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Medicine consumptions and occupational road risk

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What is new in the paper/what are the policy implications of the paper

It is the first study which focus on the association between exposure to ten classes of medicines and the risk of being responsible for a road traffic crash according to the type of journey (private, commuting or mission) in France.

Medicines exposure levels were generally lower for drivers during occupational journeys.

The risk of being responsible for a road traffic crash was higher on commuting or mission journeys than on private journeys for antiepileptics, psycholeptics, psychoanaleptics and other nervous system drugs.

The implementation of preventive measures about some treatments and diseases in the context of occupational journeys should be developed.

1 **Abstract**

2

3 **Background:** Whereas an increased risk of road traffic crashes has been highlighted as linked
4 to some medicine consumptions, there is no available data on this risk according to the type
5 of journey (private, commuting or mission). Drivers on occupational journey (commuting or
6 mission) are likely to have different coping behaviors related to the use of medicines than
7 drivers on private journey.

8 The aim of our study was to investigate the association between exposure to ten classes of
9 medicines and the risk of being responsible for a road traffic crash according to the type of
10 journey (private, commuting or mission).

11

12 **Methods:** The data used came from three French national databases: the national police
13 database of injurious crashes, the police reports and the national health care insurance
14 database. A total of 179,269 drivers aged between 18 and 65 years old involved in an
15 injurious crash in France between July 2005 and December 2015 were included in the
16 analyses. Logistic regression models stratified by journey were used to estimate the Odds
17 Ratios (OR) and 95% confidence intervals (95% CI), adjusted for potential confounding
18 factors.

19

20 **Results:**

21 Medicines exposure levels were generally lower for drivers during occupational journeys, the
22 risk of being responsible for a road traffic crash seems to be higher on commuting or mission
23 journeys than on private journeys for four medicines.

24 Indeed, for antiepileptics the OR was 1.59 [1.01-2.51] for mission journeys, 1.63 [1.24-2.15]
25 for commuting journeys, and 1.47 [1.25-1.73] for private journey. For psycholeptics the OR
26 was 1.02 [0.80-1.28] for mission journey, 1.19 [1.03-1.39] for commuting and 1.17 [1.08-
27 1.26] for private journey. For psychoanaleptics OR was 1.35 [1.02-1.78] for mission journeys,
28 1.37 [1.17-1.60] for commuting journeys and 1.26 [1.14-1.40] for private journeys. Finally,
29 for other nervous system drugs OR reached 2.04 [1.35-3.07] for mission journeys compared
30 to 1.43 [1.21-1.70] for private journeys.

31

32 **Conclusion:** Our results encourage the implementation of preventive measures about some
33 treatments and diseases in the context of occupational journeys.

34

35 **Keywords:** Road safety, responsibility analysis, road traffic crash, professional drivers,
36 medicines

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48 **Introduction**

49

50 Several studies in France (1) and around the world have been carried out about the link
51 between the consumption of several medicines and the risk of road traffic crash (2). Some
52 drugs are identified as strongly associated to an increased risk of road crash, especially
53 benzodiazepines which represent the most studied class in the literature (3–9).

54 Other drugs have been less studied, with sometimes inconsistent or contradictory results.
55 This is the case, for example, with anti-epileptic drugs (10–12), analgesics (13,14),
56 antidepressants (15–19), muscle relaxants (20) and antihistamines (21–25). In addition,
57 there are several substances in some of these drugs classes that may have an impact on
58 driving ability. This is the case of substances used as hypnotics or antiepileptics, which are
59 likely to have a sedative effect; or some substances used for diabetes that can cause
60 hypoglycemia (26).

61 Studies on the effects of medicines on the risk of road traffic crash are often focused on the
62 elderly (14–16,21,27)). Studies that examined the relationship between drug use and the risk
63 of work-related motor vehicle crashes are scarce, often inconsistent and mainly focused on
64 truck drivers (27–29).

65 However, it can be argued that drivers on work-related journeys are more likely to have a
66 different coping behavior due to many factors (30,31). For example, they may be more
67 exposed to stress and fatigue because they are often required to move quickly and
68 efficiently and because of the pressure that hierarchy can exert. This could lead to different
69 medicine consumption behaviors compared to non-professional drivers.

70 On the other hand, there is reason to believe that some drivers on occupational journeys
71 may have lower consumption prevalence than drivers on private journeys. Indeed, some of

72 them are subjects to specific regulations. Moreover, their journeys do not have the same
73 stakes or objectives as drivers on private journeys, as driving may represent a (financial)
74 livelihood.

75 To our knowledge, no study has compared the differences in consumption and road crash
76 risk according to the type of journey, private or work-related (either commuting or mission).

77 The objective of this study was to determine whether the prevalence of drivers' medicines
78 use differed between work-related journeys (commuting or mission) and non-work-related
79 (private) for ten major classes of drugs and to describe the impact of these drugs on the risk
80 of being responsible for a road crash according to the type of journey.

81

82 **Methods**

83

84 **Data sources**

85 The study is based on three French nationwide databases: police reports (PR), the national
86 police database of injurious crashes (IC) and the national healthcare insurance database (HCI
87 database).

88 The drivers were included in the study by their national ID number (NID, also called social
89 security number) that was extracted from police reports (PRs) by an automatic procedure.

90 Next, drivers were linked to prescription medicines reimbursement data around the date of
91 the crash by their NID. Then, PRs were linked to the National police database of injurious
92 road traffic crashes (IC) records by a probabilistic linkage method (26).

93

94 *Police reports (PRs)*

95 In France, when a road crash with injuries occurs, police forces are called and have to file a
96 report. This report contains general information about the crash. It is then scanned and
97 stored as an image file by TransPv. Almost 70,000 reports are completed each year. The NID
98 is sometimes recorded in the PR. It has been estimated, through manual assessment on a
99 small sample in a previous study, that this NID could be found in 28 % of the drivers
100 concerned (26).

101

102 *National police database of injurious road traffic crashes*

103 Details collected by police forces on each injurious crash are stored in the IC database
104 (Bulletins d'Analyse des Accidents Corporels [BAAC]).

105 This standardized database is led by the National Interministerial Road Safety Observatory
106 (Observatoire national interministériel de sécurité routière [ONISR]). It is filled after police
107 reports.

108 This database contains details about injurious road traffic crashes like on the circumstances
109 of the crash or the vehicles and persons involved.

110 It can contain the severity of the driver's injuries: unhurt, slightly injured, seriously injured
111 (hospitalized for more than 24 hours) or killed (died within the 30 days following the crash)
112 because the police may have to go to the hospital in order to carry out further
113 investigations.

114 It also contains data on alcohol consumption. Indeed, police forces test every driver involved
115 in an injurious crash for the presence of alcohol, using a breathalyzer. In the case where the
116 test is positive (≥ 0.5 g/l), the driver refuses or is incapable of doing the breath test, the blood
117 alcohol level is measured.

118 When the breath test is negative, the driver is recorded as not being under the influence of
119 alcohol.

120

121

122

123 **National health-care insurance database (HCI database)**

124 The HCI database (Système National d'Informations Inter Régimes de l'Assurance Maladie)
125 covers the entire French population. Each time a medicine is delivered to an outpatient in a
126 pharmacy, a record is added, containing different information like the NID, the day of
127 dispensing and the seven-digit code that identifies the medicine prescription. The HCI
128 database also records 30 long-term chronic diseases (for which patients' health care
129 expenses are fully reimbursed) by their ICD-10 code (International Classification of Diseases,
130 Tenth Revision) and by the dates of the beginning and the end of the disease.

131

132 **Participant inclusion**

133 In order to mitigate the impact of previous crashes on medicine exposure, drivers were
134 censored at their first involvement in a road traffic crash if they were involved in more than
135 one crash during the study period.

136 The drivers included in the study are those aged between 18 and 65 years old, who were
137 involved in a road crash in France between July 2005 and December 2015. Subjects whose
138 police reports did not contain their national ID or responsibility were not included.

139

140 **Medicines and exposure periods**

141 Daily exposure to drug prescription was estimated for ten medicines: drugs used in diabetes,
142 antihypertensives, muscle relaxants, analgesics, antiepileptics, anti-parkinson drugs,
143 psycholeptics (containing all benzodiazepines), psychoanaleptics, other nervous system
144 drugs and antihistamines for systemic use.

145

146 Drivers for whom treatment had been delivered on the day of the accident were not
147 considered to be exposed to this treatment because the prescription of this drug could be a
148 consequence of the crash.

149

150 **Concomitant medicine exposure**

151 In France, a four-level risk classification system of medicines affecting driving abilities is
152 established, ranging from level 0 (no or negligible risk) to level 3 (major risk) (32,33).
153 Comparisons were adjusted for exposure to other medicines classified in the highest risk
154 levels (levels 2 and 3) used the day of the crash.

155

156 **Determining driver crash responsibility**

157 A method adapted from Robertson and Drummer (34) was used to determine responsibility
158 levels related to the crash.

159 This method is frequently used in the field of road safety. Six factors who are likely to reduce
160 the responsibility of the driver were considered: road, vehicle and driving conditions, type of
161 crash, traffic rule obedience, and difficulty of task involved. Each driver was then assigned a
162 score for each of these factors. This score went from 1 (favorable for driving) to 4 (not
163 favorable for driving). The scores were then added together to obtain a final score. If the

164 sum was between 8 and 15, the driver was considered to be responsible or partially
165 responsible and if it was greater than or equal to 15 then he was considered not responsible.
166 Then, the principle of responsibility analysis was to compare the probabilities of exposure on
167 the day of the crash between non-responsible drivers and those deemed responsible for the
168 crash. It allowed to include responsible and non-responsible drivers who were directly
169 selected from the driver population.

170 **Statistical analysis**

171

172 *Descriptive analysis*

173 Drivers were classified according to the type of journey when the crash occurred (private,
174 commuting, mission). Using proportions and Chi-2 squared tests, we compared age, gender,
175 socioeconomic category, injury severity, responsibility, vehicle type, time of day, location,
176 alcohol level, frequencies of exposure to medicines of interest and pictogram's levels.

177

178 *Responsibility analysis*

179 A cases-control study approach was developed, where cases were responsible drivers
180 involved in road crashes and the controls were non-responsible drivers involved in road
181 crashes with two assumptions: The first one is that non-responsible drivers are
182 representative of the driving population (reference population). The second one is that
183 responsible and non-responsible drivers were both driving a vehicle on the day of the crash
184 so they had the same probability of being on the road at the same time (especially in the
185 case where several vehicles were involved). It also allowed providing as much information on
186 others exposures and risk factors for both categories.

187 The association between driver responsibility in the crash and exposure to drugs used in
188 diabetes, antihypertensives, muscle relaxants, analgesics, antiepileptics, anti-parkinson
189 drugs, psycholeptics, psychoanaleptics, other nervous system drugs (which include
190 parasympathomimetics, drug used in addiction disorders, antivertigo preparations and
191 other nervous system drugs) and antihistamines for systemic use by the type of journey was
192 then investigated using univariate and multivariate logistic regression models with a
193 stratification on the type of journey.

194 Interaction tests (likelihood ratio tests) were performed to determine if the type of journey
195 did significantly modify the effect of medicines on responsibility.

196 Multivariate models included adjustment variables identified in the literature as potential
197 risk or confounding factors: socio-economic characteristics (age, gender, socioeconomic
198 category), health characteristics (exposure to another drug of level 2 or level 3 on the day of
199 the crash), alcohol level and characteristics of the crash (year, month, day of week, time of
200 day (daytime vs nighttime), location (urban area vs nonurban area), vehicle type, blood
201 alcohol level, and injury severity).

202 An adjustment on the existence of the long-term chronic disease "epilepsy" was also
203 performed for the model about antiepileptics use in order to look at the potential confusion
204 effect of the disease. Indeed, epileptic seizures could be the triggering factor for the crash,
205 independently of the effects of the drugs while antiepileptics are widely used for other
206 indications as neuropathic pain, bipolar disorder or migraine. On private journeys, 1,644
207 drivers were exposed to antiepileptic drugs. Among them, 138 had a long-term chronic
208 disease related to epilepsy. It was the case for 43 drivers on commuting journeys (398
209 drivers were exposed to antiepileptics) and 15 drivers on mission journeys (147 drivers were
210 exposed to antiepileptics).

211 Missing data only concerned blood alcohol concentration (n = 22,225, 12.4 %). We estimated
212 that it was not possible to make imputations on these missing values and consequently
213 created a specific category “missing data”.

214 Data were analysed using R® statistical software package, version 3.2.3 and 3.5.0 (R
215 foundation for statistical computing, Vienna, Austria).

216

217 **Ethical statement**

218 Confidentiality was ensured by using the anonymization function of the Health Care
219 Insurance system (35). The study was approved by the French data protection authority
220 (Commission Nationale Informatique et Libertés).

221

222

223 **Results**

224

225 **Study population**

226 Police reports were available for 229,962 persons involved in road crashes with injuries
227 during the study period. Among them, 22,196 were excluded because they were under 18
228 years of age or over 65 years of age and 28,465 NIDs were excluded because they were
229 pedestrians or passengers. 179,301 drivers were then included.

230 Responsibility in the crash was established for 179,269 drivers: 85,684 were identified as
231 responsible and 93,585 as non-responsible (figure 1).

232 Drivers aged between 35 and 45 years were more represented among drivers on commuting
233 (25.5%) or mission (27.8 %) journeys compared to drivers on private journeys (21.7 %).

234 The proportion of men was significantly higher among drivers on mission journeys (84.3 %)
235 than among drivers on commuting (66.1%) or private journeys (67.4 %) (table 1).

236

237 **Exposure to Medicines**

238 Fourteen percent of the drivers included in the study (n = 25,466) were exposed to at least
239 one prescription medicine on the day of the crash.

240 This proportion was about fifteen percent (n = 17,746) for private journeys, about thirteen
241 percent (n = 5,400) for commuting journeys and about eleven percent for mission journeys
242 (n = 2,320).

243 Standardized incidences on sex and age groups were also different depending on the type of
244 journey with an incidence higher for private journeys (15,942 for 100,000 road crashes) than
245 for commuting (12,963 for 100,000 road crashes) or mission (11,636 for 100,000 road
246 crashes) journeys.

247 Drivers on private journeys had consumption prevalences twice as high as drivers on mission
248 journeys for four classes of medicines: antiepileptics (1.4 % on private journeys and 0.7 % on
249 mission journeys), psycholeptics (6.4 % on private journeys and 2.8 % on mission journeys),
250 psychoanaleptics (4.8 % on private journeys and 2.2 % on mission journeys) and other
251 nervous system drugs (1.3 % on private journeys and 0.7 % on mission journeys).

252 Consumption prevalences were similar among drivers regardless the type of journey for five
253 medicines: antihypertensives, muscle relaxants, analgesics, anti-parkinson drugs and
254 antihistamines (table 2).

255 Almost sixty-four percent (n = 16,775) of drivers exposed to one of the tenth medicines
256 studied on the day of the crash were exposed to a level 2 treatment and more than five
257 percent (n = 1,412) to a level 3 treatment (table 3).

258 After adjusting for risk factors identified from the literature (age, gender, socioeconomic
259 category, blood alcohol concentration, year, month, day of the week and time of day of the
260 crash, localization, vehicle type and injury severity) and for exposure to other level 2 or 3
261 drugs on the day of the crash, the risk of being responsible for a road traffic crash was
262 significantly increased for drivers on private journeys for four medicines: antiepileptics
263 (N03), psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07).

264 For drivers on commuting journeys positive associations were found for three medicines:
265 antiepileptics (N03), psycholeptics (N05) and psychoanaleptics (N06) and for drivers on
266 mission journeys for three treatments: antiepileptics (N03), psychoanaleptics (N06) and other
267 nervous system drugs (N07) (table 4).

268 After taking account of the existence of a long-term chronic disease for epilepsy, the
269 association of the responsibility and the exposure to antiepileptics were lower but still
270 significant for private journeys (OR=1.39 [1.17-1.64]) and for commuting journeys (OR=1.43

271 [1.08-1.89]) whereas the association was no more significant for mission journeys (OR= 1.31
272 [0.81-2.11]). In the same time, the association with the existence of a long-term chronic
273 disease for epilepsy were significant (OR= 1.54 [1.15-2.06] for private journeys, OR= 2.94
274 [1.73-4.99] for commuting journeys and OR= 3.49 [1.43-8.52] for mission journeys).

275 The results of the responsibility and interaction tests analysis revealed a significantly higher
276 risk for drivers on commuting and mission journeys than for drivers on private journeys for
277 four medicines: antiepileptics, psycholeptics and psychoanaleptics for drivers on commuting
278 journeys and antiepileptics, psychoanaleptics and other nervous system drugs for drivers on
279 mission journeys.

280 Indeed, for antiepileptics, the risk was 1.47 [1.25-1.73] for drivers who were on private
281 journeys, 1.63 [1.24-2.15] for drivers who were on commuting journeys and 1.59 [1.01-2.51]
282 for drivers who were on mission journeys.

283 For psycholeptics low differences were observed between private and commuting journeys.
284 The risk reached 1.17 [1.08-1.26] on private journeys and 1.19 [1.03-1.39] on commuting
285 journeys. The association was not significant for drivers on mission journeys.

286 For psychoanaleptics, the risk was lower for drivers on private journeys, 1.26 [1.14-1.40]
287 journeys, and similar among drivers on commuting (OR = 1.37 [1.17-1.60]) and mission (OR =
288 1.35 [1.02-1.78]) journeys.

289 Surprisingly, for private journeys, drivers exposed to antihistamines were less likely to be
290 responsible for a road crash than unexposed drivers (OR = 0.89 [0.81-0.97]). Exposures to
291 drugs used in the treatment of diabetes or hypertension, muscle relaxants, analgesics or
292 anti-parkinson drugs were not significantly associated with an increase or a decrease in the
293 risk of being responsible for a road crash, regardless of the type of journey performed.

294

295 **Discussion**

296

297 Lower medicines consumption prevalences were identified for drivers who were on
298 commuting or mission journeys. On the other hand, slightly higher risks of being responsible
299 for the crash were observed for drivers who were on commuting or mission journeys for four
300 medicines: antiepileptics, psycholeptics (only for commuting journeys, not significant for
301 mission journeys), psychoanaleptics and other nervous system drugs (only for mission
302 journeys, not significant for commuting journeys). These differences may be explained by
303 several factors.

304 First, it is possible that the effects highlighted for some medicines, particularly antiepileptic
305 drugs, are more related to the expression of the pathology itself (epileptic seizures) than to
306 the treatment taken. As shown before, results of responsibility analysis did suggest a
307 confusion effect of epilepsy after adjusting on the existence of a long-term chronic disease
308 (epilepsy) for drivers. Nevertheless, these results are based on low numbers (196 drivers
309 under anti-epileptics were identified as having a long-term chronic disease related to
310 epilepsy (138 on private journeys, 43 on commuting and 15 on mission).

311 Epilepsy is one of the pathologies that can contraindicate driving vehicles. These findings
312 may suggest that it is probably not antiepileptics but the disease itself or related seizures
313 that are likely to represent a risk factor for a car crash. Furthermore, it can possibly be
314 because of the use of antiepileptics for other diseases than epilepsy (36). Further studies
315 should be made in order to investigate this hypothesis.

316 Anyhow, the risk found in our study for antiepileptics is partially consistent with other
317 studies. Indeed, one previous study performed within the framework of CESIR project (10)
318 found a positive and significant association between the exposure to antiepileptics and the

319 risk of road crash (OR = 1.74 [1.29-2.34]) whereas other studies did not find any significant
320 association (11,12).

321 The slightly higher increase in risk for crashes in mission and commuting may reflect the fact
322 that there may be more drivers with severe epileptic conditions driving for professional sake.
323 Drivers with a higher risk of seizure could be more easily be deterred to drive for private
324 reasons than when facing the need to exercise a professional activity in order to have an
325 income.

326 In this study, the most important association on mission journeys has been highlighted for
327 other nervous system drugs (OR = 2.04 [1.35-3.07] on mission journeys against 1.43 [1.21-
328 1.70] on private journeys and 1.33 [0.99-1.77] on commuting journeys). 87,5% of these
329 drivers were males, 35,6% were between 25 and 34, 32,7% between 35 and 44 and 20,2%
330 between 45 and 54. 31,7% were professional drivers. 26,9% drove a car, 22,1% a commercial
331 vehicle and 17,3% a truck. Other nervous system drugs contain parasympathomimetics,
332 drug used in addiction disorders, antivertigo preparations and other nervous system drugs.
333 Those treatments are used in order to treat specific pathologies so we can make the
334 assumption that the risk of being responsible for a car crash is, like for antiepileptics, maybe
335 linked to the pathology itself more than to the treatment.

336 Medicine exposure was ascertained from computerized records of reimbursed prescriptions
337 filled at the pharmacy. It allowed to have data that was not subject to underreporting, which
338 is a real problem often encountered when people self-report medicine exposure
339 information.

340 On the other hand, the HCl database does not provide information about compliance or self-
341 medication. Non-compliance can sometimes induce exposure misclassification that would
342 lead to underestimate the risk. Another limitation with this database is that real

343 consumption dates were not available and we had to impute them from dispensing dates.
344 Our exposure measure should therefore be considered as a surrogate for actual
345 consumption.

346 The responsibility analysis is a real strength of the study because it allowed using non-
347 responsible drivers, who are sharing common characteristics with responsible drivers as
348 control group (being a driver, road type, hour of the day...). Furthermore, the responsibility
349 analysis is based on two main assumptions. The first one is that non-responsible drivers are
350 representative of the driving population. **The second one is that responsible and non-**
351 **responsible drivers were both driving a vehicle on the day of the crash so it also allowed**
352 **providing the same information on other exposures for both categories (especially for**
353 **accidents where several vehicles were involved). This would not have been the case in a**
354 **case-control study where controls were only selected from medical or from driver's license**
355 **databases.**

356 Finally, it is a method frequently used in the field of road traffic safety. This method has been
357 approved by an independent expert evaluation of responsibility in a previous study (37)
358 performed on the impact of illegal drug consumption, using this method and the same
359 national database (but limited to fatal crashes). However, this method does not capture the
360 risk, for non-responsible drivers, of being unable to avoid a crash that could be related to
361 medicine use. This would lead to risk under-estimation.

362 **However, as responsibility studies typically report the increased odds of responsibility**
363 **associated with some factor and as non-responsible drivers are considered to be comparable**
364 **to non-accidented drivers, this study design could lead to interpretational bias and over**
365 **estimation of the odds ratio when the responsibility odds ratio are considered as direct road**
366 **crash odds ratio (38).**

367 Seriously injured drivers were more likely to be taken to the hospital and so to have their
368 national id number registered in police reports. Consequently, there was an association
369 between injury severity and being part of the study and drivers who were more seriously
370 injured and implicated in more serious traffic crashes were slightly over-represented in our
371 sample. Killed or uninjured drivers had lower inclusion rates than severely injured driver.

372

373 In addition, the databases used for this study only include drivers involved in road crashes
374 resulting in personal injury (to the driver or to someone else). Drivers who were involved in
375 non-injury road crashes are not included. It could have led to a selection bias.

376 Other studies used the responsibility analysis approach in order to look at the relation
377 between the exposure to some medicines classes and the risk of being responsible for a road
378 crash (24,39,40). Nevertheless, to our knowledge, no study assessed the consumptions and
379 risks differences between drivers on private journeys and drivers on professional journeys.

380 However, several studies assessed the consumptions and risks differences between
381 professional and nonprofessional drivers. We found no association between the exposure to
382 antihistamines during occupational journeys and the risk of being responsible for a road
383 traffic crash unlike a previous study conducted among professional drivers (OR = 3.44 [1.06-
384 11.16]). However, this latter study included truck drivers only.

385 The risks identified in our study for psycholeptics and psychoanaleptics are consistent with
386 other previous studies not conducted but no data have been so far published on professional
387 drivers in particular (19,21,41).

388

389 **Conclusion**

390

391 This study brings original results about the problematic of medicines consumptions and
392 driving for purposes of work. Firstly, in terms of the prevalence of the exposure that is higher
393 for drivers on private journeys. Then, in terms of the risk of being responsible for a road
394 traffic crash linked to those consumptions, with a risk higher for drivers on commuting or
395 mission journeys compared to private journeys for four medicines: antiepileptics,
396 psycholeptics (only for commuting journeys, not significant for mission journeys),
397 psychoanaleptics and other nervous system drugs (only for mission journeys, not significant
398 for commuting journeys).

399

400 This study brings new information to health professionals (general practitioners,
401 occupational practitioners and practitioners approved for driving licenses), especially about
402 antiepileptics, psycholeptics, psychoanaleptics and other nervous system drugs
403 consumptions. For those four medicines, an increased-risk was observed for drivers on
404 commuting or mission journeys.

405 Preventive measures could be implemented in order to make occupational practitioners and
406 employees aware of the occupational road risks associated with the use of some
407 medications.

408 Further studies to confirm these results would be useful, including studies on the time to
409 onset of work-related road crashes after the start of a drug prescription. This would clarify
410 the impact of drugs and improve prevention and recommendations currently implemented
411 by, for example, adjusting the time to return to driving.

412

413

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415

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417

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Figure 1: Flowchart of the inclusion procedure.

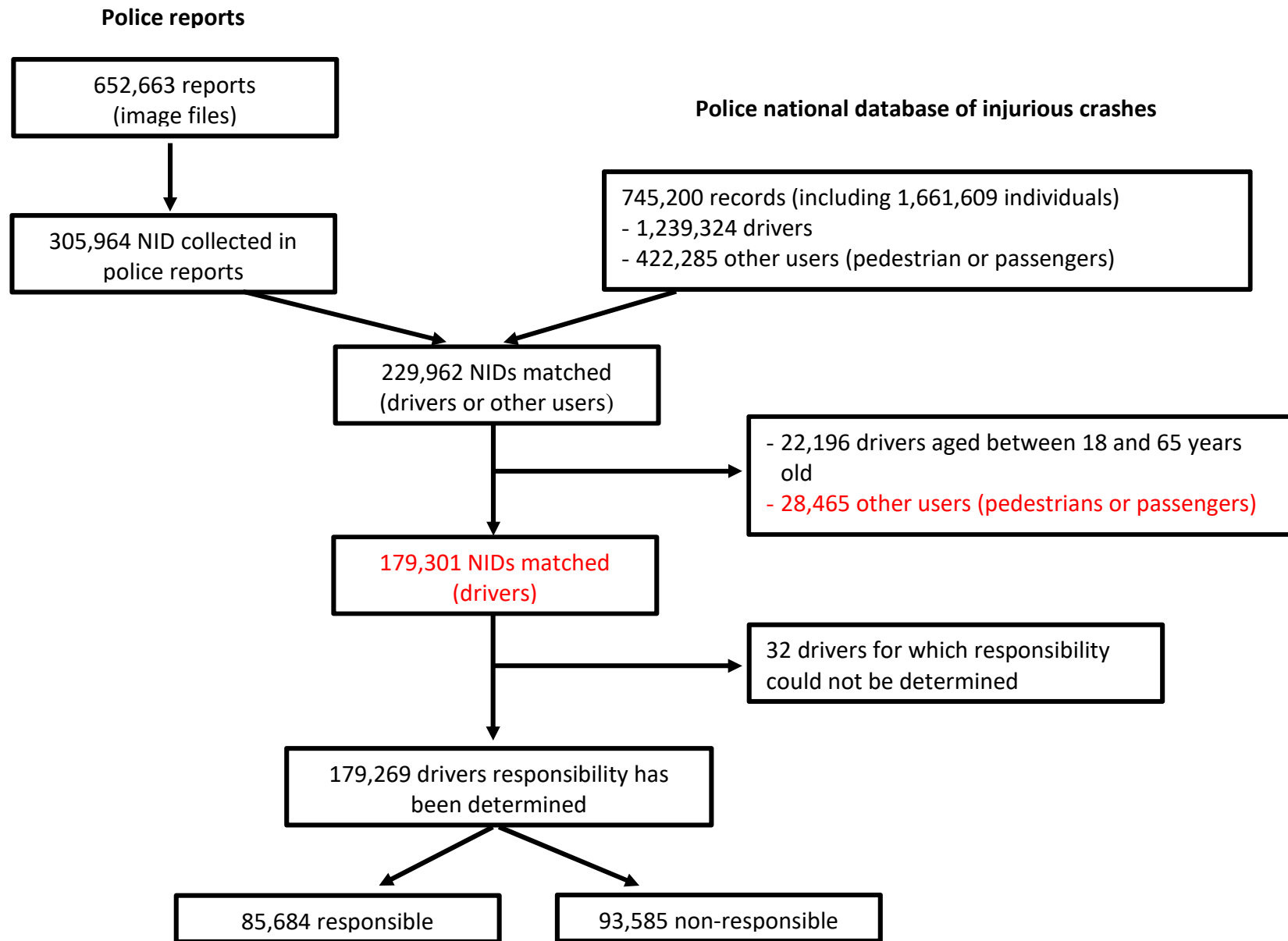


Table 1: Baseline characteristics according to the type of journey, N = 179,269.

	Private N = 114,767 (64%)		Commuting N = 43,012 (24%)		Mission N = 21,490 (12%)	
	n	%	n	%	n	%
Age (years) **						
[18-25[27,423	23.9	7,964	18.5	2,580	12.0
[25-35[28,262	24.6	12,253	28.5	5,828	27.1
[35-45[24,941	21.7	10,984	25.5	5,971	27.8
[45-55[20,145	17.6	8,622	20.0	4,999	23.3
[55-65]	13,996	12.2	3,189	7.5	2,112	9.8
Sex**						
Men	77,342	67.4	28,451	66.1	18,115	84.3
Women	37,425	32.6	14,561	33.9	3,375	15.7
Socioeconomic category **						
Professionnal driver	1,579	1.4	757	1.8	4,513	21.0
Farmer	580	0.5	243	0.6	372	1.7
Craftsman, trader, intermediate profession	4,189	3.7	1,969	4.6	1,729	8.0
Higher managerial and professional occupations	4,613	4.0	3,118	7.2	1,465	6.8
Intermediate occupations	28,958	25.2	19,161	44.5	7,489	34.8
Workers	16,903	14.7	9,349	21.7	3,306	15.4
Retired	5,938	5.2	65	0.2	50	0.2
Unemployed	8,504	7.4	187	0.4	71	0.3
Toher/missing	33,465	29.2	6,888	16.0	2,266	10.5
Student	10,038	8.7	1,275	3.0	229	1.1
Long-term chronic disease**						
Yes	10,177	8.9	2,605	6.1	1,380	6.4
No	104,590	91.1	40,407	93.9	20,110	93.6
Injury severity**						
Unhurt	32,530	28.4	10,515	24.5	10,183	47.4
Slightly injured	40,672	35.4	18,042	41.9	7,294	33.9
Seriously injured	39,689	34.6	13,839	32.2	3,794	17.7
Killed	1,876	1.6	616	1.4	219	1.0
Responsibility**						
Non-responsible	57,608	50.2	24,122	56.1	11,855	55.2
Responsible or partially responsible	57,159	49.8	18,890	43.9	9,635	44.8
Pictogram levels **						
Level 0	73,841	64.3	28,272	65.7	12,625	58.7
Level 1	6,632	5.8	2,779	6.5	1,629	7.6
Level 2	3,471	3.0	1,338	3.1	670	3.1
Level 3	61	0.1	24	0.1	29	0.1
NI	30,762	26.8	10,599	24.6	6,537	30.5

(Continuation of table 1)

	Private		Commuting		Mission	
	N = 114,767 (64%)		N = 43,012 (24%)		N = 21,490 (12%)	
	n	%	n	%	n	%
Vehicle type**						
Bicycle	6,105	5.4	2,180	5.1	296	1.4
Scooter	11,044	9.6	3,855	9.0	1,189	5.5
Motorbike	21,129	18.4	10,364	24.1	2,225	10.4
Light vehicle	72,235	62.9	24,211	56.2	7,623	35.5
Commercial vehicle	2,994	2.6	1,872	4.3	3,915	18.2
Heavy goods vehicle	470	0.4	282	0.7	3,018	14.0
Other	790	0.7	248	0.6	3,224	15.0
Time of the day**						
Day [7h-20h]	94,786	82.6	37,899	88.1	19,177	89.2
Night [21h-6h]	19,981	17.4	5,113	11.9	2,313	10.8
Alcohol (g/L) **						
Not applicable, rate of 0	90,163	78.5	36,657	85.2	18,889	87.9
<0,5	1,025	0.9	134	0.3	52	0.2
[0,5 – 0,8[1,775	1.5	130	0.3	41	0.2
[0,8-1,2[4,122	3.6	294	0.7	94	0.4
[1,2-2,0[3,389	3.0	214	0.5	65	0.3
NI	14,293	12.5	5,583	13.0	2,349	10.9
Localisation**						
Urban areas	64,945	56.6	23,519	54.7	9,916	46.1
Suburban areas	49,822	43.4	19,493	45.3	11,574	53.9
Exposure to a level 2 medicine**						
	12,187	10.6	3,277	7.6	1,311	6.1
Exposure to a level 3 medicine**						
	1,066	0.9	250	0.6	96	0.4

**p<0,001 (Chi-2 square test). NI : No Information

Table 2: Numbers and proportions of exposed drivers on the crash day by classification of medicines used (overall and according to the type of journey), N = 179,269.

	Full population N = 179,269		Private N = 114,767		Commuting N = 43,012		Mission N = 21,490	
	n	%	n	%	n	%	n	%
Drug used in diabetes (A10)	2,689	1.5	1,837	1.6	502	1.2	350	1.6
Antihypertensives (C02)	316	0.2	220	0.2	56	0.1	40	0.2
Muscle relaxants (M03)	715	0.4	485	0.4	174	0.4	56	0.3
Analgesics (N02) ^a	9,527	5.3	6,546	5.7	2,064	4.8	917	4.3
Antiepileptics (N03)	2,189	1.2	1,644	1.4	398	0.9	147	0.7
Anti-Parkinson drugs (N04)	294	0.2	233	0.2	45	0.1	16	0.1
Psycholeptics (N05) ^b	9,525	5.3	7,342	6.4	1,583	3.7	600	2.8
Psychoanaleptics (N06) ^c	7,415	4.1	5,491	4.8	1,443	3.4	481	2.2
Other nervous system drugs (N07) ^d	1,983	1.1	1,486	1.3	340	0.8	157	0.7
Antihistamines for systemic use (R06)	4,462	2.5	2,949	2.6	1,064	2.5	449	2.1

a Including opioids (n= 4,288), other analgesics and antipyretics (n= 4,448) and antimigraine preparations (n= 791)

b Including antipsychotics (n= 1,833), anxiolytics (n= 6,195) and hypnotics and other sedatives (n= 1,497)

c Including antidepressants (n= 7,256), psychostimulants (n= 66) and antidementia drugs (n= 93)

d Including parasympathomimetics (n = 17), drug used in addiction disorders (n= 1,634), antivertigo preparations (n= 303) and other nervous system drugs (n= 29)

Table 3: Exposure prevalence (overall and by type of medicines) to at least another medicine of level 2 or level 3, N = 179,269.

	N global* = 25,466		Drugs used in diabetes N = 2,689		Anti-hypertensives N = 316		Muscle relaxants N = 715		Analgesics N = 9,527		Anti-epileptics N = 2,189		Anti-parkinson drugs N = 294		Psycho-leptics N = 9,525		Psycho-analeptics N = 7,415		Other nervous system drugs N = 1,983		Anti-histamines for systemic use N = 4,462	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Exposure to at least another treatment of level 2	16,775	63.8	732	27.2	129	40.8	369	51.6	2,706	28.4	1,228	56.1	218	74.1	5,632	59.1	4,571	61.6	997	50.3	1,092	24.5
Exposure to at least another treatment of level 3	1,412	5.4	97	3.6	19	6.0	28	3.9	361	3.8	104	4.8	7	2.4	0	0	400	5.4	90	4.5	111	2.5

*drivers under one of the ten medicines studied on the day of the crash

Table 4: Associations between the exposition to ten medicines and the risk of being responsible for a road traffic accident according to the type of journey (private, commuting, mission). Multivariate logistic regression, N = 179,269.

Medicines (yes/no)	Private N = 114,767			Commuting N = 43,012			Mission N = 21,490		
	n Responsible/ Non- responsible	% Responsible/ Non- responsible	adjusted OR [95% IC] ^a	n Responsible/ Non- responsible	% Responsible/ Non- responsible	Adjusted OR [95% IC] ^a	n Responsible/ Non- responsible	% Responsible/ Non- responsible	Adjusted OR [95% CI] ^a
Drugs used in diabetes (A10)	909 / 928	1.6 / 1.6	1.05 [0.93-1.18]	219 / 283	1.2 / 1.2	1.07 [0.87-1.31]	167 / 183	1.7 / 1.5	1.13 [0.89-1.43]
Antihypertensives (C02)	92 / 122	0.2 / 0.2	0.83 [0.58-1.20]	26 / 30	0.1 / 0.1	0.95 [0.47-1.91]	18 / 22	0.2 / 0.2	1.09 [0.53-2.24]
Muscle relaxants (M03)	219 / 266	0.4 / 0.5	0.75 [0.56-1.00]	75 / 99	0.4 / 0.4	0.99 [0.65-1.49]	19 / 37	0.2 / 0.3	0.77 [0.35-1.70]
Analgesics (N02) ^b	3,232 / 3,314	5.7 / 5.8	0.95 [0.90-1.02]	890 / 1 174	4.7 / 4.9	0.99 [0.89-1.10]	398 / 519	4.1 / 4.4	0.91 [0.78-1.06]
Antiepileptics (N03)	983 / 661	1.7 / 1.1	1.47 [1.25-1.73]**	202 / 196	1.1 / 0.8	1.63 [1.24-2.15]**	86 / 61	0.9 / 0.5	1.59 [1.01-2.51]*
Anti-parkinson drugs (N04)	125 / 108	0.2 / 0.2	1.25 [0.74-2.10]	18 / 27	0.1 / 0.1	0.80 [0.20-3.24]	7 / 9	0.1 / 0.1	0.62 [0.14-2.64]
Psycholeptics (N05) ^c	4,265 / 3,077	7.5 / 5.3	1.17 [1.08-1.26]**	767 / 816	4.1 / 3.4	1.19 [1.03-1.39]*	297 / 303	3.1 / 2.6	1.02 [0.80-1.28]
Psychoanaleptics (N06) ^d	3,192 / 2,299	5.6 / 4.0	1.26 [1.14-1.40]**	681 / 762	3.6 / 3.2	1.37 [1.17-1.60]**	247 / 234	2.6 / 2.0	1.35 [1.02-1.78]*
Other nervous system drugs (N07) ^e	997 / 489	1.7 / 0.8	1.43 [1.21-1.70]**	188 / 152	1.0 / 0.6	1.33 [0.99-1.77]	104 / 53	1.1 / 0.4	2.04 [1.35-3.07]**
Antihistamines for systemic use (R06)	1,346 / 1,603	2.4 / 2.8	0.89 [0.81-0.97]*	460 / 604	2.4 / 2.5	0.99 [0.87-1.14]	199 / 250	2.1 / 2.1	1.03 [0.83-1.27]

a ORs adjusted for age, gender, socioeconomic category, blood alcohol concentration (g/L), year, month, day of the week and time of the day (day/night), localisation (urban/nonurban area),

vehicle type, injury severity and other medicines of level 2 or level 3

b Including opioids (n= 4,288), other analgesics and antipyretics (n= 4,448) and antimigraine preparations (n= 791)

c Including antipsychotics (n= 1,833), anxiolytics (n= 6,195) and hypnotics and other sedatives (n= 1,497)

d Including antidepressants (n= 7,256), psychostimulants (n= 66) and antidementia drugs (n= 93)

e Including parasympathomimetics (n = 17), drug used in addiction disorders (n= 1,634), antivertigo preparations (n= 303) and other nervous system drugs (n= 29)

*p<0.05 **p<0.001