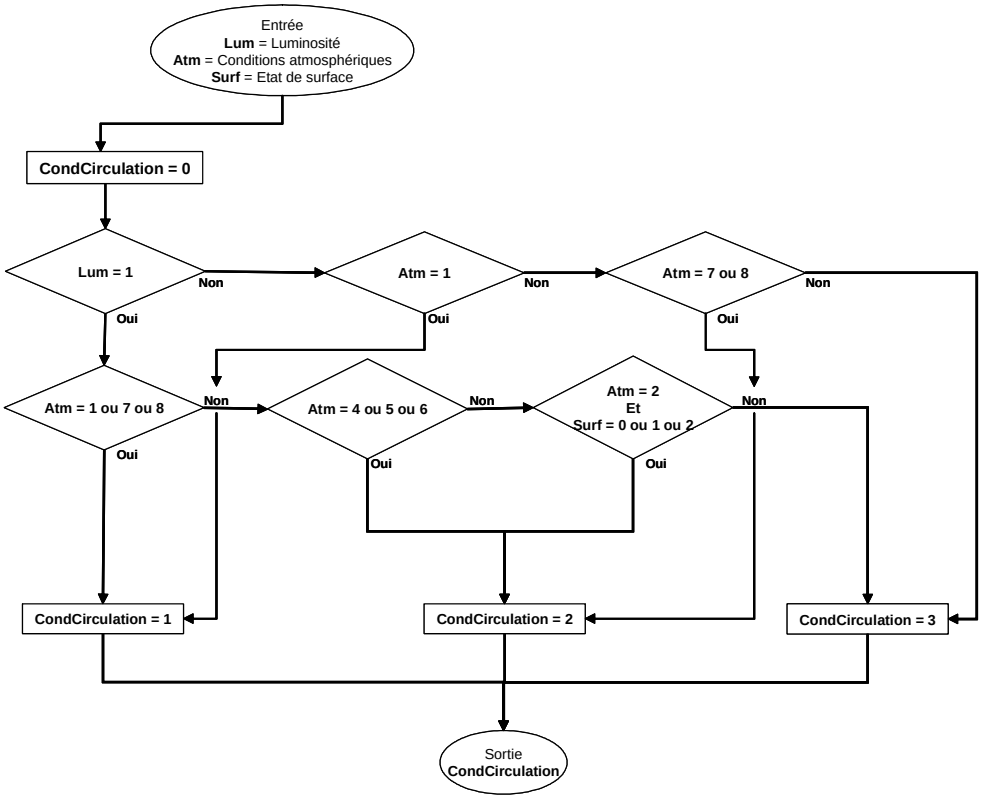

Figure 3 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié aux conditions de circulation.

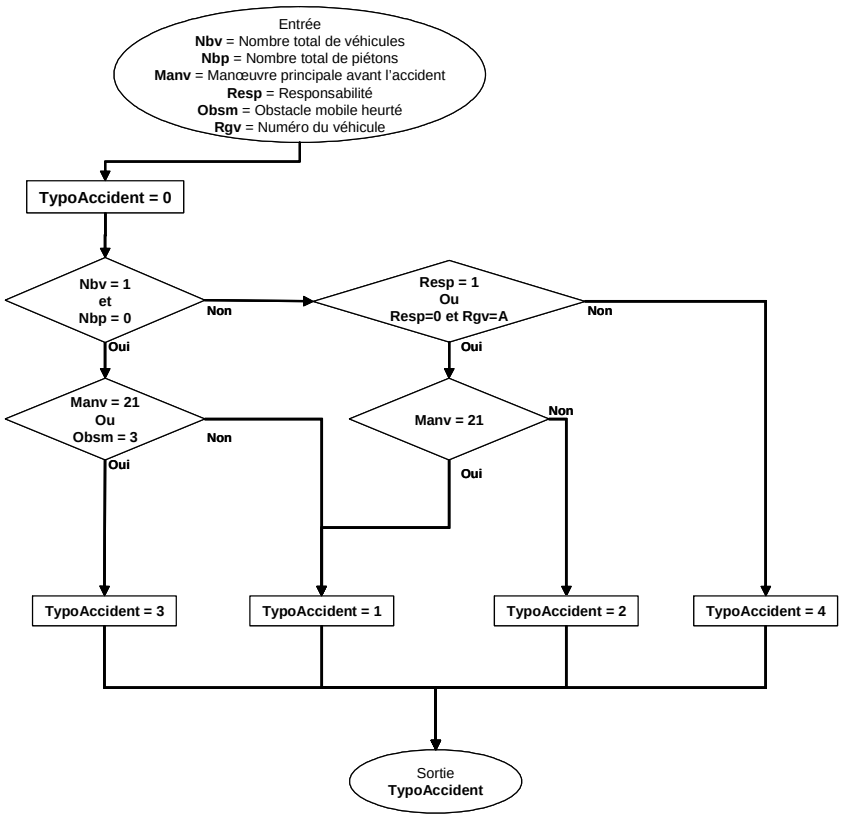

Figure 4 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié à la typologie de l'accident.

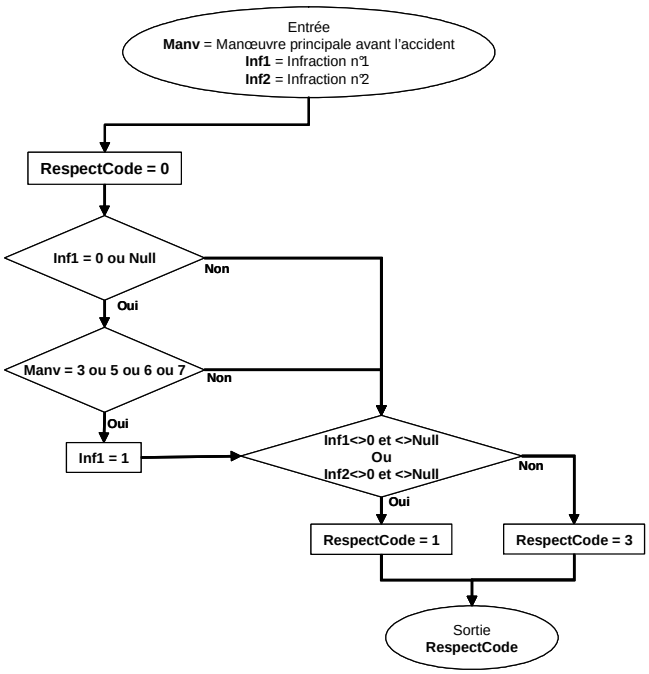

Figure 5 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié au respect du code de la route.

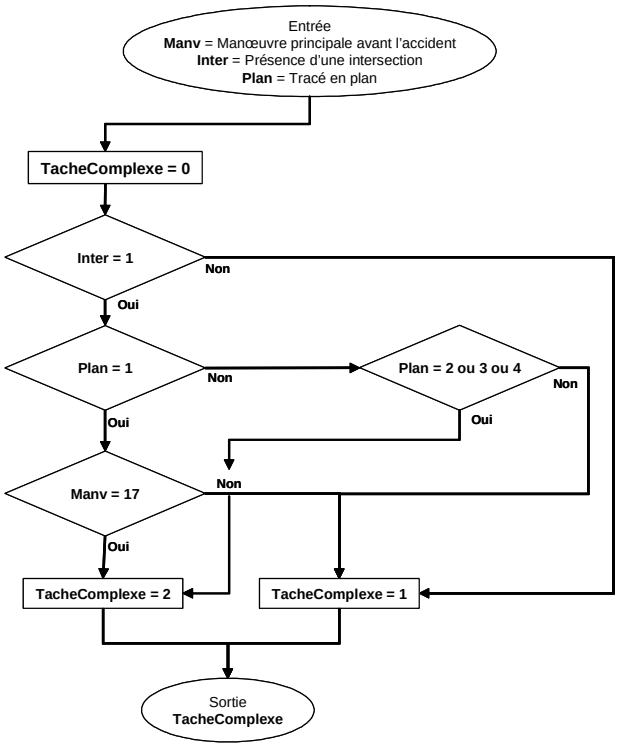

Figure 6 : Algorithme utilisé pour le calcul du score pour la classe relative au facteur lié à la complexité de la tâche effectuée par le conducteur.

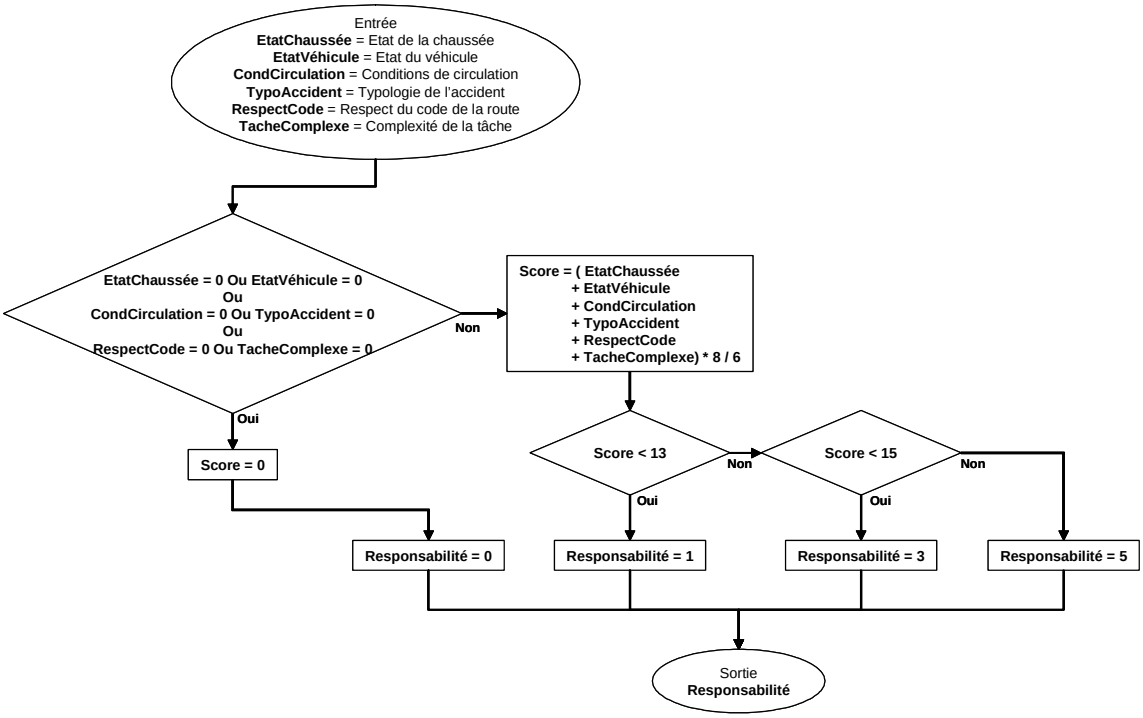

Figure 7 : Algorithme de détermination de la responsabilité à partir de l'attribution des scores.

APPENDIX 5
Revision submitted; Plos Medicine

PRESCRIBED MEDICINES AND THE RISK OF ROAD TRAFFIC CRASHES: RESULTS OF A FRENCH REGISTRY-BASED STUDY

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ABSTRACT

***Background*:** In recent decades, increased attention has been focused on the impact of disabilities and medicinal drug use on road safety. The aim of our study was to investigate the association between prescribed medicines and the risk of road traffic crashes, and estimate attributable fraction.

Methods and findings: We extracted and matched data from three exhaustive French nationwide databases: the national healthcare insurance database, police reports, and the police national database of injurious crashes. Drivers identified by their national healthcare number, involved in an injurious crash in France, between July 2005 and May 2008, were included. Medicines were grouped according to the four risk levels of the French classification system [from 0 (no risk) to 3 (high risk)]. We included 72,685 drivers involved in injurious crashes. Users of level 2 (OR=1.31 [1.24-1.40]) and level 3 (OR=1.25 [1.12-1.40]) prescribed medicines were at higher risk of being responsible for the crash. The association remained after adjustment for the presence of a long-term chronic disease. The fraction of road traffic crashes attributable to levels 2 and 3 medicines was 3.3% [2.7%-3.9%]. A within-person case-crossover analysis showed that drivers were more likely to be exposed to level 3 medicines on the crash day than on a control day, 30 days earlier (OR=1.15 [1.05-1.27]).

***Conclusion*:** The use of prescribed medicines is associated with a substantial number of road traffic crashes in France. A follow-up study is needed to evaluate the impact of the warning labeling system on road traffic crash prevention.

INTRODUCTION

The risk of road traffic crashes associated with the use of benzodiazepines on the risk of road traffic crashes has now been documented with consistent results in several studies [1,2,3,4,5,6,7,8,9,10,11,12,13] but the effect of other medicines has hardly been assessed and results of available studies are often inconsistent [14]. This is particularly true for opioids [2,8,9,12,15,16] and antidepressants [1,12,16,17]. Psychoactive medicines may impair driving abilities due to their action on the central nervous system (e.g. sedation in the morning following administration of an hypnotic), while other medicines may affect psychomotor functions by their action on physiological functions (e.g hypoglycaemic seizures related to diabetic treatment) or due to central side effects (e.g. central nervous system depressant potential of carisoprodol).

Within the European Union, it is mandatory for a pharmaceutical company to provide data regarding the effect of a medicine on the ability to drive and to use machinery prior its commercialization.

The European Medicine Agency requested in 2003 the definition of a standardized classification of medicines according to four levels of driving impairment risk, from level 0 (no or negligible risk) to level 3 (major risk), in order to provide healthcare professionals and patients with proper information regarding the effects of medicines on driving abilities. The European DRUID project (Driving Under the Influence of Drugs, alcohol and medicines) identified 16 classification systems worldwide. [18] The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) proposed, in 2006, a classification list based on the Belgium, Spanish and French classifications. In France, a multidisciplinary group of experts was appointed to classify all medicines according to four levels of risk in terms of their effect on driving performances. [19] A graded pictogram was to be printed on the medicine packs of all level 1 to 3 medicines (Figure 1). Pharmaceutical companies gradually implemented this policy from 2005 to 2008.

The aim of our study was to estimate the association between medicine use, as estimated using prescribed medicine dispensation data of a healthcare reimbursement database, and the risk of injurious road traffic crashes, as well as the fraction of crashes attributable to medicine use in France.

METHODS

Ethics statement

This study was approved by the French Data Protection Authority.

Data sources

The study used three databases: the national healthcare insurance database, and two police databases referring to the same road traffic crash events but with different format and content.

Police reports

French police forces are supposed to fill in a police report for each injurious crash occurring in the country (about 70,000 reports each year). For some of the drivers involved in these injurious road traffic crashes, the national healthcare number (national ID) is recorded in the police report and can later be matched with medicine dispensing records of the healthcare insurance database. Police reports are scanned and stored as image files. All available police reports in France were gathered over the study period.

Police national database of injurious road traffic crashes

Police forces also collect details on each injurious crash event which are computerized in the police national database of injurious crashes (Bulletins d'Analyse d'Accident Corporel [BAAC]). This standardized database contains descriptive variables about crash characteristics, vehicles and people involved. Police forces also conduct additional investigations regarding injury severity from hospital records and categorize the people involved in four groups: unhurt, slightly injured, seriously injured (hospitalized more than 24 hours) or killed (in the 30 days following the crash). All drivers involved in a road traffic crash are supposed to be tested for the presence of alcohol using a breath test. If this test is positive ($\geq$ 0.5 g/L), the driver refuses to take the test or the severity of the crash makes the test impossible, then the blood alcohol concentration is measured. If the breath test is negative, then the driver is registered as not being under the influence of alcohol. Missing data on alcohol impairment correspond to the following situations: the result of the blood measurement was unknown at the time of data entry in the database, the blood measurement was impossible (not enough blood for example), the breath test was not done by the police, the breath test was positive but the measurement of blood alcohol concentration was not realised or the breath test was negative but it was not coded in the database.

Healthcare insurance database

The national healthcare insurance database (SNIIR-AM) covers the whole French population (64 million people in 2008) and includes data on reimbursed prescription medicines. A record is added to the database each time a prescription medicine is dispensed to an outpatient at the pharmacy, including national ID, date of dispensing and the seven-digit code (CIP code) assigned to the medicine at the time of its marketing authorization. Data on long-term chronic

diseases are also registered in this database, with the ICD-10 code (International Classification of Diseases code), start and end dates of the disease. In France, patients are fully reimbursed for health care expenses, including medicines, related to 30 recognized long-term chronic diseases. [20]

National ID extraction and matching procedures

The first step of the study consisted in extracting and matching data from the French exhaustive nationwide databases described above.

Drivers involved in an injurious crash in France, between July 2005 and May 2008, were included through their national ID, gender and date of birth extracted from police reports. An application, based on Optical Character Recognition (OCR), was developed for automatic extraction from the image files of the crash date, and individual's national ID, gender and date of birth. The extraction procedure was validated on a subsample of 293 police reports, which were printed and coded manually.

A procedure was implemented to match each individual whose ID was extracted from police reports, with the corresponding record from the police national database of injurious crashes. Two records were considered matched if they were concordant for six descriptive variables. If a pair was discordant for three or more variables, it was considered unmatched. For pairs with concordance for less than six variables and more than three variables, a probabilistic linkage method was developed [21]. When a decision could not be made automatically, pairs were reviewed by hand.

Data on reimbursed medicines, dispensed within six months before the crash, were obtained by linking included drivers to the national healthcare insurance database using their national ID, gender and date of birth.

Security of personal information was ensured by using the personal information anonymization function of the healthcare national insurance system [22].

Medicines and exposure periods

Day-by-day medicine exposure was estimated for each pharmacotherapeutic class, according to the WHO Anatomical Therapeutic Chemical (ATC) classification. Medicine exposure was considered starting on the day following dispensing and exposure duration was estimated from median values reported within a survey on medicine prescription in France.[23] This survey was conducted among 800 practitioners, representative of French physicians, three times a year, over a seven-day period. To ensure that prescribed medicines were not a consequence of the crash, medicines dispensed on the crash day were not considered.

We studied all dispensed and reimbursed prescription medicines grouped according to the French risk classification. [24]

A multidisciplinary group of experts elaborated this four-level risk classification. The grading method considered all available data: pharmacodynamics and kinetics effects, individual sensitivity, conditions of use of each medicine, pharmacovigilance data, experimental and crash study data. [25] This classification ranks the four levels of driving impairment risk from level 0 (no or negligible risk) to level 3 (major risk). A graded pictogram is printed on the medicine packs of all level 1 to 3 medicines, together with a written warning (Figure 1).

Level 0: Medicinal products with no pharmacodynamics effect likely to alter the ability to drive, in the present state of knowledge. (6,282 medicines)

Level 1: Medicinal products which do not generally question the ability to drive but require patient information. (1,190 medicines)

Level 2: Medicinal products which could affect the ability to drive and require medical advice before use. (1,601 medicines)

Level 3: Medicinal products which affect the ability to drive during their use. (194 medicines)

Responsibility determination

Responsibility levels in the crash were determined by a standardized method adapted from Robertson and Drummer's [26]. This method, recently validated in France within the police national database of fatal crashes [27], takes into account the different factors likely to reduce driver responsibility: road, vehicle and driving conditions, type of accident, traffic rule obedience and difficulty of task involved. A score is assigned to each driver for each of these factors from 1 (favourable to driving) to 4 (not favourable to driving). The higher the sum of the scores is, the more the conditions are unfavourable to driving, and thus the more likely the driver will be considered as non-responsible for the crash. Drivers are further grouped into responsible drivers (score < 15) or non-responsible drivers (score ≥ 15).

This method used to determine the driver's responsibility in the crash was approved by an independent expert evaluation of responsibility (kappa=0.71).

Analysis

Subject inclusion

Subjects whose police reports did not contain their national ID could not be included. Drivers were censored at their first involvement in a road traffic crash in order to mitigate the impact of previous crashes on medicine exposure. We compared included with non-included subjects, regarding age, gender, injury severity, vehicle type, crash location, type of police

forces who filled in the police report, alcohol level and responsibility status. This analysis was performed by logistic regression.

Responsibility analysis

The principle of responsibility analysis is to compare exposure probabilities on the day of crash between responsible drivers (cases) and non-responsible drivers (controls) [26]. This method ensures that both cases and control are selected from the same driving population.

Statistical analyses were conducted using logistic regression. The associations between responsibility and age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level and injury severity were initially investigated using bivariate analysis: associated variables were included in the multivariate model when their p-value was less than 20% (Chi-squared test). This was the case for all variables except for year of crash which was forced into the model because prescription patterns may have changed between the 2005-2006 and 2007-2008 periods. Further analyses adjusted for the presence of long-term chronic diseases. We tested the interactions between exposure and each of the adjustment variables.

Attributable fractions were estimated from the adjusted odds ratio estimates and the prevalence of exposure in responsible drivers [28]. Confidence intervals were computed using the bootstrap method [29,30], estimated from the 2.5^{th} and the 97.5^{th} percentiles of the distribution resulting from 500 simulations.

Case-crossover analysis

The case-crossover analysis consisted on a pair-matched analytical approach to compare medicine exposure during a period immediately before the crash (case period) with exposure during an earlier period (control period) for the same subject [31]. We compared medicine exposure on the crash day with medicine exposure on the control day. The washout period between the case and control periods prevents any residual effect of an exposure in the control period on the case period. In France, the duration of a treatment dispensed at the pharmacy cannot usually exceed 30 days (almost without exception, i.e. contraceptive pills), so the duration of the washout period was determined at 30 days. Odds ratios were estimated by conditional logistic regression, using the PHREG procedure in SAS®.

Data were analyzed using the SAS® statistical software package, version 9.0 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Study population

The validation study conducted on 293 police reports showed that the national ID was recorded for 140 of the 455 drivers involved (28%). The automatic OCR software extracted 110 of these 140 national IDs (extraction rate=79%). Matching with the police national database of injurious crashes was possible for 90% of them. The inclusion rate of drivers was thus expected to be around 20%.

The result of the overall extraction and matching procedures for our study is illustrated in Figure 2. We extracted 109,078 national IDs/gender/date of birth, from 210,818 police reports available from July 2005 to May 2008, corresponding to any individual involved in an injurious road traffic crash. Ninety percent of these individuals were matched with a corresponding record in the police national database of injurious crashes (72.8% fitted on all variables, 14.0% were matched by the probabilistic linkage method and 3.1% manually). The linkage failed for 10% of the individuals, because the ID corresponded either to a driver involved in the crash but not captured in the police national database or to an individual not involved in the crash (e.g. a witness, the owner of a vehicle involved).

The procedure finally led to the inclusion of 72,685 drivers (34,896 responsible and 37,789 non-responsible drivers), i.e.18.5% of the 392,169 drivers registered in the police national database of injurious crashes. Baseline characteristics of the study population are presented in Table 1. Injury severity was the main factor associated with the probability of being part of the study (OR=3.43 [3.29-3.58] for seriously injured drivers and OR=2.67 [2.57-2.77] for slightly injured drivers), thus explaining higher rates of inclusion for bicycle (OR=1.24 [1.16-1.33] and scooter drivers (OR=1.09 [1.03-1.16]) and drivers involved in non-urban accidents (OR=1.14 [1.10-1.18]), all of whom have been consistently documented in literature to be more seriously injured. The inclusion rate was slightly lower for responsible drivers than for non-responsible drivers (OR=0.91 [0.88-0.94]).

Exposure to medicines

Twenty seven percent (n=19,777) of the drivers included in the study were exposed to at least one prescribed medicine on the crash day. There were 13,167 drivers (18%) exposed to at least one prescribed medicine of level 1, 2 or 3. (Table 2)

Table 3 shows the main pharmacotherapeutic classes used on the crash day among level 2 and 3 medicines by ATC class (3rd level of the ATC system).

When adjusted for variables found to be associated with responsibility in the crash (age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity) and for medicines of others levels, the use of at least one

medicine of level 2 or level 3 was associated with the risk of being responsible for a crash (OR=1.31 [1.24-1.40] and OR=1.25 [1.12-1.40]). The use of level 0 medicines was associated with a decreased risk of being responsible for a crash (OR=0.92 [0.88-0.97]). The risk of being responsible was not significant for the risk level 1 (Table 4). The fractions of road traffic crashes attributable to levels 2 and 3 medicine use were 3.0% [2.4%-3.5%] and 0.7% [0.4%-0.9%] respectively. The global fraction attributable to both level 2 and 3 medicines (considering exposure to level 2 or level 3 medicines on the crash day) was 3.3% [2.7%-3.9%]. The associations remained after adjustment for long-term chronic diseases (OR=0.92 [0.88-0.97] for level 0, OR=1.30 [1.22-1.38] for level 2 and OR=1.24 [1.11-1.39] for level 3). There was no interaction of medicine use with alcohol consumption (p=0.84 for level 2 and p=0.23 for level 3). The information on alcohol level was missing for 9,919 subjects (13.6%). Excluding these subjects from the univariate analysis led to no significant change in estimated odds ratios. We did not find any interaction between the use of level 2 or level 3 medicines and the adjustment variables.

Among level 2 medicines, the risk of being responsible for a crash was significantly higher for drugs used in diabetes (A10), antiepileptics (N03), psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07). The odds ratio for psycholeptics of level 3 was similar to that estimated for all level 3 medicines (Table 5).

The risk of being responsible for a crash gradually increased from 1.14 [1.06-1.22] for users of one medicine of level 2 or 3 to 1.88 [1.58-2.25] for users of more than 3 medicines of level 2 or 3 (Table 6).

Results from the case-crossover analysis showed a statistically significant association between the use of level 3 medicines and the risk of road traffic crash. There was no association with level 0, level 1 and level 2 medicines (Table 7).

DISCUSSION

We extracted data from exhaustive nationwide French police and health insurance databases, over a three-year period. The process of national ID extraction and matching led to the inclusion of 72,685 drivers involved in an injurious road traffic crash, giving unprecedented statistical power for a study on the impact of medicines on the risk of road traffic crashes.

We evidenced an increased risk of being responsible for a crash for users of prescribed medicines defined as presenting a level 2 or level 3 risk of driving impairment according to the French classification. The fraction of road traffic crashes attributable to levels 2 and 3 medicine use was 3.3% [2.7%-3.9%].

The study protocol planned for the inclusion of a large range of descriptive variables related to the crash and to the drivers involved. In particular, we were able to determine the responsibility status of the driver in the crash and to adjust for key confounding factors. The responsibility analysis is a real strength of the study as it allows for the comparisons of cases and controls that share the same characteristic of being drivers. In a previous study on the impact of illegal drug consumption, using the same police national database but limited to fatal crashes [27], the same method used to determine responsibility was approved by an independent expert evaluation of responsibility. Furthermore, because the responsibility analysis relies on the assumption that non responsible drivers are representative of the driving population, the authors of the previous study validated the comparison of a subset of the non responsible subjects with the driving population in France [27]. Finally, the strong dose-effect relationship found in our study between alcohol level and responsibility is a further indirect validation of the method. Importantly, responsibility levels were computed independently of alcohol and illicit drug use because of their potential interactions with medicine use.

Medicine exposure was ascertained from computerized records of reimbursed prescriptions filled at the pharmacy. These data were not subject to underreporting, a major problem encountered when medicine exposure data is self-reported [5]. On the other hand, it is one of the study limitations that dispensing dates were considered in this study as a surrogate for actual consumption. We did not know whether the medicines were actually ingested or not. Non-compliance, which we were not able to check, would therefore result in exposure misclassification. Other studies using patient-derived data and the same dispensation database showed that the healthcare insurance data are reliable indicators of actual exposure for chronically used medicines, less for episodically used medicines. [32] We assumed that the exposure period started on the day after dispensing, as medicine dispensation on the day of crash may have been a consequence of the crash. Another limitation was that exposure to self-medication drugs can also not be estimated from the healthcare insurance database. However, less than 15% of medicines sold in France correspond to non-reimbursable medicines and most of these products have no or negligible influence on the ability to drive.

The comparison between included drivers by means of their national ID and non-included drivers showed that injury severity was associated with the probability of being part of the study. Thus severely injured drivers were more likely to be included than slightly injured drivers. Killed drivers and uninjured drivers still had lower inclusion rates. This can be explained by the fact that injured drivers were more likely to be admitted to hospital so their healthcare number was more frequently noted in the police report. Thus, our study sample slightly over-represented drivers injured in more severe crashes.

After adjustment for crash and individual variables, including exposure to other medicines, the risk of being responsible estimate was lowered for level 3 medicines, the association however remaining significant (from 1.56 [1.42-1.71] to 1.25 [1.12-1.40]). The crude risk of being responsible measured for level 3 medicines was thus partly related to these crash and individual variables and particularly to a co-consumption of alcohol and level 2 medicines.

The protective effect of level 0 medicines could be explained by the treatment of those minor acute diseases that may lead to an increased risk of being responsible for the crash. Indeed, a number of specific physical and/or psychological conditions are likely to influence driving ability.

Surprisingly, we found no interaction between alcohol level reported by police forces and medicine use, while alcohol is known to potentiate medicine effects. It should be noted however that, as the presence of alcohol is not always tested in drivers involved in slight injury crashes, this variable may be underestimated. Moreover, drivers who had a negative breath test were not tested for precise blood alcohol concentration which is supposed to be less than 0.5g/L. Information about illicit drug use was not available in any database.

According to our results, the French risk classification seems relevant regarding medicines classified as levels 2 and 3 of risk for road traffic crashes. Even if the risk for levels 2 and 3 is similar, we believe that it is useful to differentiate these two levels. For level 2 medicines, their effect on driving abilities depends both on the pharmacodynamics of the drug and on individual susceptibility; medical advice is therefore needed to appreciate the potential risk for each individual. Various medicines are classified as level 2. The risks found for psycholeptics and psychoanaleptics, mainly anxiolytics and antidepressants, are concordant with others studies. [2,10,11,12,16,17] The results on antiepileptics and other nervous system drugs (in particular medicines used in opioid dependence) are of interest and deserve further investigation. For some of the ATC classes in this level, the association in the responsibility analysis was not significant; however, the number of drivers exposed to antihypertensives, muscle relaxants, anti-Parkinson drugs and antihistamines for systemic use, was small. On the other hand, despite a relatively large number of subjects exposed to analgesics (including opioid analgesics), we found no association with the risk of being responsible for a crash. Concerning level 3 medicines, the pharmacodynamic effect is predominant, so all users are advised not to drive. The effects of level 1 medicines may be so dependent on individual susceptibility that an effect on driving abilities might be a rare event. The relevance of labeling medicines grouped in this level 1 should therefore be questioned.

The respective role of disease and the medicines used to treat it is difficult to disentangle. After adjustment for the presence of a long-term chronic disease, results from the responsibility analysis did not suggest an important confounding effect. In the case-crossover

method, each subject is his own control and confounding due to individual factors is therefore eliminated, particularly fixed characteristics such as long-term chronic diseases. Other studies used this approach to examine the relationship between medicines and the risk of injury [1,12,33]. The use of level 3 medicines was found to be associated with an increased risk of road traffic crash both in the responsibility analysis and in the case-crossover analysis. However, the risk associated with level 2 medicines in the responsibility analysis (OR=1.31 [1.24-1.40]) disappeared in the case-crossover analysis (OR=1.00 [0.95-1.05]). The risk of road traffic crashes associated with chronic exposure to level 2 medicines can not be assessed by a case-crossover design. Indeed, an individual using a medicine throughout the study period would be exposed on the crash date and on the control day. Our results on level 2 medicines are therefore likely to be related to the impact of chronic medicine consumption, i.e. mainly drugs used in diabetes, opioids, antiepileptics, anxiolytics and antidepressants. On the other hand, hypnotics and sedatives, mainly representing level 3 medicines, can be used on an acute basis and their impact on road traffic crashes are detected with the case-crossover analysis.

Our study provides evidence of the contribution of medicines to the risk of road traffic crashes. Improving driver behaviour is one of the challenges for road safety. Providing patients with proper information on the potential effect of medicines on their driving abilities is the main objective of drug and risk classifications such as the French one. The European Union is currently aiming to harmonise these classification systems, using a reliable methodology based on scientific evidences. The present epidemiological study provides some sound evidence. A follow-up study is now needed to evaluate the effect of the French warning system on medicine packs on the prevention of road traffic crashes.

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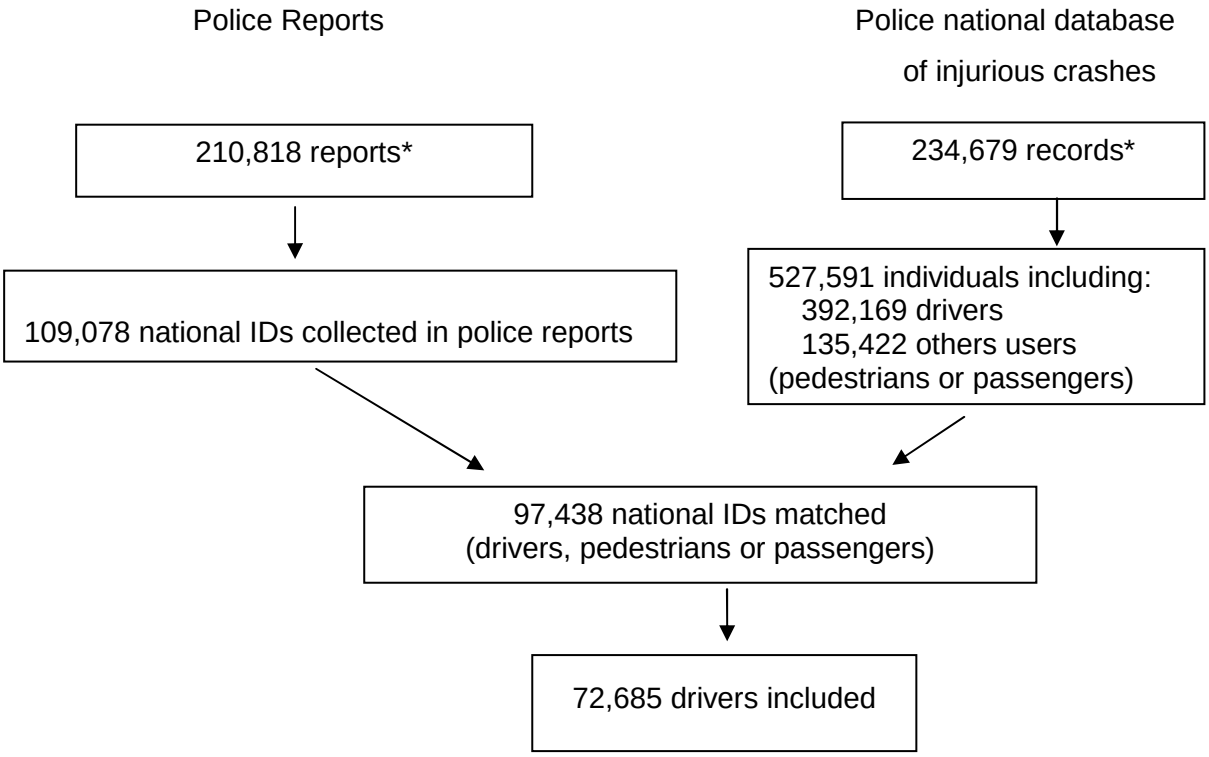
Competing interests

The authors declare that they have no conflicts of interest.

Figure 1. French labeling system.

Figure 2. Flowchart of the inclusion procedure.



* The discrepancy between the number of police reports and the number of records in the police national database of injurious crashes is explained by the fact that a small proportion of unavailable reports were being used for on-going further legal investigations.

Table 1. Baseline characteristics.

	N	%
	72,685	
Gender		
Men	49,770	68.5
Women	22,915	31.5
Age (years)		
< 18	3,055	4.2
18-24	14,814	20.4
35-34	16,666	22.9
35-44	15,488	21.3
45-54	11,796	16.2
55-64	5,990	8.2
65-74	2,837	3.9
≥ 75	2,039	2.8
Socio-economic category		
Higher managerial and professional occupations	2,784	3.8
Intermediate occupations	24,984	34.4
Workers	11,887	16.4
Retired	6,449	8.9
Unemployed	3,021	4.2
Other/missing	16,014	22.0
Student	7,546	10.4
Vehicle type		
Light vehicle	42,792	58.9
Bicycle	3,867	5.3
Scooter	10,099	13.9
Motorbike	10,458	14.4
Commercial vehicle	2,550	3.5
Heavy goods vehicle	1,342	1.9
Other	1,577	2.2
Injury severity		
Unhurt	19,093	26.3
Slightly injured	26,327	36.2
Seriously injured	25,864	35.6
Killed	1,401	1.9
Alcohol (g/L)		
<0.5	58,700	93.5
[0.5-0.8[	568	0.9
[0.8-1.2[	786	1.3
[1.2-2[	1,392	2.2
≥ 2	1,320	2.1
Long-term chronic disease		
No	61,698	84.9
Yes	10,987	15.1

Table 2. Number of exposed drivers on the crash day by classification and number of medicines used

Number of medicines	Exposed drivers
Level 0 medicines	15,715 (21.6%)*
1	6,917
2	3,757
3	2,161
4	1,233
>4	1,647
maximum level 0	6,610[#]
Level 1 medicines	7,415 (10.2%)*
1	5,681
2	1,361
3	315
4	49
>4	9
maximum level 1	4,432[#]
Level 2 medicines	8,268 (11.4%)*
1	5,102
2	2,029
3	745
4	253
>4	139
maximum level 2	6,753[#]
Level 3 medicines	1,982 (2.7%)*
1	1,724
2	234
3	23
4	1
maximum level 3	1,982[#]

* exposed to at least one medicine of the risk level considered

[#] only considering exposure to medicine of the highest level of risk

Table 3. Level 2 and level 3 pharmacotherapeutic classes used on the crash day.

ATC class	Level 2 medicines	Level 3 medicines
Total	13,147	2,265
Alimentary tract and metabolism (A)	1,056	-
Insulins and analogues (A10A)	370	-
Blood glucose- lowering drugs, excl. insulins (A10B)	668	-
Cardiovascular system (C)	196	-
Antiadrenergic agents, centrally acting (C02A)	195	-
Musculo-skeletal system (M)	277	-
Muscle relaxants, centrally acting (M03B)	248	-
Nervous system (N)	10,870	2,265
Opioids (N02A)	1,935	2
Antimigraine preparations (N02C)	337	-
Antiepileptics (N03A)	1,053	-
Anti-Parkinsonian drugs (N04)	175	-
Antipsychotics (N05A)	804	8
Anxiolytics (N05B)	2,843	471
Benzodiazepine derivatives (N05BA)	2,362	471
Antidepressants (N06A)	3,122	-
Selective serotonin reuptake inhibitors(N06AB)	2,188	-
Hypnotics and sedatives (N05C)	-	1,784
Benzodiazepine derivatives (N05CD)	-	295
Benzodiazepine related drugs (N05CF)	-	1,196
Hypnotics and sedatives in combination, excl. barbiturates (N05CX)	-	293
Drugs used in addictive diseases (N07B)	443	-
Drugs used in alcohol dependence (N07BB)	69	-
Drugs used in opioid dependence (N07BC)	374	-
Antihistamines for systemic use (R)	327	-
Phenothiazine derivatives (R06AD)	216	-

ATC -= Anatomical Therapeutic Chemical classification system

Some drivers may have been exposed to several substances from the same pharmacological subgroup, explaining the difference with the number of exposed drivers presented in Table 2.

Table 4. Odds ratios for responsible road traffic crashes in users of prescribed medicines.

	Exposed drivers	OR_c [95% CI] [§]	Exposed drivers [Ω]	OR_a [95% CI] [#]	OR_a [95% CI] [α]
Level 0	15,715	0.92 [0.88-0.95]***	13,702	0.92 [0.88-0.97]*	0.92 [0.88-0.97]**
Level 1	7,415	0.96 [0.92-1.01]	6,478	0.96 [0.90-1.02]	0.95 [0.89-1.01]
Level 2	8,268	1.24 [1.19-1.30]***	7,102	1.31 [1.24-1.40]***	1.30 [1.22-1.38]***
Level 3	1,982	1.56 [1.42-1.71]***	1,679	1.25 [1.12-1.40]***	1.24 [1.11-1.39]**

Reference group = drivers not exposed to medicines of the risk level considered

[§] Crude Odds Ratios

[Ω] Model computed for the 62,766 drivers with no missing values for the adjustment variables

[#] Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity and other level medicines

[α] Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity, long-term chronic diseases and other level medicines

* p<0.01, ** p<0.001, *** p<0.0001

Table 5. Odds ratios for responsible road traffic crashes in users of prescribed medicines by ATC classes.

	Exposed drivers [Ω]	OR_a [95% CI] [α]
Level 2		
Drugs used in diabetes (A10)	795	1.20 [1.03-1.40]*
Antihypertensives (C02)	172	1.07 [0.78-1.47]
Muscle relaxants (M03)	219	0.82 [0.62-1.09]
Analgesics (N02) [§]	1,845	1.04 [0.94-1.15]
Antiepileptics (N03)	755	1.41 [1.21-1.65]***
Anti-Parkinson drugs (N04)	125	1.15 [0.79-1.68]
Psycholeptics (N05) [‖]	2566	1.27 [1.15-1.40]***
Psychoanaleptics (N06) [†]	2572	1.31 [1.19-1.44]***
Other nervous system drugs (N07) [¶]	369	1.46 [1.16-1.84]**
Antihistamines for systemic use (R06)	267	1.05 [0.81-1.35]

[Ω] Model computed for the 62,766 drivers with no missing values for the adjustment variables

[α] Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level, injury severity, long-term chronic diseases and other medicines

[§] Including opioids (N=1585), other analgesics and antipyretics (N=22) and antimigraine preparations (N=281)

[‖] Including antipsychotics (N=558) and anxiolytics (N=2250)

[†] Including antidepressants (N=2509), psychostimulants (N=56) and anti-dementia drugs (N=33)

[¶] Including drugs used in alcohol dependence (N=51), drugs used in opioid dependence (N=295), antivertigo preparations (N=7) and other nervous system drugs (N=16)

* p<0.05, ** p<0.001, *** p<0.0001

Table 6. Odds ratios for responsible road traffic crashes by number of level 2 and/or level 3 medicines used.

Number of level 2 / level 3 medicines	Exposed drivers	OR_a [95% CI] [μ]
0	55,264	Reference
1	4,259	1.14 [1.06-1.22]*
2	1,829	1.30 [1.17-1.43]**
3	817	1.86 [1.59-2.16]**
>3	597	1.88 [1.58-2.25]**

[μ] Odds Ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, location, vehicle type, alcohol level and injury severity

* p<0.001, ** p<0.0001

Table 7. Case crossover analysis - Odds ratios for road traffic crashes in users of prescribed medicines.

	Exposed drivers[#]	OR [95% CI] [μ]
Level 0	4,047	1.02 [0.98-1.07]
Level 1	2,249	1.02 [0.96-1.08]
Level 2	3,131	1.00 [0.95-1.05]
Level 3	896	1.15 [1.05-1.27]*

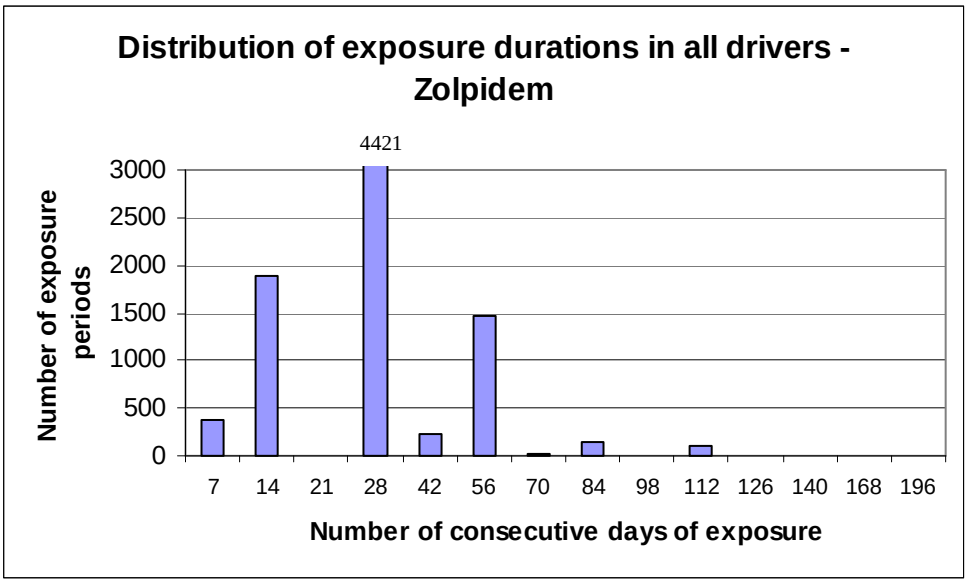
[#] drivers exposed in the case period and not exposed in the control period

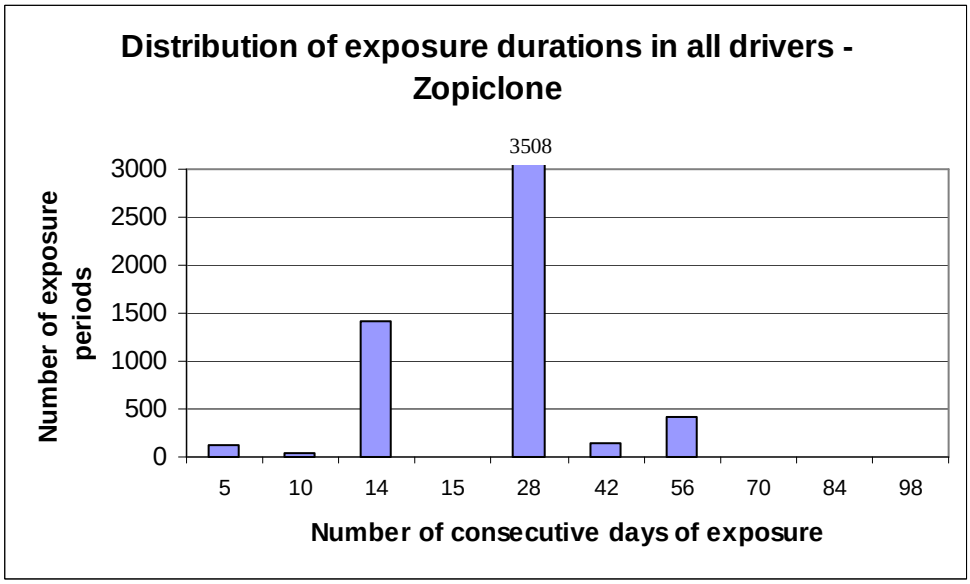
[μ] only considering exposure to medicine of the highest level of risk

* p<0.01

APPENDIX 6

Determination of the wash-out periods
Zolpidem and Zopiclone





APPENDIX 7
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BENZODIAZEPINE-LIKE HYPNOTICS AND THE RISK OF ROAD TRAFFIC CRASHES

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ABSTRACT

Objective: To investigate the association between the use of benzodiazepine-like hypnotics, benzodiazepine hypnotics and the risk of road traffic crashes.

Design: French national registries linkage study

Settings: Data from three French national databases were extracted and matched: the national healthcare insurance database, police reports, and the police national database of injurious crashes.

Participants: Drivers identified by their national healthcare number who were involved in an injurious crash in France, from July 2005 to May 2008.

Main outcome measures: Case-control analysis was conducted comparing responsible versus non-responsible drivers. Case-crossover analysis compared exposure to medicines on the day of crash and on a preceding control day.

Results: 72,685 drivers involved in injurious crashes were included. Zolpidem use was associated with an increased risk of being responsible for a road traffic crash (OR=1.28 [1.07-1.53]) whereas zopiclone and benzodiazepine hypnotics use were not. Among the 600 drivers exposed to zolpidem on the day of crash, the responsibility risk was only increased in the 139 drivers with dispensing of more than one pill of zolpidem a day during the five months before the crash (OR=2.38 [1.61-3.52]). Case-crossover analysis showed an increased risk of crash for benzodiazepine hypnotic users only (OR=1.42 [1.09-1.85]). Hypnotic users shared similar crash characteristics, with crashes more likely to occur alone on highways.

Conclusions: The road traffic crash risk of zolpidem users should be further investigated in search of potential abuse and risky driving behaviors. Zopiclone appears to be used safely.

INTRODUCTION

Benzodiazepines are commonly prescribed as hypnotics for the treatment of insomnia. The clinical effects (i.e. sedation) should occur during a limited time (a few hours after bedtime administration) in order to avoid any residual effect the next day. Several pharmacoepidemiological studies have shown that patients using benzodiazepine hypnotics are at increased risk of road traffic crashes.[1-4] The duration of the sedative effect partly depends on drug kinetics: long half-life benzodiazepines have been shown to be associated with an increased risk of road traffic crashes whereas, in the same study, short half-life benzodiazepines have not.[5] Rapidly acting hypnotics have been developed to avoid next-day sedation. Zolpidem and zopiclone are benzodiazepine-like hypnotics with short elimination half-lives (2.5 and 5 hours respectively). Zopiclone is a racemic mixture of two stereoisomers, one of which, eszopiclone, is marketed in the US. Hypnotics with a short half-life can have residual effects, depending on individual responses to the drug and on the actual conditions of use.[6] In 2008, in France, zolpidem was in thirteenth position and zopiclone in twenty-first position in number of boxes reimbursed by the healthcare insurance. Despite their importance in the sleep medicine market, there are few epidemiological studies of their effects on the crash risk in the scientific literature. A case-crossover study conducted in the UK showed that the use of zopiclone was associated with an increased risk of road traffic crashes (OR=4.00 [1.31-12.2]).[7] A recent Norwegian study found an increased risk of traffic crashes in drivers who had received a prescription for zopiclone as compared with non-users (SIR=2.3 [2.0-2.8]).[3] Two literature reviews on residual effects of hypnotics recommended that users of zopiclone should be advised not to drive whereas the use of zolpidem was considered safer.[6 8] However, zolpidem has recently been also found to be associated with an increased risk of road traffic crashes (SIR=2.2 [1.4-3.4]).[3]

The aim of our study was to provide further insights into the impact of zopiclone, zolpidem and benzodiazepine hypnotics on the risk of road traffic crashes, using a large database extracted from national population-based registries.

METHODS

The study consists in extracting and matching data from three French nationwide databases: the national healthcare insurance database, police reports and the police national database of injurious crashes. Drivers were included by means of their national ID, extracted from police reports by an automatic procedure. The ID was used to link drivers to medicine reimbursement data around the crash date. Police reports were matched to records in the police national database of injurious crashes by a probabilistic linkage method.

Data sources

Police reports

Police forces are supposed to fill in a report for each injurious crashes occurring in the country (about 70 000 reports are created each year). For some of the individuals involved in these injurious road traffic crashes, the national healthcare number (national ID) is recorded in the police report. Preliminary assessment on a small sample of reports estimated that this is the case for 28% of drivers. Police reports are scanned and archived as image files. All the 210,818 available police reports in France over the study period (from July 2005 to May 2008) were gathered.

Police national database of injurious crashes

Police forces also collect details on the same injurious crash events which are computerized in the police national database of injurious crashes (Bulletins d'Analyse d'Accident Corporel [BAAC]). This standardized database contains descriptive variables about crash characteristics, vehicles and people involved. Police forces also conduct additional investigations regarding injury severity from hospital records and categorize the people involved in four groups: unhurt, slightly injured, seriously injured (hospitalized more than 24 hours) or killed (died within 30 days following the crash). All drivers involved in an injurious road traffic crash are supposed to be tested for the presence of alcohol using a breath test. If this test is positive ($\geq$ 0.5 g/L), the driver refuses the test or the severity of the crash makes it impossible, then the blood alcohol concentration is measured. If the breath test is negative then the driver is registered as not being under the influence of alcohol. Missing data on alcohol impairment correspond to the following situations: the result of the blood measurement was unknown at the time of data entry in the database, the blood measurement was impossible (not enough blood for example), the breath test was not done by the police, the breath test was positive but the blood alcohol concentration was not measured, the breath test was negative but it was not coded in the database.

Healthcare insurance database

The national healthcare insurance system database (SNIIR-AM) covers the whole French population (64 million people in 2008) and includes data on reimbursed prescription medicines. A record is added to the database each time a prescription medicine is dispensed to an outpatient at a pharmacy, including national ID, date of dispensing and the seven-digit marketing authorization code (CIP code) that identifies medicinal products including dosage and quantity delivered. Data on long-term chronic diseases are also registered in this database, with the ICD-10 code (International Classification of Diseases code), start and end dates of the disease.

Medicines and exposure periods

Zopiclone and zolpidem

In France, zopiclone is available as 3.75 mg and 7.5 mg pills while zolpidem is only dispensed as 10 mg divisible pills. Exposure duration was estimated from the number of drug boxes dispensed and the number of pills in each box. For elderly people (>65 years old) taking zolpidem, it is recommended to reduce the dose to 5 mg so the duration of the estimated exposure period was doubled for this population.[9]

Benzodiazepine hypnotics

Treatment duration for each benzodiazepine hypnotic was estimated using median values from a survey on medicine prescription in France.[10]

Concomitant exposure

In France, a classification of medicines affecting driving abilities has been established, with four levels of risk.[11-13] Consequently, analyses were adjusted for the use of other medicines grouped according to this classification system.

Exposure was considered starting on the day following dispensing. To ensure that medicines were not prescribed as a consequence of the crash, medicines dispensed on the crash day were not considered.

Analysis

Subject inclusion

Several reasons may explain the non-inclusion of drivers: the police reports did not contain the driver's national ID, the extraction procedure failed or the linkage with the corresponding record in the police national database of injurious crashes did not succeed. We compared included with non-included subjects, regarding age, gender, injury severity, vehicle type, crash location, type of police forces who filled in the police report, alcohol level and responsibility status. This analysis was performed by logistic regression.

Drivers were censored at their first involvement in a road traffic crash in order to mitigate the impact of previous crashes on medicine exposure.

Responsibility analysis

The principle of responsibility analysis is to compare exposures probabilities on the day of crash between responsible drivers (cases) to non-responsible drivers (controls). This method ensures that both cases and controls are selected from the same driving population. Responsibility levels in the crash were determined by a method adapted from Robertson and Drummer [14]. This method, recently validated in France using data from the police national

database of injurious crashes [15], takes into account the different factors likely to reduce driver responsibility: road, vehicle and driving conditions, type of accident, traffic rule obedience and difficulty of task involved. A score is assigned to each driver for each of these factors from 1 (favourable to driving) to 4 (not favourable to driving). The higher the sum of the scores is, the more the conditions are unfavourable to driving, and thus the more likely the driver will be considered as non-responsible for the crash.

Statistical analyses were conducted using logistic regression. The model included terms for age, gender, socioeconomic category, day of week and time of crash, vehicle type, injury severity, blood alcohol level, concomitant treatment group using the French classification system and chronic long-term disorders.

Case-crossover analysis

The case-crossover analysis consisted on a pair-matched analytical approach to compare medicine exposure during a period immediately before the crash (case period) with exposure during an earlier period (control period) for the same subject.[16] This method is particularly suited to acute events and intermittent exposures. We compared exposure to the medicine on the day before the crash to exposure to the medicine on the control day. The wash-out period between the case and control periods prevents any residual effect of an exposure in the control period on the case period. In France, no more than 30 day's worth of treatment with benzodiazepines may be dispensed by pharmacies, so the duration of the wash-out period was 30 days. The duration of the wash-out period for zopiclone and zolpidem was determined by the 95th percentile of the exposure period distribution. This was computed from the estimation of exposure distribution described above (number of pills*number of boxes) in all subjects exposed to these medicines. This led to a wash-out period of 56 days for the two medicines. Odds ratios were estimated by conditional logistic regression.

Data were analyzed using the SAS statistical software package, version 9.0 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Extraction and matching procedures led to the inclusion of 72,685 drivers/riders (34,896 responsible and 37,789 non-responsible), 18.5% of the 392,169 drivers/riders registered in the corresponding police national database of injurious crashes.

Injury severity was the main factor associated with the probability of being part of the study (OR=3.43 [3.29-3.58] for seriously injured drivers and OR=2.67 [2.57-2.77] for slightly injured drivers), thus explaining higher rates of inclusion for bicycle (OR=1.24 [1.16-1.33] and

scooter drivers (OR=1.09 [1.03-1.16]) and drivers involved in non-urban accidents (OR=1.14 [1.10-1.18]), all of whom have been consistently documented in literature to be more seriously injured. The inclusion rate was slightly lower for responsible drivers than for non-responsible drivers (OR=0.91 [0.88-0.94]).

Exposures to zopiclone, zolpidem or benzodiazepine hypnotics were compared according to individual and crash characteristics (Table 1). Exposures were higher among women, drivers aged more than 45 years and retired or unemployed drivers. Proportions of exposed drivers were also higher among those under the influence of alcohol. Hypnotic exposures were more likely among drivers involved in single-vehicle crashes, occurring on highways and, in the case of benzodiazepines, occurring in the morning.

Exposure to zolpidem was associated with an increased risk of being responsible for a crash (OR=1.28 [1.07-1.53]), whereas zopiclone was slightly associated with a decreased risk (OR=0.78 [0.64-1.00]) and there was no association for benzodiazepine hypnotics (OR=1.24 [0.95-1.63]) (Table 2). No interaction was found between the use of the medicines of interest and the adjustment variables. Data on alcohol level was missing for 9,919 subjects (13.6%).

Further analysis showed that, out of the 600 drivers exposed to zolpidem on the crash day, the responsibility risk was only increased in the 139 drivers exposed to zolpidem on the day of crash and who had dispensing data corresponding to more than one pill a day during the five months period preceding the crash. The corresponding odds ratio was 2.38 [1.61-3.52] versus 1.07 [0.88-1.31] for the remaining 461 patients with a lower level of consumption.

Results from the case-crossover analysis showed a statistically significant association between the risk of road traffic crash and the use of benzodiazepine hypnotics (OR=1.42 [1.09-1.85]) and no association for zopiclone or zolpidem (Table 3).

DISCUSSION

The analysis of medicines dispensed to 72,685 drivers involved in injurious crashes from July 2005 to May 2008 in France found that zolpidem users were at increased risk of being responsible for their crash, and more particularly those with a high consumption level in the past 5 months. No such association was found for zopiclone or benzodiazepine hypnotic users. Drivers exposed to hypnotics were more likely to be involved in crashes of one vehicle on highway.

The study protocol planned for the inclusion of a large range of descriptive variables related to the crash and to the drivers involved. In particular, we were able to determine the responsibility status of the driver in the crash and to adjust for key confounding factors. The responsibility analysis is a real strength of the study as it allows for the comparisons of cases and controls that share the same characteristic of being drivers. In a previous study on the impact of illegal drug consumption, using the same police national database but limited to fatal crashes [15], the same method used to determine responsibility was approved by an independent expert evaluation of responsibility. Furthermore, because the responsibility analysis relies on the assumption that non responsible drivers are representative of the driving population, the authors of the previous study validated the comparison of a subset of the non responsible subjects with the driving population in France.[15] Finally, the strong dose-effect relationship found in our study between alcohol level and responsibility is a further indirect validation of the method. Importantly, responsibility levels were computed independently of alcohol and illicit drug use because of their potential interactions with medicine use.

The comparison between included drivers by means of their national ID and non-included drivers showed that injury severity was associated with the probability of being part of the study. Thus severely injured drivers were more likely to be included than slightly injured drivers. Killed drivers and uninjured drivers still had lower inclusion rates. This can be explained by the fact that injured drivers were more likely to be admitted to hospital so their healthcare number was more frequently noted in the police report. Thus, our study sample slightly over-represented drivers injured in more severe crashes.

Medicine exposure was ascertained from computerized records of reimbursed prescriptions filled in at the pharmacy, avoiding any recall bias. We estimated exposure periods from the date of dispensing and the amount of drug dispensed. We did not know if the medicines were actually ingested or not. However, it has been shown that for benzodiazepine derivatives the French health insurance database is a reliable indicator of actual use (kappa=0.7).[17]

A large range of variables was available in the police national database of injurious crashes, allowing a detailed description of the crash and drivers involved. Patterns of exposure to hypnotic benzodiazepines (higher for single vehicle crashes, on highways and in the morning) were suggestive of crashes due to sleepiness.[18] These medicines may thus have carry-over effects in the morning. Such a pattern was not observed for zopiclone and zolpidem, reinforcing the idea that these medicines do not have residual effects in the morning.

We were able to adjust our analysis for several factors which may influence the risk of crash, particularly other medicines used, long-term chronic diseases and, importantly, blood alcohol concentration. All drivers involved in an injurious crash are supposed to be tested for the

presence of alcohol but data were missing for 14% of the sample, corresponding to drivers involved in the less serious crashes. Moreover, drivers who had a negative breath test were not tested for precise blood alcohol concentration which is supposed to be less than 0.5g/L. Finally, it should be noted that we had no reliable information about illicit drugs.

The presence and severity of insomnia are not recorded in any database. Consequently, we cannot exclude a potential confounding by indication. If such an effect had an impact on the association between medicine use and crash or responsibility risk, it would be difficult to explain why we found no association for zopiclone and why the association with zolpidem was restricted to users with very high consumption levels (more than one pill a day).

The use of benzodiazepine hypnotics was not associated with the risk of being responsible for a crash, but an association was found in the case-crossover analysis, reflecting an effect of acute exposures to benzodiazepine hypnotics on the risk of crash. The latter result is consistent with a case crossover study conducted in the UK in 1992-1995 which measured an odds ratio of 1.62 [1.24-2.12] for all benzodiazepines.[7] However, a strong association was also found with zopiclone consumption in the same study. Despite its longer half-life than zolpidem, zopiclone did not increase in our study the risk of being responsible for a crash whereas zolpidem did. A review article on the residual effects of hypnotics on driving abilities concluded that zopiclone had no advantage over benzodiazepines, whereas driving after zolpidem intake was considered safer.[8] However, the magnitude of impairment depends on various factors including dosage and time of intake. Zolpidem has been shown to have a potential for abuse and inappropriate use (high doses, daytime consumption, stimulant action).[10 19] The high risk found for users who had more than one pill of zolpidem a day dispensed over a five months period led us to think that the difference observed between zolpidem and zopiclone relies on their usage pattern. Moreover, we found no association between zolpidem and the risk of road traffic crashes in the case-crossover analysis, suggesting that the prescription is not immediately followed by a risk of road traffic crash, strengthening the hypothesis that the risk is linked to more consistent driver behaviours, perhaps to episodic inappropriate use of zolpidem that could not be captured in this study because exposure days were estimated from dispensing data.

Literature data suggested that the use of hypnotics represent an avoidable risk factor for road traffic crashes. Our study provides further insights into the impact of zopiclone and zolpidem on traffic safety. While driving is considered safe the morning following bedtime intake, we observed an increased risk of traffic crash among zolpidem users. Their road traffic crash risk should be further investigated in search of potential abuse and risky driving behaviors. Zopiclone appears to be used safely.

What is already known on this subject

Zolpidem and zopiclone are benzodiazepine-like hypnotics with short half-lives. They were introduced in clinical practice as an alternative to benzodiazepines which have residual effects and present a risk for road traffic crashes.

Experimental studies suggest that zolpidem is safer than zopiclone regarding driving performances. However, a recent epidemiological study found a two-fold increased risk for road traffic crashes for both medicines.

What this study adds

Zolpidem users are at increased risk of being responsible for a crash, probably due to risky driving behaviors.

Zopiclone appears to be used safely and does not contribute to the crash burden in France.

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Everyone who contributed to the work is listed in this section.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) No support from companies for the submitted work; (2) No relationships with companies that might have an interest in the submitted work in the previous three years; (3) No spouses, partners, or children with financial relationships that may be relevant to the submitted work; and (4) No non-financial interests that may be relevant to the submitted work.

Contributors

EL is study guarantor.

Conception and design: EL; *Acquisition of data*: LO, AC, BG, BD, EL; *Statistical analysis*: LO, BG; *Interpretation of the data*: All authors; *Drafting of the manuscript*: LO; *Critical revision of the manuscript for important intellectual content*: All authors and members of the group; *Obtaining funding*: EL; *Supervision*: EL

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Role of the study sponsors

Members of the French Health Products Agency (Afssaps) participated to data collection, interpretation and review of the manuscript.

Ethical approval

This study was approved by the French Data Protection Authority (CNIL - Commission Nationale Informatique et Libertés).

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Table 1. Exposure to zopiclone, zolpidem and benzodiazepine hypnotics on the crash day according to drivers and crashes characteristics

	N	Exposed to zopiclone		p† (p)‡	Exposed to zolpidem		p† (p)‡	Exposed to BZD hypnotics		p† (p)‡
		n	%		n	%		n	%	
	72,685	455	0.6		685	0.9		289	0.4	
Gender				<0.0001			<0.0001			<0.0001
Men	49,770	267	0.5	(0.0026)	375	0.8	(<0.0001)	161	0.3	(<0.0001)
Women	22,915	188	0.8		310	1.4		128	0.6	
Age				<0.0001			<0.0001			<0.0001
< 18	3,055	2	0.1	(<0.0001)	0	0	(<0.0001)	0	0	(<0.0001)
18-24	14,814	19	0.1		18	0.1		14	0.1	
35-34	16,666	56	0.3		84	0.5		27	0.2	
35-44	15,488	104	0.7		122	0.8		73	0.5	
45-54	11,796	136	1.2		159	1.4		97	0.8	
55-64	5,990	71	1.2		130	2.2		48	0.8	
65-74	2,837	36	1.3		108	3.8		13	0.5	
≥ 75	2,039	31	1.5		64	3.1		17	0.8	
Socio-economic				<0.0001			<0.0001			<0.0001
Higher managerial and professional occupations	2,784	16	0.6	(0.0144)	19	0.7	(<0.0001)	8	0.3	(<0.0001)
Intermediate occupations	24,984	125	0.5		175	0.7		70	0.3	
Workers	11,887	40	0.3		61	0.5		33	0.3	
Retired	6,449	94	1.5		200	3.1		52	0.8	
Unemployed	3,021	34	1.1		49	1.6		20	0.7	
Other/missing	16,014	124	0.8		165	1.0		95	0.6	
Student	7,546	22	0.3		16	0.2		11	0.2	
Injury severity				0.0953			0.0251			(0.1839)
Unhurt	19,093	96	0.5	(0.0180)	157	0.8	(0.0073)	61	0.3	(0.1428)
Slightly injured	26,327	176	0. 7		258	1.0		113	0.4	
Seriously injured	25,864	173	0. 7		248	1.0		107	0.4	
Killed	1,401	10	0.7		22	1.6		8	0.6	
Alcohol				<0.0001			<0.0001			0.0002
< 0.5	58,700	318	0.5	(<0.0001)	528	0.9	(<0.0001)	213	0.4	(<0.0001)
0.5-1.2	1,354	15	1.1		23	1.7		10	0.7	
1.2-2.0	1,392	24	1.7		27	1.9		14	1.0	
> 2	1,320	21	1.6		22	1.7		8	0.6	
Time of day				0.1441			0.0005			0.0033
04.00 - 08.59	11,001	56	0.5	(0.6426)	85	0.8	(0.8779)	36	0.3	(0.0188)
09.00 - 11.59	9,804	77	0.8		121	1.2		59	0.6	
12.00 - 17.59	28,895	178	0.6		297	1.0		120	0.4	
18.00 - 22.59	18,696	120	0.6		147	0.8		63	0.3	
23.00 - 03.59	4,289	24	0.6		35	0.8		11	0.3	
Accident type				0.0265			0.0143			0.0118
1 vehicle				(0.1320)			(0.0315)			(0.0474)
Highway	1,303	8	0.6		19	1.5		12	0.9	
Secondary road	7,896	65	0.8		92	1.2		42	0.5	
Urban	4,941	39	0.8		61	1.2		20	0.4	
≥ 2 vehicles										
Highway	3,827	20	0.5		35	0.9		14	0.4	
Secondary road										
Intersection	6,313	28	0.4		48	0.8		16	0.3	
No intersection	23,129	142	0.6		193	0.8		80	0.4	

Urban								
Intersection	11,973	59	0.5	114	1.0	48	0.4	
No intersection	11,879	84	0.7	112	0.9	52	0.4	

Reference group=not exposed to the medicine considered

† Bivariate analysis, Chi squared test

‡ Multivariate analysis, logistic regression, model computed for 62,766 drivers without missing values

Table 2. Odds ratios for responsible road traffic crashes in users of zopiclone, zolpidem and benzodiazepines

	Bivariate model		Adjusted model	
	Exposed drivers	OR [95% CI] †	Exposed drivers ‡	OR [95% CI] §
Zopiclone	455	1.17 [0.97-1.41]	378	0.78 [0.64-1.00]*
Zolpidem	685	1.57 [1.35-1.83]***	600	1.28 [1.07-1.53]**
BZD hypnotics	289	1.60 [1.26-2.02]***	245	1.24 [0.95-1.63]

Reference group = drivers not exposed to medicines considered

† Crude odds ratios

‡ Model computed for 62,766 drivers without missing values for the adjustment variables

§ Odds ratios adjusted for age, gender, socioeconomic category, year, month, day of week, time of day, vehicle type, alcohol level, injury severity, concomitant exposure and long-term chronic diseases

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table 3. Case-crossover analysis - Odds ratios for road traffic crashes

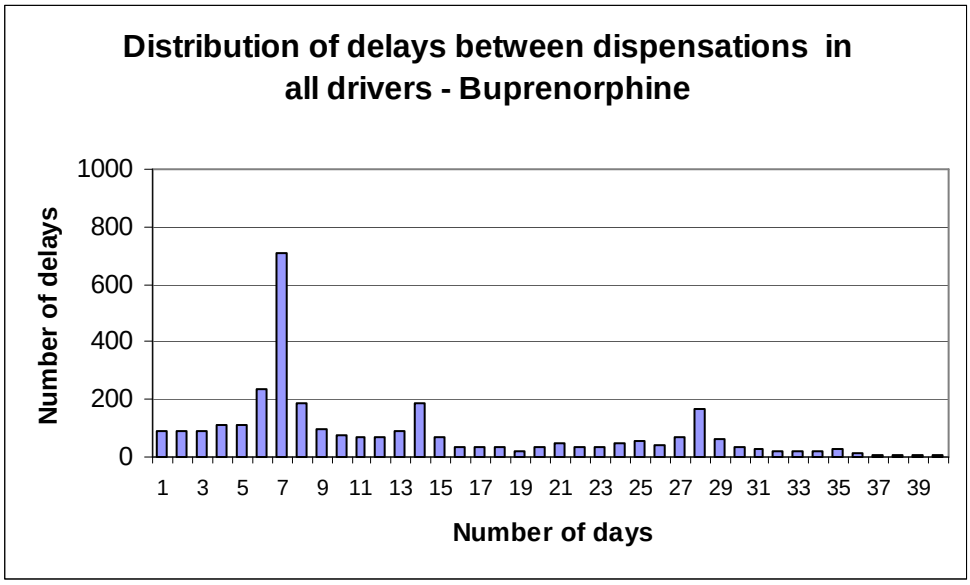
	Exposed drivers†	OR [95% CI]
Zopiclone	243	1.17 [0.97-1.41]
Zolpidem	313	1.05 [0.90-1.24]
BZD hypnotics	135	1.42 [1.09-1.85]*

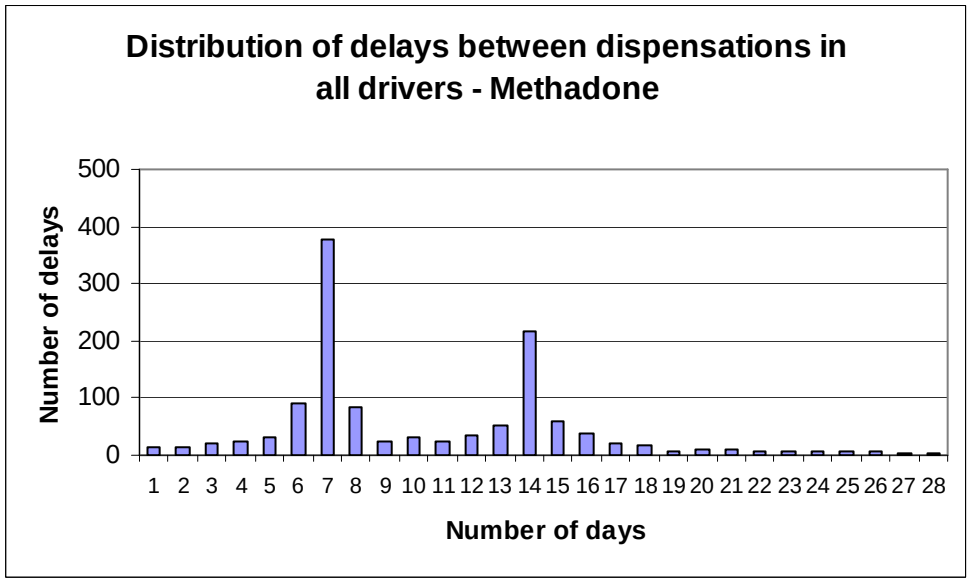
† drivers exposed in the case period and not exposed in the control period

* $p<0.01$

APPENDIX 8

Determination of the exposure and wash-out periods
Buprenorphine and Methadone





Résumé: La prise de conscience de l'implication des médicaments dans la genèse des accidents de la route date d'une vingtaine d'années. Les médicaments psycho-actifs peuvent altérer les capacités de conduite par leur action sur le système nerveux (par exemple, un effet sédatif le lendemain d'une prise d'hypnotique). D'autres médicaments sont susceptibles d'affecter les fonctions psychomotrices par leur action sur les fonctions physiologiques (tel que les hypoglycémies liées à un traitement antidiabétique). L'étude CESIR-A a été mise en place pour contribuer à la connaissance du lien épidémiologique entre médicaments et accidents de la route. L'étude utilise trois bases de données françaises : le Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIR-AM), les Procès Verbaux d'accidents (PV) et les Bulletins d'Analyse des Accidents Corporels de la circulation (BAAC). L'appariement de ces données a conduit à l'inclusion de 72,685 conducteurs impliqués dans un accident corporel sur la période juillet 2005-mai 2008. L'analyse a été réalisée grâce à deux méthodes: une analyse cas-témoin comparant les responsables aux non-responsables des accidents et une analyse dite en case-crossover. Les périodes d'exposition aux médicaments ont été estimées à partir des dates de délivrances de médicaments prescrits, puis remboursés par l'assurance maladie. L'étude des médicaments regroupés selon les quatre niveaux de risque sur la conduite définis par l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) [du niveau 0 (pas de risque) au niveau 3 (risque élevé)], a montré que les utilisateurs de médicaments prescrits de niveau 2 et de niveau 3 ont un risque significativement plus élevé d'être responsables de leur accident (OR=1,31 [1,24-1,40] et OR=1,25 [1,12-1,40], respectivement). La fraction de risque attribuable à l'utilisation de ces médicaments était de 3,3% [2,7%-3,9%]. Le risque d'être responsable d'un accident était augmenté chez les utilisateurs de zolpidem (OR=1,28 [1,07-1,53]) mais pas chez les utilisateurs de zopiclone ou de benzodiazépines hypnotiques. Plus particulièrement, ce risque était augmenté chez les 139 conducteurs ayant eu plus d'un comprimé de zolpidem délivré par jour au cours des cinq mois précédant l'accident (OR=2,38 [1,61-3,52]). L'analyse case-crossover a mis en évidence un sur-risque d'accident de la route chez les utilisateurs de benzodiazépines hypnotiques seulement (OR=1,42 [1,09-1,85]). Les conducteurs exposés aux hypnotiques partagent les mêmes caractéristiques au regard du type d'accident, qui survenaient plus fréquemment sur autoroute. Dans notre base de données, 196 conducteurs ont été exposés à la buprénorphine et/ou à la méthadone, le jour de leur accident. Cette population spécifique était jeune, essentiellement masculine, avec d'importantes co-consommations, notamment d'alcool de médicaments de niveau 3. Les conducteurs exposés à la buprénorphine et/ou à la méthadone présentaient un risque accru d'être responsables de leur accident (OR= 2,19 [1,51-3,16]). Notre étude fournit des informations importantes sur la contribution des médicaments au risque d'accident de la route. D'après nos résultats, la classification de l'AFSSAPS semble appropriée concernant les médicaments de niveaux 2 et 3. Les sur-risques d'être responsable d'un accident chez les exposés au zolpidem ou aux traitements de substitution pourraient être liés, au moins en partie, au comportement à risque de ces conducteurs. L'amélioration du comportement des conducteurs représente un des défis pour la sécurité routière. L'objectif de la classification française et de la signalétique apposée sur les boîtes de médicaments est donc de fournir aux patients une information appropriée sur les effets des médicaments sur leur capacité de conduite.

Abstract: In recent decades, attention has been increasingly focused on the impact of disabilities and medicinal drug use on road safety. Psychoactive medicines may impair driving abilities due to their action on the central nervous system (e.g. sedation in the morning following administration of a hypnotic), while other medicines may affect psychomotor functions by their action on physiological functions (e.g hypoglycaemic seizures related to diabetic treatment). The CESIR-A project was set up to improve the epidemiological knowledge on medicines and the risk of road traffic crashes. The study matched three French nationwide databases: the national healthcare insurance database, police reports, and the police national database of injurious crashes, leading to the inclusion of 72,685 drivers involved in an injurious road traffic crash from July 2005 to May 2008. Two methods were performed for data analysis: a case-control analysis in which cases where responsible drivers and controls non-responsible ones and a case-crossover analysis. Medicine exposures were estimated from prescription drug dispensations in the healthcare reimbursement database. The study of medicines grouped according to the four levels of driving impairment risk of the French classification system [from 0 (no risk) to 3 (high risk)], showed that users of level 2 and level 3 prescribed medicines were at higher risk of being responsible for the crash (OR=1.31 [1.24-1.40] and OR=1.25 [1.12-1.40], respectively). The fraction of road traffic crashes attributable to levels 2 and 3 medicines was 3.3% [2.7%-3.9%]. Zolpidem use was associated with an increased risk of being responsible for a road traffic crash (OR=1.28 [1.07-1.53]) whereas use of zopiclone and benzodiazepine hypnotics use was not. Responsibility risk was only increased in the 139 drivers with dispensing of more than one pill of zolpidem a day during the five months before the crash (OR=2.38 [1.61-3.52]). Case-crossover analysis showed an increased risk of crash for benzodiazepine hypnotic users only (OR=1.42 [1.09-1.85]). Hypnotic users shared similar crash characteristics, with crashes more likely to occur on highways. In our database, 196 drivers were exposed to buprenorphine and/or methadone on the day of crash. This specific population was young, essentially males, with important co-consumption of other substances, in particular alcohol and level 3 medicines. Injured drivers exposed to buprenorphine and/or methadone on the day of crash, had an increased risk of being responsible (OR=2.19 [1.51-3.16]). The case cross-over analysis did not demonstrate any association (OR=1.26 [0.93 - 1.70]). Our study provides evidence of the contribution of medicines to the risk of road traffic crashes. According to our results, the French risk classification seems relevant regarding medicines classified as levels 2 and 3 of risk for road traffic crashes. The observed increased risks of being responsible for a crash for zolpidem and substitution maintenance treatment users may be linked to risky behaviors. Improving driver behaviour is one of the challenges for road safety. Providing patients with proper information on the potential effect of medicines on their driving abilities is the main objective of drug and risk classifications such as the French one.

Mots Clés: épidémiologie, accidents de la route, médicaments / Keywords : epidemiology, road traffic crashes, medicines