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Driving under the Influence of Drugs, Alcohol and Medicines

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Relative accident risk of patients using psychotropic medicines in the Netherlands: A pharmacoepidemiological study

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Deliverable 2.3.1.

Relative accident risk of patients using psychotropic medicines in the Netherlands: A pharmacoepidemiological study.

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List of Abbreviations

ATC: Anatomical Therapeutic Chemical

CI: Confidence Interval

CNS: Central Nervous System

DDD: Defined Daily Dose

DRUID: Driving Under the Influence of Drugs, Alcohol and Medicines

DVS: Dienst Verkeer en Scheepvaart (Dutch Traffic and Navigation Authority)

EU: European Union

KNMP: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (Royal Dutch Association for the Advancement of Pharmacy)

MAO: Monoamine Oxidase A Inhibitor

OTC: Over The Counter (medication)

OR: Odds Ratio

PID: Patient Identification Number

RDW: Rijks Dienst Wegverkeer (Dutch Road Transport Authority)

SSRI: Selective Serotonin Reuptake Inhibitor

TCA: Tricyclic antidepressant

TTP: Trusted Third party

UMCG: University Medical Centre Groningen

WINAp: Wetenschappelijk Instituut Nederlandse Apothekers (Scientific Institute of Dutch Pharmacists)

WMO: Wet Medisch-wetenschappelijk Onderzoek met mensen (Medical Research Involving Human Subjects Act)

WP: Work Package

Executive Summary

This Deliverable is part of the European Union (EU) project Driving Under the Influence of Drugs, alcohol and medicines (DRUID).

The consumption of psychoactive substances can influence people's motor and cognitive performances, and, therefore, affect people's ability to drive safely. Alcohol is a well-known risk factor for motor vehicle collisions, but the use of other substances (i.e. illegal and legal drugs) can also play an important role in endangering traffic safety. Therefore, special efforts must be taken in order to obtain a better knowledge on psychoactive substance use and driving impairment, and, consequently, improve road safety.

The aim of this study was to assess the association between traffic accident risk and psychotropic medication exposure by means of a case-control study.

A record-linkage database was used to perform the current study, in the Netherlands, between 2000 and 2007. The data came from three sources: pharmacy prescription data, police traffic accident data, and driving license data. Cases were defined as adults, who had a traffic accident between 2000 and 2007 and were driving, and received medical assistance. Controls were defined as adults, who had a driving license and had no traffic accident during the study period. Four controls were matched for each case; the matching was by sex, age within five years, zip-code, and date of the accident. The following medicine groups were included in order to cover the most frequently prescribed psychotropic medicines and medicines with central nervous system (CNS) side effects that are known to be of relevance for traffic safety: opioids, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants (antidepressants as a total group, sedative antidepressants, and SSRIs), and antihistamines for systemic

use. Various variables, such as age, sex, medicine half-life, mono and combination therapy, alcohol use were considered for the analysis.

3963 cases and 18828 controls were selected for the case-control analysis. Due to the lack of complete data on drivers' characteristics of cases and controls (e.g. co-morbidities; annual mileage; risky behavioural tendencies; etc.) and driving conditions of controls (e.g. season; weather conditions; time of the day; alcohol use; etc.), only crude odds ratios were calculated and reported in this deliverable. These latter showed a positive association between the risk of having a traffic accident and the exposure to at least one psychotropic medication [Crude OR=1.28 (95% CI: 1.12 - 1.46)]. This association was found to be higher in combination therapy users [Crude OR=1.55 (95% CI: 1.20 - 2.02)] and SSRI users [Crude OR=1.76 (95% CI: 1.38 - 2.24)]. The highest risk groups were new users (although the association was not statistically significant), intermediate and long half-life benzodiazepine users (the association was statistically significant only for hypnotic intermediate half-life users), female users (the association was statistically significant only for hypnotic, antidepressant, and SSRIs users), and young/middle-aged users (the association was statistically significant only for anxiolytic, antidepressant, and SSRIs users).

The crude ORs of this study indicated that psychoactive medications can constitute a problem in traffic safety. Therefore, both health care providers and patients should be properly informed and aware of the potential risks associated with the use of these medications.

Introductory Note

This report has been produced under the integrated European project DRUID (Sixth Framework Program - Contract No TREN-05-FP6TR-S07.61320-518404-DRUID).

The main aim of DRUID is to gain new insights to the real degree of impairment caused by psychoactive medications and their actual impact on road safety [1].

The DRUID activities consist of 7 technical Work Packages (WP1 - WP7). The current study has been performed within DRUID WP2 which aims to assess the increased risk for drivers being involved in a traffic accident after consumption of various psychoactive substances including alcohol. This assessment will be obtained by means of case-control studies, and the WP2 results will reflect both the use of the most common psychoactive substances in the driving population and the accident risks while impaired by alcohol and other psychoactive substances and/or various combinations [1].

Introduction

Impaired driving involving alcohol, illegal and legal drugs causes, each year, a great number of traffic accidents all over the world. Alcohol is a recognized leading contributor to road accidents and the relation between alcohol and the traffic accident risk has been extensively demonstrated, but, on the contrary, except for a few active substances, the evidence of the medicine role is still limited [2 - 6].

Experimental studies (e.g. driving simulator tests, “real” driving tests, laboratory tests) have shown a correlation between the use of certain non-alcoholic drugs and impaired psychomotor performance. In particular, numerous studies have demonstrated a dose and user type dependent impairment of driving performance associated with the use of psychoactive medications including hypnotics, anxiolytics, tricyclic antidepressants, opioids, and first generation antihistamines. However, due to the heterogenity of the tests and the target populations, it is still difficult to assess the generalizability and reliability of the outcomes, and establish how well these outcomes can be translated in real life driving situations [5 - 9] .

Epidemiological studies have also shown a positive association between medication exposure and the risk of having a traffic accident. A substantial number of studies have reported an increased traffic accident risk associated with the use of benzodiazepines; however, there is still uncertainty on the traffic accident risk associated with other medications. In particular, owing to methodological limitations and data availability, there is a limited evidence of the relationship between road traffic accidents and medication dose regimen, first and new generations of medications, acute and chronic treatment, and polypharmacy [5 - 11].

This present pharmacoepidemiological study will examine the association between the use of different medicine classes and road traffic accidents.

Aims

The aims of the current study are as follows:

a) To determine whether drivers who are exposed to psychoactive medications are more involved in a traffic accident than those who are not exposed to psychoactive medications.

b) To determine the association between the use of psychoactive medications and road-traffic accidents in case of mono and combination therapy users.

c) To determine the association between the use of different psychoactive medication groups and road-traffic accidents in case of new and chronic users.

d) To determine the association between the use of different psychoactive medication groups and road-traffic accidents in case of low, intermediate and high dose regimen users.

e) To determine the association between the use of different psychoactive medication groups and road-traffic accidents in case of short half-life, intermediate half-life and long half-life benzodiazepine users.

f) To determine the association between the use of different psychoactive medication groups and road-traffic accidents in case of male and female users.

g) To determine the association between the use of different psychoactive medication groups and road-traffic accidents in case of young, middle-aged and old drivers.

h) To determine the association between the use of a category I (minor impairment), category II (moderate impairment) or category III (severe impairment) psychoactive medication and road-traffic accidents.

Methods

A population-based record-linkage database was used to perform this case-control study, in the Netherlands, between the years 2000 and 2007.

The study research protocol was reviewed by the Medical Ethics Committee of the University Medical Centre Groningen (UMCG) - The Netherlands, which resulted in the decision that, according the Dutch Medical Research Involving Human Subjects Act (WOM), this case-control study did not need an ethical approval.

Databases

The following databases were used in order to obtain the final database that was used to conduct the case-control analysis:

1) PHARMO Pharmacy database: the PHARMO Pharmacy Database is a pharmacy prescription database which covers a population of more than 2 million residents in the Netherlands, corresponding with 14% of the Dutch population. The data assembled in this database are derived from approximately 200 community pharmacies in more than 80 municipalities scattered over the Netherlands. In the Netherlands people commonly register with one pharmacy, and obtain all their medications from that pharmacy, so that a complete medication history is available in the pharmacy dispensing records; registration is irrespective of health insurance (including people who are not insured), and thus is representative for the general population. All medicines are coded with the Anatomical Therapeutic Chemical (ATC) classification system and the dispensing date, the prescriber, the prescribed dosage regimen, the dispensed quantity, the cost and the estimated duration of use are available. The PHARMO pharmacy

database only contains de-identified information (i.e. all personal identifiers are removed from the final dataset). A unique patient identification number (PID) is assigned to each subject who is included in this database; the PID refers to unique patient information (e.g. date of birth, initials, sex, etc.) that is stored in a separate central database and that is used to perform database linkages [12].

2) Dienst Verkeer en Scheepvaart (DVS) database: the DVS the Dutch Traffic and Navigation Authority. Its database contains data on all the traffic accidents that occurred in the Netherlands and required the intervention of the police. In particular, this database stores data on drivers who were involved in the traffic accident (e.g. initials, age, sex, etc.) as well traffic accident details such as the date of accident, day of the week, time, weather conditions, light conditions, severity of injuries incurred, and breath test for alcohol excess [13].

3) Rijks Dienst Wegverkeer (RDW) database: the RDW is the Dutch Road Transport Authority. Its database contains all the available data on registered vehicles, their owners, vehicle registration numbers and driving license numbers [14].

Database linkage - Cases

The database linkage was carried out by a Trusted Third party (TTP), within the PHARMO Institute, which granted the full compliance with the current Dutch privacy regulations.

Table 1 illustrates the type of data that was available in the three different databases and allowed to perform the database linkage.

Table 1. Data available in the three databases that are used to perform the database linkage

	Date of birth	Sex	Driving license number	Date and time of accident	Injury severity	Subject 's initials	Hospital code	Zip-code
PHARMO	+	+	-	-	-	+	-	+
DVS	+	+	+	+	+	-	+	-
RDW	+	+	+	-	-	+	-	+

The database linkage was carried out in two phases.

In the first phase of the linking process, the DVS database was linked to the RDW database by following a deterministic linkage methodology (1:1) based on the driving license numbers belonging to those subjects who were involved in a traffic accident, and, consequently, stored in both databases.

Table 2 illustrates the data that was obtained from the DVS and RDW database linkage and used to perform the second phase of the linking process.

Table 2. DVS and RWD data used to perform the second phase of the database linkage

DVS	RDW	DVS + RDW
Hospital code	-	Hospital code
Date of birth	Date of birth	Date of birth
Sex	Sex	Sex
-	Zip-code	Zip-code
Date and time of the accident	-	Date and time of the accident
Injury severity	-	Injury severity
Driving license number	Driving license number	Driving license number
-	Initials	Initials

Data on 155470 traffic accidents were available in the DVS database while 64937 license numbers were associated to a traffic accident in the RDW database during the years 2000 - 2007. After the first phase of the linking process, data on 90533 traffic accidents were used in the second phase of the linking process. The loss of data that resulted after the first phase of the linking process was due to the following reasons:

1) The driving license number stored in the DVS database was not found in the RDW database.

2) The driving license number stored in the DVS database was not associated to any vehicle holder in the RDW database.

3) The vehicle holder was a company.

4) The vehicle holder did not have a valid driving license.

5) The vehicle holder was not associated to a Dutch address.

In the second phase of the linking process, the DVS + RDW database was linked to the PHARMO pharmacy database. This phase was based on a probabilistic record linkage technology which is a purely statistical methodology. This technology involved three major steps: 1) blocking, 2) matching, and 3) linking [15; 16].

1) Blocking: In this phase the postcode was used to perform a preliminary match between the data that were included in the DVS + RDW database and in the PHARMO pharmacy database. In particular, the postcode was coupled with dates of birth and sex in order to create record pairs.

2) Matching: In this phase the initials and the postcode were used to select the best combination among the record pairs that were created in the blocking phase. The process was carried out by using AXON, a program which has been developed by PHARMO. AXON uses statistical calculations and it assigns each record pair a “linkage weight” that will be used in the linking phase.

3) Linking: The database linkage was finalized, mainly by looking at the “linkage weight”. In particular, the record pair with the highest “linkage weight” value above the PHARMO threshold was defined as positive link (same patient) and all other pairs were defined as negative links (different patients), as only one record could logically belong to the same patient.

After the second phase of the linkage process, 4784 traffic accidents that satisfied the study inclusion criteria were available .The loss of data that occurred after this second phase was due to the following reasons:

1) The driving license holder did not belong to any of the municipalities included in the PHARMO database.

2) The driving license holder was not registered with a (PHARMO) pharmacy.

3) Details such as date of birth, sex, zip-code were missing.

4) The driving license holder did not fit into the study inclusion criteria.

Database linkage - Controls

Only the RDW and the PHARMO pharmacy databases were linked in order to obtain the final database to be used for the selection of the controls.

The database linkage was carried out in two phases.

In the first phase of the linking process, 6916598 driving license holders who did not have a traffic accident in the years 2000 - 2007 were selected in the RDW database.

In the second phase of the linking process, the RDW and the PHARMO pharmacy databases were linked by using the probabilistic record linkage technology that was described before; the zip-code and the initials of the selected driving license holders were used to carry this phase out.

After this second phase, a database consisting of 858039 subjects was available to perform the final control selection.

Study population - Cases and controls

Cases were defined as adults (18 years or older), who had a traffic accident attended by the Dutch police between 1st January 2000 and 31st December 2007.

At the time of the accident, the subjects were driving, and, after their traffic accident, medical assistance was received.

Controls were defined as adults (18 years or older), who had a driving license and had no traffic accident during the study period. Four controls were matched for each case; the matching was by sex, age within five years, zip-code, and date of the accident of the correspondent case (i.e. the control's complete medication record had to be available in the PHARMO database at the time the correspondent case had an accident).

Study medications

The following ATC subgroups (Table 3) were included in order to cover the most frequently used psychotropic medications that are known to be of relevance for traffic safety [5; 6; 8; 9; 11; 17 - 21].

Table 3. ATC groups included in the study

ATC CODE	**DESCRIPTION**
N02A	Opioids
N05A	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A - N06AA, N06AG, N06AX - N06AB	Antidepressants - Sedative antidepressants - SSRIs
R06A	Antihistamines for systemic use

All the active substances belonging to these ATC groups were categorized into four different categories, according to the categorization of medicines on driving that was developed within DRUID WP4 [1]. The active substances that did not

have a DRUID categorization were categorized according to the KNMP/WINAp categorization; this latter was developed for a Dutch campaign on medication use and driving that was launched in October 2008 by the Dutch Ministry of Transport, Public Works and Water Management and the Dutch Ministry of Health, Welfare and Sports [22] (Annexes - Table 1). As a general rule, the categories are assigned to the active substance at the normal therapeutic dosage given to an adult for the main indication of the medication and the warning given for a specific category refers to the use of one medication at a time and to the start of the treatment [23]. Therefore, the analysis on medicine categories was performed including all those subjects who were exposed to only one psychotropic medication (i.e. monotherapy), and, moreover, ORs referred to new and chronic users were calculated, as well.

Benzodiazepines were stratified according to their half-life (short ≤ 12 hours; intermediate > 12 hours and ≤ 24 hours; long > 24 hours) [24].

Antidepressants were stratified in sedative antidepressants [non-selective monoamine reuptake inhibitors; monoamine oxidase A inhibitors (MAOs); other antidepressants], and selective serotonin reuptake inhibitors (SSRIs).

Medication exposure

The PHARMO pharmacy database includes information on medications dispensed to patients. Therefore, in both cases and controls, medication exposure was calculated based on the available data on the dispensed medicine, such as the dispensing date, the prescribed dosage regimen, and the dispensed quantity.

Cases and controls were considered to be exposed to a medication if this medication was used during the week before the index date (i.e. accident date).

The day after the dispensing date was considered as the start of the therapy. If the therapy ended up to and including 2 days before the index date, the subjects were still considered as exposed. Medications dispensed exactly on the day of the accident were excluded because it could not be established whether, for the cases, exposure occurred before or after the car crash.

A six month period was chosen to define new and chronic users. New users were defined as all those subjects who used a driving impairing medication in the week before the index date, started their therapy up to 2 weeks before the index date, but did not received any prescriptions for this medication in the 6 months before the initiation of the therapy. Chronic users were defined as all those subjects who used a driving impairing medication in the week before the index date and also used this medication in the 6 months before the index date.

The prescribed dosage regimen was considered low if less than 1 Defined Daily Dose (DDD) was prescribed per day. The prescribed dosage regimen was considered regular if 1 DDD was prescribed per day. Lastly, the prescribed dosage regimen was considered high if more than 1 DDD was prescribed per day. However, since the data on medication dosage in the PHARMO database resulted not to be fully reliable (e.g. missing; not correctly entered in the database; etc.), dosage stratifications were not performed, and, consequently, no case-control analysis assessing the role of dosage regimen was finally carried out.

Monotherapy was defined as the use of only one study medication; combination therapy was defined as the concomitant use of at least two study medicines.

Statistical analysis

The statistical analysis was performed by using the statistical package SPSS (SPSS 16.0 for Windows).

Descriptive statistics was used to examine both accident and demographic characteristics of cases and controls.

Binary logistic regression analysis was used to calculate crude odds ratios (ORs) of a traffic accident after exposure to the study medications. The analysis compared the odds of exposure to the study medications among the cases to the odds of exposure among the controls. All analyses were first conducted including all cases and then repeated excluding those cases who were considered positive for alcohol (alcohol concentration <0.5 promille and alcohol concentration ≥ 0.5 promille) or cases for which data on alcohol concentrations were not available. In each analysis, cases and controls who were not exposed to any study medications in the six months before the accident were used as the reference group. 95% confidence intervals (CIs) were calculated for all ORs to establish whether the findings were statistically significant. No additional adjustments for confounding factors were made so far.

Results

Only crude ORs were calculated and presented in this report. This is due to the fact that data on drivers' characteristics (e.g. co-morbidities; annual mileage; risky behavioural tendencies; etc.) were not available, and to the fact that, since controls were non-crash-involved subjects, data on driving conditions (e.g. season; weather conditions; time of the day; alcohol use; etc.) were available only in the case group. As a consequence, it was decided not to conduct further analyses and to investigate the role of other influential factors associated to the medication exposure by performing and presenting stratified analyses (e.g. user type; half-life; etc.).

The results of the analyses that were performed including the total population (i.e. alcohol population and alcohol-free population) were similar to the results of the analyses that were performed with the alcohol-free population only. Therefore, for brevity, hereafter, only the results referring to the alcohol-free population are presented and discussed (the results referring to the total population are included in the annexes).

Accident and demographic characteristics - Alcohol-free study population

The study population with no alcohol use consisted of 3963 cases and 18828 controls.

Figure 1 and Figure 2 illustrate the demographic characteristics of the study subjects.

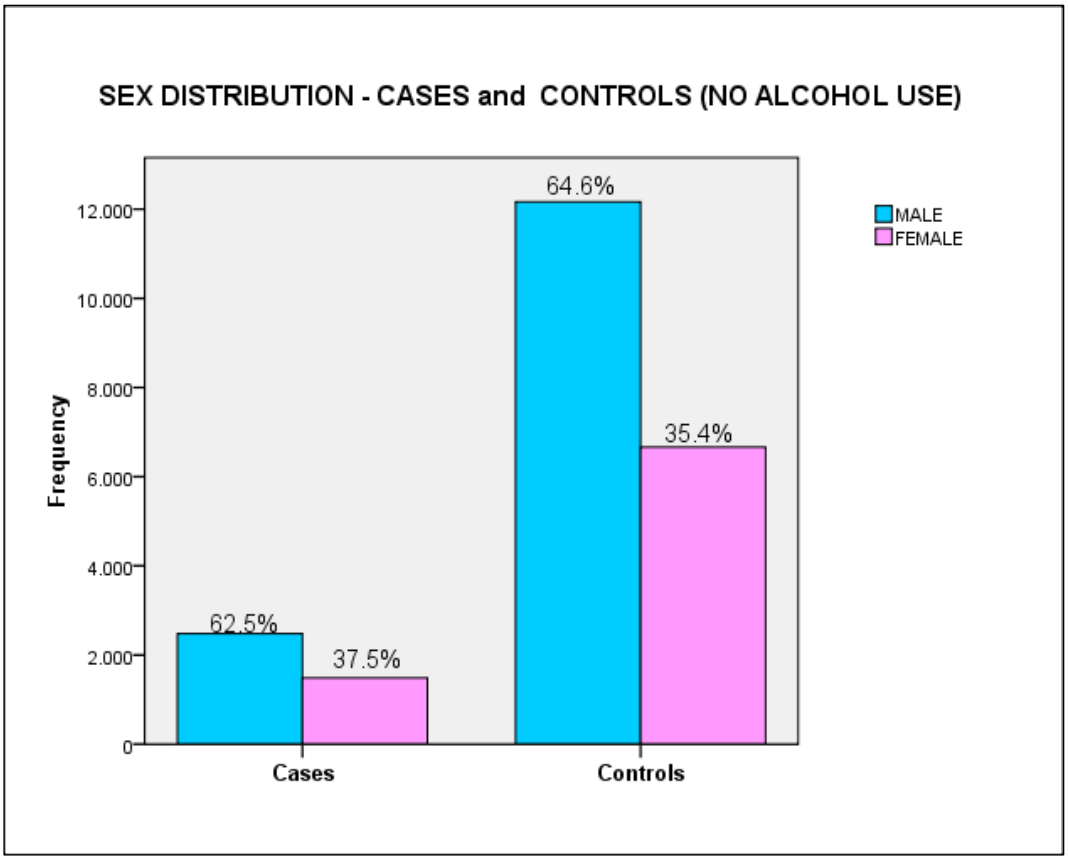

Figure 1. Sex distribution among cases and controls (Alcohol-free population)

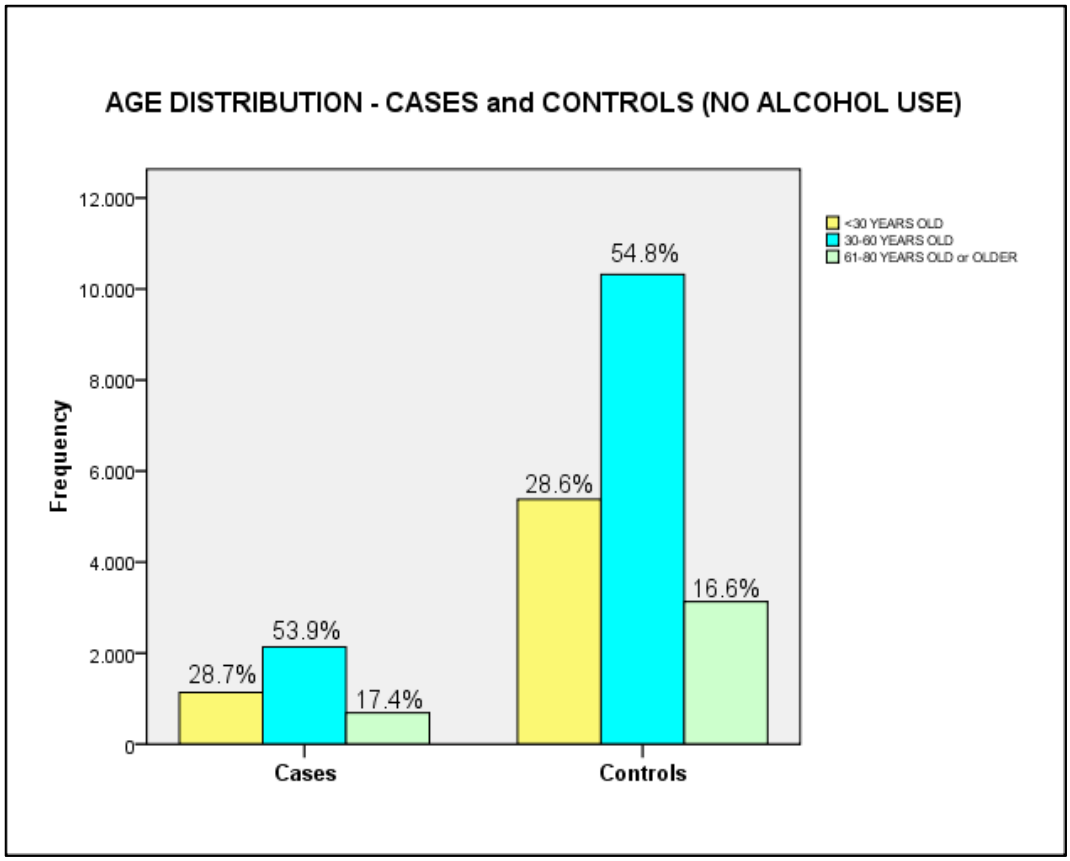

Figure 2. Age distribution among cases and controls (Alcohol-free population)

From these two figures it can be seen that accidents were more frequent in the male population and in the age group 30 - 60 years.

Table 4 - 9 present the accident characteristics of the alcohol-free cases.

Table 4 . Season in which the accidents occurred (Alcohol-free population)

SEASON	N (%)
Winter	963 (24.30)
Spring	1019 (25.71)
Summer	881 (22.23)
Autumn	1100 (27.76)
Total	**3963 (100)**

Table 5. Weather conditions in which the accidents occurred (Alcohol-free population)

WEATHER	N (%)
Dry	3199 (80.72)
Rain	635 (16.02)
Snow/Hail	49 (1.24)
Fog	52 (1.31)
Hard wind	3 (0.08)
Unknown	24 (0.61)
Missing	1 (0.03)
Total	**3963 (100)**

Table 6. Time of the week in which the accidents occurred (Alcohol-free population)

WEEK/WEEKEND	N (%)
Week day	3044 (73.81)
Weekend	919 (23.19)
Total	**3963 (100)**

Table 7. Time of the day in which the accidents occurred (Alcohol-free population)

TIME	N (%)
1 a.m. - 6.59 a.m.	249 (6.28)
7 a.m. - 12.59 p.m.	1245 (31.42)
13 p.m. - 18.59 p.m.	1803 (45.50)
19 p.m. - 0.59 a.m.	666 (16.81)
Total	**3963 (100)**

Table 8. Light conditions in which the accidents occurred (Alcohol-free population)

LIGHT	N (%)
Daylight	2865 (72.30)
Dark	872 (22.00)
Dawn	226 (5.70)
Missing	-
Total	**3963 (100)**

Table 9. Seriousness of the accidents (Alcohol-free population)

SERIOUSNESS	N (%)
Fatal	24 (0.61)
Seriously injured (Hospitalization > 24 hours)	1365 (34.44)
Moderately injured (1st aid point or hospitalization < 24 hours)	1486 (37.50)
Slightly injured (Treated on scene)	1088 (27.45)
Total	**3963 (100)**

From these data it can be seen that accidents were equally distributed during the four seasons, they mainly occurred during the week days, with dry weather conditions, at daylight, between 1 p.m. and 7 p.m., and the majority was classified as either serious or moderately serious.

Case-control analysis - Alcohol-free study population

Medication exposure

Table 10 presents the crude ORs of the case-control analysis with regard to the exposure to at least one medication. It is apparent from this table that the exposure to at least one of the study medications was positively and significantly associated with the risk of having a traffic accident.

Table 10. Crude ORs for road-traffic accident in psychotropic medication users (Alcohol-free population)

MEDICATION EXPOSURE	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
EXPOSED AT LEAST TO ONE MEDICATION	313 (7.90)	1203 (6.39)	1.28 (1.12 - 1.46)*
NOT EXPOSED AT ALL**	3650 (92.10)	17625 (93.61)	-

* Statistically significant

**** Reference group for the case-control analysis

Type of therapy

Table 11 presents the outcomes of the case-control analysis with regard to the type of therapy. As can be seen from this table, the concomitant use of more than one psychotropic medication was significantly associated with a higher risk of having a traffic accident.

Table 11. Crude ORs for road-traffic accident in mono and combination therapy users (Alcohol-free population)

TYPE OF THERAPY	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
MONOTHERAPY	237 (5.98)	967 (5.14)	1.18 (1.02 - 1.37)*
COMBINATION THERAPY (≥ 2 PSYC. MEDICINES)	76 (1.92)	236 (1.25)	1.55 (1.20 - 2.02)*

* Statistically significant

Medicine groups - General

Table 12 presents the outcomes of the case-control analysis with regard to the medicine group. A positive association between medication exposure and traffic accident was found with all the study medicine groups, with the exception of the antihistamines for systemic use which showed no association (no association

was found in all the performed stratifications either). However, it can be seen from the data in this table that this association was found to be statistically significant only in case of exposure to anxiolytics, hypnotics, antidepressants as a total group, and SSRIs. Lastly, this table also shows that SSRIs were associated with the highest accident risk increase, followed by the antidepressants as a total group.

Table 12. Crude ORs for road-traffic accident in different psychotropic medicine group users (Alcohol-free population)

MEDICINE GROUP	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
N02A Opioids	23 (0.58)	95 (0.50)	1.17 (0.74 - 1.85)
N05A Antipsychotics	20 (0.50)	96 (0.51)	1.01 (0.62 - 1.63)
N05B Anxiolytics	94 (2.37)	310 (1.65)	1.46 (1.16 - 1.85)*
N05C Hypnotics	76 (1.92)	273 (1.45)	1.34 (1.04 - 1.74)*
N06A Antidepressants	131 (3.31)	398 (2.11)	1.59 (1.30 - 1.94)*
Sedative antidepressants (TCAs, MAOs + Others)	40 (1.01)	146 (0.78)	1.32 (0.93 - 1.88)
N06AB SSRIs	92 (2.32)	252 (1.34)	1.76 (1.38 - 2.24)*
R06 Antihistamines for systemic use	47 (1.19)	304 (1.61)	0.75 (0.55 - 1.02)

* Statistically significant

Opioids

Table 13 presents the outcomes of the case-control analysis with regard to the opioid exposure. This table illustrates that, in relation to user type, sex, and age stratifications, respectively new users, female users, and the age group < 30 years were associated with a higher traffic accident risk. However, none of these associations were found to be statistically significant.

Table 13. Crude ORs for road-traffic accident in opioid users, stratified by user type, sex, and age (Alcohol-free population)

N02A OPIOIDS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	5 (0.13)	18 (0.10)	1.34 (0.5 - 3.62)
Chronic user	18 (0.45)	77 (0.41)	1.13 (0.68 - 1.88)
SEX			
Male	13 (0.33)	57 (0.30)	1.10 (0.60 - 2.01)
Female	10 (0.25)	38 (0.20)	1.27 (0.63 - 2.55)
AGE (Years)			
< 30	2 (0.05)	5 (0.03)	1.93 (0.38 - 9.96)
30 - 60	19 (0.48)	62 (0.33)	1.48 (0.88 - 2.48)
> 60	2 (0.05)	28 (0.15)	0.35 (0.08 - 1.45)

Antipsychotics

Table 14 presents the outcomes of the case-control analysis with regard to the antipsychotic exposure. This table illustrates that, with reference to user type, sex, and age stratifications, respectively new users, female users, and the age group < 30 years were associated with the highest traffic accident risk. However, none of these outcomes were found to be statistically significant.

Table 14. Crude ORs for road-traffic accident in antipsychotic users, stratified by user type, sex, and age (Alcohol-free population)

N05A ANTIPSYCHOTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	1 (0.03)	3 (0.02)	1.61 (0.17 - 15.48)
Chronic user	19 (0.48)	93 (0.49)	0.99 (0.60 - 1.62)
SEX			
Male	12 (0.30)	63 (0.33)	0.92 (0.50 - 1.71)
Female	8 (0.20)	33 (0.18)	1.17 (0.54 - 2.54)
AGE (Years)			
< 30	3 (0.08)	19 (0.10)	0.76 (0.23 - 2.58)
30 - 60	15 (0.38)	63 (0.33)	1.15 (0.65 - 2.02)
> 60	2 (0.05)	14 (0.07)	0.69 (0.16 - 3.04)

Anxiolytics

Table 15 presents the outcomes of the case-control analysis with regard to the anxiolytic exposure. This table illustrates that, with reference to user type, half-life, sex, and age stratifications, respectively new users, long half-life benzodiazepine users, female users and the age group < 30 years were associated with a higher traffic accident risk. However, this association was statistically significant only in case of user type (chronic users), sex, and age group (30 - 60 years old).

Table 15. Crude ORs for road-traffic accident in anxiolytic users, stratified by user type, half-life, sex, and age (Alcohol-free population)

N05B ANXIOLYTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	15 (038)	41 (0.22)	1.77 (0.98 - 3.20)
Chronic user	79 (1.99)	269 (1.43)	1.41 (1.01 - 1.83)*
HALF-LIFE			
Short half-life	0	0	-
Intermediate half-life	42 (1.06)	222 (1.18)	0.91 (0.66 - 1.27)
Long half-life	26 (0.66)	84 (0.45)	1.50 (0.96 - 2.32)
SEX			
Male	49 (1.24)	162 (0.86)	1.46 (1.06 - 2.01)*
Female	45 (1.14)	148 (0.79)	1.47 (1.05 - 2.05)*
AGE (Years)			
< 30	8 (0.20)	19 (0.10)	2.03 (0.89 - 4.65)
30 - 60	58 (1.46)	185 (0.98)	1.51 (1.12 - 2.04)*
> 60	28 (0.71)	106 (0.56)	1.28 (0.84 - 1.94)

* Statistically significant

Hypnotics

Table 16 presents the outcomes of the case-control analysis with regard to the hypnotic exposure. This table shows that, with reference to user type, half-life, sex, and age stratifications, a higher traffic accident risk was found in case of, respectively, new users, intermediate half-life benzodiazepine users, female

users and the age group > 60 years. However, the outcomes were statistically significant only with respect to the half-life (intermediate half-life), and sex (female) stratifications.

Table 16. Crude ORs for road-traffic accident in hypnotic users, stratified by user type, half-life, sex, and age (Alcohol-free population)

N05C HYPNOTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	6 (0.15)	21 (0.11)	1.38 (0.56 - 3.42)
Chronic user	70 (1.77)	252 (1.34)	1.34 (1.03 - 1.75)*
HALF-LIFE			
Short half-life	20 (0.50)	128 (0.68)	0.75 (0.47 - 1.21)
Intermediate half-life	6 (0.15)	4 (0.02)	7.24 (2.04 - 25.68)*
Long half-life	31 (0.78)	138 (0.73)	1.10 (0.73 - 1.60)
SEX			
Male	33 (0.83)	142 (0.75)	1.12 (0.77 - 1.64)
Female	43 (1.09)	131 (0.70)	1.59 (1.12 - 2.24)*
AGE (Years)			
< 30	2 (0.05)	11 (0.06)	0.88 (0.2 - 3.96)
30 - 60	33 (0.83)	123 (0.65)	1.30 (0.88 - 1.91)
> 60	41 (1.03)	139 (0.74)	1.42 (1.00 - 2.02)

* Statistically significant

Antidepressants

Table 17 presents the outcomes of the case-control analysis with regard to the antidepressant exposure (antidepressants as a total group, sedative antidepressants, SSRIs). In relation to the exposure to antidepressants as a total group, it can be seen from this table that a higher traffic accident risk association was found in case of new users (not statistically significant), female users and the age group < 30 years. In relation to the exposure to sedative antidepressants, this table illustrates that new users, female users, and the age group 30 - 60 years were associated with a higher traffic accident risk. However, none of these outcomes were found to be statistically significant. Lastly, in relation to the

exposure to SSRIs, this table indicates that an increased motor vehicle collision risk was associated with new users, female users and the age group < 30 years. However, these associations were found to be statistically significant only in case of sex, age stratifications and chronic users.

Table 17. Crude ORs for road-traffic accident in antidepressant users (Antidepressants as a total group, sedative antidepressants, SSRIs), stratified by user type, sex, and age (Alcohol-free population)

N06A ANTIDEPRESSANTS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	8 (0.20)	23 (0.12)	1.68 (0.75 - 3.76)
Chronic user	123 (3.10)	375 (1.99)	1.58 (1.29 - 1.95)*
SEX			
Male	55 (1.39)	188 (1.00)	1.41 (1.04 - 1.91)*
Female	76 (1.92)	210 (1.12)	1.75 (1.34 - 2.28)*
AGE (Years)			
< 30	18 (0.45)	43 (0.23)	2.02 (1.17 - 3.51)*
30 - 60	84 (2.12)	278 (1.48)	1.46 (1.14 - 1.87)*
> 60	29 (0.73)	77 (0.41)	1.82 (1.19 - 2.79)*
SEDATIVE ANTIDEPRESSANTS (TCAs, MAOs + Others)			
USER TYPE			
New user	3 (0.08)	7 (0.04)	2.07 (0.54 - 8.00)
Chronic user	37 (0.93)	139 (0.74)	1.29 (0.89 - 1.85)
SEX			
Male	16 (0.40)	66 (0.35)	1.17 (0.68 - 2.02)
Female	24 (0.61)	80 (0.42)	1.45 (0.92 - 2.29)
AGE (Years)			
< 30	2 (0.05)	13 (0.07)	0.74 (0.17 - 3.29)
30 - 60	28 (0.71)	95 (0.50)	1.42 (0.93 - 2.17)
> 60	10 (0.25)	38 (0.20)	1.27 (0.63 - 2.55)
SSRIs			
USER TYPE			
New user	7 (0.18)	16 (0.08)	2.11 (0.87 - 5.14)
Chronic user	85 (2.14)	236 (1.25)	1.74 (1.35 - 2.23)*
SEX			
Male	40 (1.01)	122 (0.65)	1.58 (1.11 - 2.27)*
Female	52 (1.31)	130 (0.69)	1.93 (1.40 - 2.67)*

AGE (Years)			
< 30	16 (0.40)	30 (0.16)	2.58 (1.40 - 4.73)*
30 - 60	57 (1.44)	183 (0.97)	1.50 (1.12 - 2.03)*
> 60	19 (0.48)	39 (0.21)	2.35 (1.36 - 4.08)*

* Statistically significant

Antihistamines for systemic use

Table 18 presents the outcomes of the case-control analysis with regard to the antihistamine exposure. As can be seen from this table, antihistamine exposure was not associated with an increased risk of a traffic accident, with the exception of the age group > 60 years, which, however, did not report any statistically significant outcome.

Table 18. Crude ORs for road-traffic accident in antihistamine users, stratified by user type, sex, and age (Alcohol-free population)

R06A ANTIHISTAMINES FOR SYSTEMIC USE##	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	6 (0.15)	50 (0.27)	0.57 (0.25 - 1.35)
Chronic user	41 (1.03)	254 (1.35)	0.78 (0.56 - 1.09)
SEX			
Male	25 (0.63)	140 (0.74)	0.83 (0.54 - 1.28)
Female	23 (0.58)	164 (0.87)	0.68 (0.44 - 1.05)
AGE (Years)			
< 30	7 (0.18)	101 (0.54)	0.34 (0.16 - 0.72)
30 - 60	31 (0.78)	165 (0.88)	0.91 (0.62 - 1.33)
> 60	9 (0.23)	38 (0.20)	1.14 (0.55 - 2.37)

2nd generation antihistamines account for approximately 90% of this medication group as used by the study population

Medicine category

Table 19 presents the outcomes of the case-control analysis with regard to the medicine categorization. This table indicates that the association between category III medications and traffic accident risk was the highest and only statistically significant one.

Table 19. Crude ORs for road-traffic accident in different medicine category users (Alcohol-free population)

MEDICINE CATEGORY (Exposed to one medication)	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
CAT. I	98 (2.47)	422 (2.24)	1.12 (0.90 - 1.40)
CAT. II	35 (0.88)	152 (0.81)	1.11 (0.77 - 1.61)
CAT. III	104 (2.62)	388 (2.06)	1.29 (1.04 - 1.61)*

* Statistically significant

Table 20 presents the outcomes of the case-control analysis with regard to the medicine categorization and the user type. The traffic accident risk was found to be higher in case of chronic users of the all three categories. However, only category III chronic users showed a statistically significant association.

Table 20. Crude ORs for road-traffic accident in different medicine category users, stratified by user type (Alcohol-free population)

MEDICINE CATEGORY and USER TYPE (Exposed to one medication)	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
CAT. I			
New user	8 (0.20)	51 (0.27)	0.76 (0.36 - 1.60)
Chronic user	90 (2.27)	371 (1.97)	1.17 (0.93 - 1.48)
CAT. II			
New user	2 (0.05)	12 (0.06)	0.81 (0.18 - 3.60)
Chronic user	33 (0.83)	140 (0.74)	1.14 (0.78 - 1.67)
CAT. III			
New user	12 (0.30)	46 (0.24)	1.26 (0.67 - 2.38)
Chronic user	92 (2.32)	342 (1.82)	1.30 (1.03 - 1.64)*

* Statistically significant

Discussion

The crude ORs of this matched case-control study showed that the use of one or more than one psychotropic medication places drivers at a higher risk for a traffic accident. This study also indicated that the risk associated with psychotropic medication use increases with the concomitant use of at least two psychotropic medications and with the use of antidepressants (in particular, SSRIs) (all these associations were statistically significant). The results of this study also showed that higher road-traffic accident risks were associated with new users (although the association was not statistically significant), intermediate and long-half life benzodiazepine users (the association was statistically significant only for hypnotic intermediate half-life users), female patients (the association was statistically significant only for hypnotic, antidepressant, and SSRIs users), and young to middle-aged drivers (the association was statistically significant only for anxiolytic, antidepressant, and SSRIs users). These findings were valid for all the stratifications that were performed across the study medicine groups, with the exception of the hypnotic age stratification which showed a higher traffic accident risk in case of elderly patients (> 60 years). Furthermore, this study found an increased risk of motor vehicle accidents in category III medication users (the association was statistically significant), and in chronic users of all the three medicine categories (the association was statistically significant only for category III chronic users).

Our study revealed a significant association between the risk of being involved in an accident as a driver and the exposure to psychotropic medications. However, contrary to expectations, our results showed that the risk is higher in antidepressant [Crude OR=1.59 (95% CI = 1.30 - 1.94)], and, in particular, SSRIs users [Crude OR=1.76 (95% CI = 1.38 - 2.24)]. These findings differ from previous experimental and epidemiological studies which showed no increased risk of road-traffic accidents in SSRI users [5; 6; 8; 9; 11; 25], but, on the other

hand, they are in line with the findings of Rapoport and colleagues who, however, focused on a very specific population [26]. A possible explanation for our findings might be that a proportion of reported car accidents could have been intentional, and, therefore, associated with the risk of suicide in relation to antidepressant use [27; 28] or with not properly diagnosed or treated depression which is well-known to play a causal role in suicidal deaths [29 - 31]. These results may also be explained by the fact that depression itself can affect driving abilities and driving related skills by causing, for example, confusion, poor concentration, and cognitive impairment [26; 32 - 34]. These outcomes may also be due to comorbid psychiatric conditions and coexisting medical illnesses, which often occur in conjunction with depression and can influence the ability to drive, as well [35]. Another possible explanation is that the side effects of a single SSRI (e.g. fluoxetine) could have accounted for the increase in ORs of SSRIs [9] or that these antidepressants were used in combination with other medicines, such as benzodiazepines, which might have interacted with antidepressants and led to a greater driving impairment [25]. It seems also possible that these results are due to the lack of therapy adherence which has been often seen in depressed patients and might result in more severe adverse drug events and treatment failure [36; 37]. Lastly, the observed increase in traffic accident risk might also be related to the fact that, generally speaking, SSRIs are considered to be unlikely to produce driving performance impairment, and, therefore, patients continue to drive in their course of treatment, exposing themselves to a greater risk of being involved in a traffic accident.

Our study did not find a strong relationship between anxiolytic and hypnotic exposure and road-traffic accidents [Anxiolytics: crude OR=1.46 (95% CI = 1.16 - 1.85); Hypnotics: crude OR=1.34 (95% CI = 1.04 - 1.74)]. These findings are rather surprising and do not fully support the previous research [5; 6; 8; 9; 11; 17; 19]. It is difficult to explain these results, but they could be related to the fact that these medicines might be often taken at subtherapeutic doses for different indications (anxiolytics) [38] or at night (hypnotics) [17], and expose their users to

a lower impairment and, therefore, a decreased likelihood of experiencing a car crash. Another possible explanation for our findings could be that anxiolytic and hypnotic users, following the advice of their health care providers, tend not to drive, and, consequently, could be less exposed to a motor vehicle collision risk [23].

The results of the current study also indicated that drivers were not at risk of being involved in a road-traffic accident after receiving a prescription for an antihistamine for systemic use [Crude OR=0.75 (95% CI = 0.55 - 1.02)]. These outcomes are consistent with those of other studies [5; 8; 9; 11; 21] and might be explained by the increasingly frequent use of the second generation antihistamines which tend to be largely free of driving impairing effects (in our study population, second generation antihistamines accounted for approximately 90% of the antihistaminic medications) [9; 11].

Another important finding was that exposure to combination therapy was associated with a higher traffic accident risk [Crude OR=1.55 (95% CI = 1.20 - 2.02)]. This finding is in line with the findings of other authors [20; 32; 39 - 41] and further supports the idea that the concomitant use of medications can increase the risk of adverse effects, medicine interactions [42; 43], and, consequently, lead to a greater impairment of patients' cognitive and psychomotor performance, and, therefore, to an increased risk of traffic accidents.

With regard to the user type, our study showed that the risk associated with psychotropic medication users was the highest among new users, and, in particular among sedative antidepressant and SSRI new users, even though these latter were not statistically significant [Sedative antidepressants: crude OR=2.07 (95% CI = 0.54 - 8.00); SSRIs: crude OR=2.11 (95% CI = 0.87 - 5.14)]. Very little was found in the literature on the higher traffic accident risk in case of antidepressant new users; nevertheless, a relationship between anxiolytic and

hypnotic new users and accident risk has been often reported in the literature [6; 19; 23; 39; 40; 44; 45]. The observed increased risk in antidepressants new users could be explained by residual depressive symptoms [25], while, in case of the other psychotropic medication new users, it could be attributed either to tolerance which gradually develops after a repeated daily use of these medications or to a reduction in use after the first weeks of treatment [11; 19; 44; 45].

On the question of medicine half-life, the current study found a positive association between the exposure to intermediate and long half-life benzodiazepines and traffic accident risk; this association was found to be very high in case of intermediate half-life hypnotics [Crude OR=7.24 (95% CI = 2.04 - 25.68)]. These crude ORs confirm previous research [8; 9; 17; 45 - 48] and may be explained by the fact that benzodiazepines with an intermediate/long half-life might have a longer duration of action or might accumulate and cause excessive sedation, and, therefore, have an extended negative effect on driving performance [9; 40; 45; 46].

The current study also indicated that female patients had a higher accident odds than male patients. These results differ from some previously published studies which found an increased accident risk in male patients [44; 47 - 49]. It is difficult to explain these outcomes, but they could be related to biological differences between females and males which might expose women to a greater risk of developing adverse medicine reactions than men [45; 50; 51]. Lastly, it is interesting to note that, according to our descriptive statistics, males were more often involved in a car crash than females; this rather contradictory result may be due to the fact that, on average, men drive more miles than women [52; 53] or to the higher propensity of male drivers to engage in aggressive and risky behaviour [54] or to the proneness of female drivers to adjust their driving behaviour when using a driving impairing medication [55].

In reference to the age stratifications, we found that the use of psychotropic medicines by young and middle-aged patients could account for a higher risk of motor vehicle crashes. It is possible that these results can be attributed either to the higher number of miles driven by the younger population (given that this population represents the working population) [52; 56] or to the fact that young/middle-aged subjects tend to use these medications intermittently or to start driving earlier while still being exposed to driving impairing medications, and, therefore, without having developed tolerance to these medicines [17; 57]. These findings are in agreement with earlier findings [17; 19; 44; 47; 48; 57] and are also reflected in the descriptive statistics of our study.

The current study also showed that the exposure to category III medications was significantly associated with a higher motor vehicle collision risk [Crude OR=1.29 (95% CI: 1.04 - 1.61)]; however, it is important to note that the ORs of category III medications were similar to those of category II [Crude OR=1.11 (95% CI: 0.77 - 1.61)] and category I medications [Crude OR=1.12 (95% CI: 0.90 - 1.40)], even if these two latter ORs were not statistically significant. Since category III medications are likely to produce severe effects or be potentially dangerous in car driving [23; 33], it is not surprising that they are associated with the highest traffic accident risk. Nevertheless, it is noteworthy that no big variation was seen in the ORs reported in the three categories. It is difficult to explain these small differences among the three category accident risk, but they might be related to the fact that category III users tend to follow their health care professionals' advice, and, therefore, drive less in the course of their treatment [23; 33]. Given that our category I medications only included antihistamines and SSRIs, it is possible to hypothesise that the ORs of this category are higher than expected because of the high traffic accident risk that was found with SSRI users. Therefore, based on this hypothesis and following the French categorization system [33], SSRIs were categorized as category II in repeated analyses and new ORs were calculated. As expected, these latter calculations showed no association between category I medication exposure and traffic accident risk

[Crude OR=0.71 (95% CI: 0.50 - 1.01)], and an increase in category II ORs [Crude OR=1.41 (95% CI: 1.13 - 1.77)], which can obviously be explained by the effect of the SSRIs.
Another unexpected finding related to the categorization stratifications was that chronic users of all three categories were found to be at a higher motor vehicle crash risk than new users. This rather contradictory result may be due to the proneness to drive less, based on the advice received by the prescribing physician or dispensing pharmacist [23; 33]. In particular, in the Netherlands, community pharmacists pay attention to advising patients not to drive at the start of the treatment if an impairing medication has been prescribed by their physician.
Lastly, it is important to underline that, to our knowledge, this is the first study that evaluated the risk associated to three different medicine categories, and, consequently, our results cannot be compared with those of previous studies.

Finally, it is relevant to point out that our study demonstrated that, with a few exceptions (e.g. hypnotics - half-life stratification; opioids - age stratification; SSRIs - age stratification), the risk of having a traffic accident was lower in the alcohol-free medication users. These outcomes confirm the findings of previous research which showed that alcohol alone or in combination with illicit/licit drugs plays a crucial role in motor vehicle crashes [2 - 5; 9; 11; 20; 39; 58; 59].

To conclude, a number of limitations need to be considered. First, a dispensing database was used for our study. The fact that the prescribed medications were dispensed does not imply that the patient actually took these medications or used them according to the prescription or to the information that was stored in the PHARMO database. Second, the data on dosage that were reported in the PHARMO dataset were not fully reliable, and, therefore, it was not possible to account for this factor which is also known to be related to an increased risk of road-traffic accidents [17; 45; 60]. Third, there was no possibility to obtain information on medications prescribed during recent hospitalization or the

concomitant use of OTC medicines which could also have played a role in endangering traffic safety. Fourth, no information was available on what medical condition psychotropic medications were prescribed for or on patients' co-morbidities which both might have biased our outcomes [6; 19; 48]. Fifth, it was assumed that both cases and controls regularly drove a car; this was a rough assumption, based on that fact that both cases and controls had a driving license, but there was no other possibility to gain better insight into the driving patterns of our study population. Sixth, it was not possible to assess other influential factors, such as number of miles driven, risk taking behaviour, driving conditions, driving patterns associated with periods of use and non-use of a medication, driving experience and skills, which can also play a role in endangering traffic safety [49]. Finally, the database linkage process led to a considerable loss of cases; this sometimes resulted in small numbers which did not allow proper stratified analyses and fully reliable outcomes (e.g. user type and age stratifications).

Despite of these limitations, it is important to stress that, to our knowledge, this matched case-control study was one of the first studies to examine the risk of having a traffic accident associated with the exposure to a large and comprehensive group of different driving impairing medications and to investigate the role of other influential predictors such as user type, sex, age, medication half-life and psychotropic combination therapy. Furthermore, it is relevant to underline that our study is also the first study to investigate the relationship between road traffic crash risk and the categorization system for medications affecting driving performance. Lastly, it is noteworthy to point out that our study used the data from a large and representative population, it combined different and reliable data-sources, and it focused on a broad time-frame, as well.

Conclusions

The crude ORs reported in this study confirmed previous findings and contributed additional evidence that psychotropic medications constitute a considerable risk to traffic safety, especially for patients with no medicine use experience, poly-therapy users, female and young/middle-aged population, category III (severely impairing) medication users, and SSRI users.

The evidence from this study suggests that, on the one hand, drivers should be aware of the risk of accident involvement associated with different treatment conditions and receive proper counselling from their health care providers, and, on the other hand, physicians and pharmacists should be able to minimize the risk of patients causing traffic accidents while driving under the influence of psychotropic medications by providing accurate advice, choosing for safer alternatives, if possible, and monitoring their patients' driving experience with the medication.

Further analyses will be performed to adjust the current crude ORs for possible confounding factors related to the exposure to the study medications (e.g. concurrent use of other psychotropic medications; medicine half-life; etc.), and, afterwards, a case-crossover study will be carried out to evaluate whether the present outcomes will be confirmed by the use of a different methodological approach.

It is recommended that more research will be undertaken to further investigate the role of medication dose and dose changes, non-psychoactive medicines, and medical conditions, as well. Lastly, it is suggested that further research will be carried out to investigate the effect of SSRIs in traffic accidents in order to better understand the extend to which these antidepressants can cause or contribute to accidents; moreover, more work needs to be done to determine the role of the DRUID categorization system in preventing car crashes in order to be able to implement and use this system in daily practice.

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Annexes

1. Medicine categorization

Annexes - Table 1. DRUID and KNMP/WINAp available categorization for medications affecting driving performance (with respect to the medications included in the current study)

ATC	ACTIVE SUBSTANCE	CATEGORIZATION
N02AA01	MORPHINE	III
N02AA03	HYDROMORPHONE	III
N02AA04	NICOMORPHINE♦	II
N02AA05	OXYCODON	III
N02AA08	DIHYDROCODEINE	II
N02AA59	CODEINE, COMBINATIONS	II
N02AB02	PETHIDINE	III
N02AB03	FENTANYL	III
N02AC01	DEXTROMORAMIDE♦	III
N02AC03	PIRITRAMIDE♦	III
N02AC04	DEXTROPROPPHENE♦	II
N02AC05	BEZITRAMIDE	III
N02AD01	PENTAZOCINE♦	III
N02AE01	BUPRENORPHINE	III
N02AF02	NALBUPHINE♦	II
N02AX02	TRAMADOL	III
N02BA01	ACETYLSALICYLIC ACID	0
N02BE01	PARACETAMOL	0
N02BG06	NEFOPAM	II
N02BG08	ZICONOTIDE	III
N02CA52	ERGOTAMINE,COMBINATIONS	I
N02CC01	SUMATRIPTAM	II
N02CC02	NARATRIPTAN	II
N02CC03	ZOLMITRIPTAN	II
N02CC04	RIZATRIPTAN	II
N02CC05	ALMOTRIPTAN	II
N02CC06	ELETRIPTAN	II
N02CC07	FROVATRIPTAN	II
N02CX01	PIZOTIFEEN	II
N02CX02	CLONIDINE	II
N05AA01	CHLOORPROMAZINE	III
N05AA02	LEVOMEPROMAZINE	III

ATC	ACTIVE SUBSTANCE	CATEGORIZATION
N05AB02	FLUPHENAZINE	II
N05AB03	PERPHENAZINE	II
N05AC01	PERICIAZINE	III
N05AD01	HALOPERIDOL	II
N05AD05	PIPAMPERON	II
N05AD06	BROOMPERIDOL	II
N05AD07	BENPERIDOL	II
N05AD08	DROPERIDOL	III
N05AE03	SERTINDOL♦	II
N05AF01	FLUPENTIXOL	II
N05AF05	ZUCLOPENTIXOL	II
N05AG01	FLUSPIRINE	II
N05AG02	PIMOZIDE	II
N05AG03	PENFLURIDOL	II
N05AH02	CLOZAPINE	II
N05AH03	OLANZAPINE	II
N05AH04	QUETIAPINE	III (Parenteral) - II (Oral)
N05AL01	SULPIRIDE	II
N05AL03	TIAPRIDE	II
N05AN01	LITHIUM	II
N05AX08	RISPERIDON	II
N05BA01	DIAZEPAM	III
N05BA02	CHLOORDIAZEPOXIDE	II
N05BA04	OXAZEPAM	III
N05BA05	POTASSIUM CLORAZEPATE	II
N05BA06	LORAZEPAM	III
N05BA08	BROMAZEPAM	III
N05BA09	CLOBAZAM	II
N05BA11	PRAZEPAM	II
N05BA12	ALPRAZOLAM	III
N05BB01	HYDROXYZINE	II
N05BC01	MEPROBAMATE♦	III
N05BE01	BUSPIRON	I
N05CD01	FLURAZEPAM	III
N05CD02	NITRAZEPAM	III
N05CD03	FLUNITRAZEPAM	III
N05CD06	LORMETAZEPAM	III
N05CD07	TEMAZEPAM	III
N05CD08	MIDAZOLAM	III
N05CD09	BROTIZOLAM	III
N05CD11	LOPRAZOLAM	III
N05CF01	ZOPICLON	III
N05CF02	ZOLPIDEM	III (Parenteral) - II (Oral)

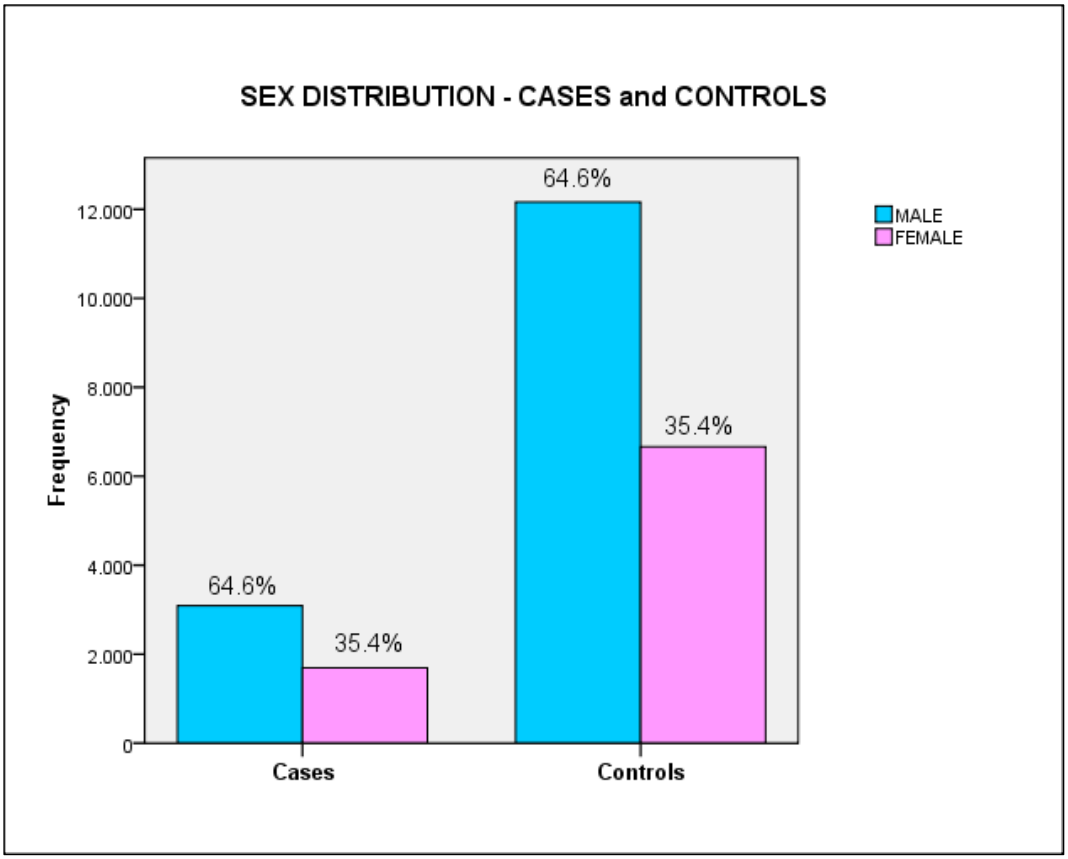
ATC	ACTIVE SUBSTANCE	CATEGORIZATION
N05CM05	SCOPOLAMINE	III
N06AA02	IMIPRAMINE	II
N06AA04	CLOMIPRAMINE	II
N06AA09	AMITRIPTYLINE	III
N06AA10	NORTRIPTYLINE	II
N06AA12	DOXEPINE	III
N06AA16	DOSULEPINE	III
N06AA21	MAPROTILINE	II
N06AB03	FLUOXETINE	I
N06AB04	CITALOPRAM	I
N06AB05	PAROXETINE	I
N06AB06	SERTRALINE	I
N06AB08	FLUVOXAMINE	I
N06AB10	ESCITALOPRAM	I
N06AF03	FENELZINE	II
N06AF04	TRANYLCYPROMINE	II
N06AG02	MOCLOBEMIDE	II
N06AX03	MIANSERINE	III
N06AX05	TRAZODON	III
N06AX11	MIRTAZAPINE	III
N06AX16	VENLAFAXINE	II
N06BA01	AMFETAMINE♦	II
N06BA04	METHYLPHENIDATE	I
N06BX03	PIRACETAM	II
N06DX01	MEMANTINE	II
R06AA04	CLEMASTINE	III
R06AB02	DEXCHLORPHENIRAMINE	II
R06AD01	ALIMEMAZINE	III
R06AD02	PROMETHAZINE	III
R06AE05	MECLOZINE	II
R06AE06	OXATOMIDE	II
R06AE07	CETIRIZINE	I
R06AE09	LEVOCETIRIZINE	I
R06AE55	MECLOZINE, COMBINATIONS♦	II
R06AX02	CYPROHEPTADINE	II
R06AX12	TERFENADINE	I
R06AX13	LORATADINE	I
R06AX17	KETOTIFEN	II
R06AX22	EBASTINE	I
R06AX25	MIZOLASTINE	I
R06AX26	FEXOFENADINE	I
R06AX27	DESLORATADINE	I

LEGEND		
CATEGORY	**IMPAIRMENT DESCRIPTION**	
0	No effect on driving abilities	
I	Presumed to be safe or unlikely to produce an effect	
II	Likely to produce minor or moderate adverse effects	
III	Likely to produce severe or presumed to be potentially dangerous	

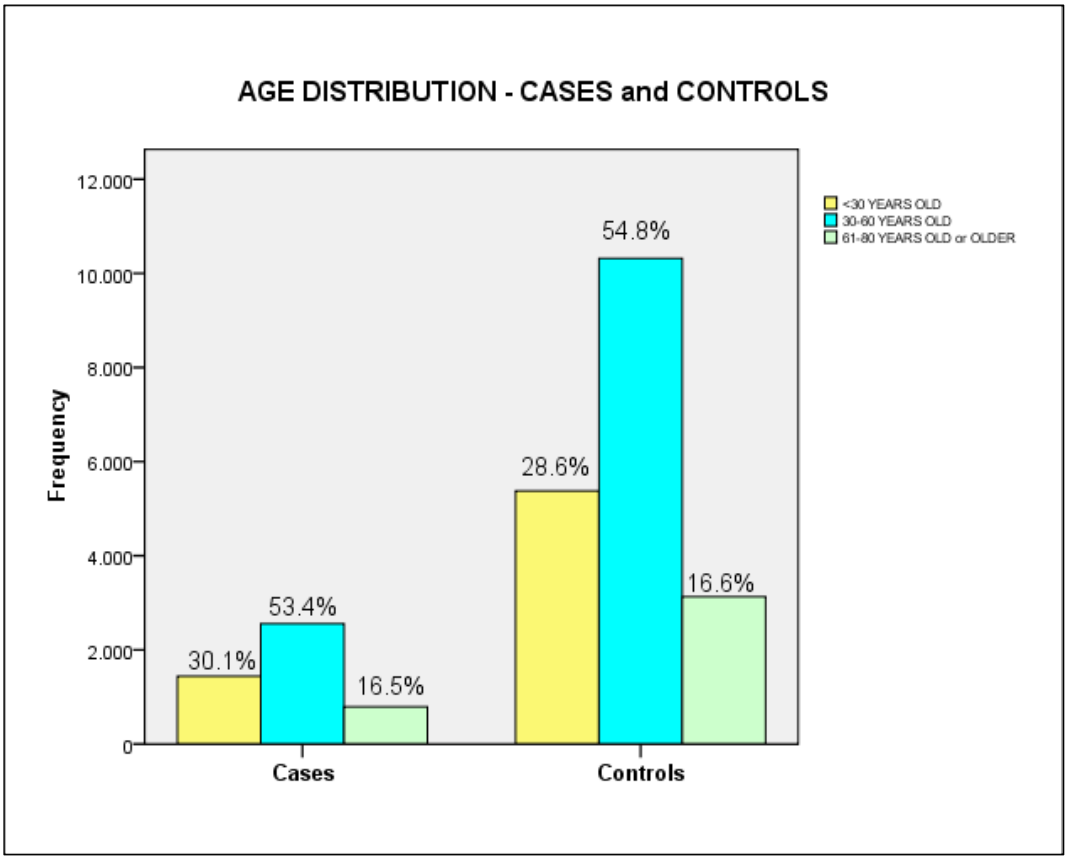
♦ KNMP/WINAp categorization

2. Demographic characteristics - Total study population

The total study population consisted of 4784 cases and 18828 controls.



Annexes - Figure 1. Sex distribution among cases and controls (Total population)



Annexes - Figure 2. Age distribution among cases and controls (Total population)

3. Accident characteristics - Total study population

Annexes - Table 2. Season in which the accidents occurred (Total population)

SEASON	N (%)
Winter	1164 (24.33)
Spring	1242 (25.96)
Summer	1059 (22.14)
Autumn	1319 (27.57)
Total	**4784 (100)**

Annexes - Table 3. Weather conditions in which the accidents occurred (Total population)

WEATHER	N (%)
Dry	3880 (81.10)
Rain	751 (15.70)
Snow/Hail	56 (1.17)
Fog	60 (1.25)
Hard wind	4 (0.08)
Unknown	29 (0.61)
Missing	4 (0.08)
Total	**4784 (100)**

Annexes - Table 4. Time of the week in which the accidents occurred (Total population)

WEEK/WEEKEND	N (%)
Week day	3529 (73.77)
Weekend	1255 (26.23)
Total	**4784 (100)**

Annexes - Table 5. Time of the day in which the accidents occurred (Total population)

TIME	N (%)
1 a.m. - 6.59 a.m.	438 (9.16)
7 a.m. - 12.59 p.m.	1376 (28.76)
13 p.m. - 18.59 p.m.	2042 (42.68)
19 p.m. - 0.59 a.m.	928 (19.40)
Total	**4784 (100)**

Annexes - Table 6. Light conditions in which the accidents occurred (Total population)

LIGHT	N (%)
Daylight	3220 (67.31)
Dark	1300 (27.17)
Dawn	263 (5.50)
Missing	1 (0.02)
Total	**4784 (100)**

Annexes - Table 7. Alcohol use (Total population)

ALCOHOL	N (%)
> 0.5 promille	376 (7.86)
< 0.5 promille	109 (2.28)
No use	3963 (82.84)
Not available	336 (7.02)
Total	**4784 (100)**

Annexes - Table 8. Concomitant alcohol and medication use (Total population)

ALCOHOL	N EXPOSED TO MED.
> 0.5 promille (N = 376)	36 (9.57)
< 0.5 promille (N = 109)	7 (6.42)
No use (N = 3963)	313 (7.90)
Not available (N = 336)	25 (7.44)

Annexes - Table 9. Seriousness of the accidents (Total population)

SERIOUSNESS	N (%)
Fatal	38 (0.79)
Seriously injured (Hospitalization > 24 hours)	1785 (37.31)
Moderately injured (1st aid point or hospitalization < 24 hours)	1704 (35.62)
Slightly injured (Treated on scene)	1257 (26.28)
Total	**4784 (100)**

4. Case-control analysis - Total study population

Annexes - Table 10. Crude ORs for road-traffic accident in psychotropic medication users (Total population)

MEDICATION EXPOSURE	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
EXPOSED AT LEAST TO ONE MEDICATION	381 (7.96)	1203 (6.39)	1.29 (1.15 - 1.46)*
NOT EXPOSED AT ALL**	4403 (92.04)	17625 (93.61)	-

* Statistically significant

** Reference group for the case-control analysis

Annexes - Table 11. Crude ORs for road-traffic accident in mono and combination therapy users (Total population)

TYPE OF THERAPY	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
MONOTHERAPY	284 (5.94)	967 (5.14)	1.18 (1.03 - 1.35)*
COMBINATION THERAPY (≥ 2 PSYC. MEDICATIONS)	97 (2.03)	236 (1.25)	1.65 (1.30 - 2.09)*

* Statistically significant

Annexes - Table 12. Crude ORs for road-traffic accident in different psychotropic medicine group users (Total population)

MEDICINE GROUP	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
N02A Opioids	31 (0.65)	95 (0.50)	1.31 (0.87 - 1.96)
N05A Antipsychotics	30 (0.63)	96 (0.51)	1.25 (0.83 - 1.89)
N05B Anxiolytics	112 (2.34)	310 (1.65)	1.45 (1.16 - 1.80)*
N05C Hypnotics	93 (1.94)	273 (1.45)	1.36 (1.08 - 1.73)*
N06A Antidepressants	161 (3.37)	398 (2.11)	1.62 (1.34 - 1.95)*
Sedative antidepressants (TCAs, MAOs + Others)	49 (1.02)	146 (0.78)	1.34 (0.97 - 1.86)
N06AB SSRIs	114 (2.38)	252 (1.34)	1.81 (1.45 - 2.27)*
R06 Antihistamines for systemic use	58 (1.21)	304 (1.61)	0.76 (0.58 - 1.01)

* Statistically significant

Annexes - Table 13. Crude ORs for road-traffic accident in opioid users, stratified by user type, sex, and age (Total population)

N02A OPIOIDS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	6 (0.13)	18 (0.10)	1.33 (0.53 - 3.36)
Chronic user	25 (0.52)	77 (0.41)	1.30 (0.83 - 2.04)
SEX			
Male	20 (0.42)	57 (0.30)	1.41 (0.84 - 2.34)
Female	11 (0.23)	38 (0.20)	1.16 (0.59 - 2.27)
AGE (Years)			
< 30	2 (0.04)	5 (0.03)	1.60 (0.31 - 8.26)
30 - 60	27 (0.56)	62 (0.33)	1.74 (1.11 - 2.74)*
> 60	2 (0.04)	28 (0.15)	0.29 (0.69 - 1.20)

* Statistically significant

Annexes - Table 14. Crude ORs for road-traffic accident in antipsychotic users, stratified by user type, sex, and age (Total population)

N05A ANTIPSYCHOTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	1 (0.02)	3 (0.02)	1.33 (0.14 - 12.83)
Chronic user	29 (0.61)	93 (0.49)	1.25 (0.82 - 1.90)
SEX			
Male	19 (0.40)	63 (0.33)	1.21 (0.72 - 2.02)
Female	11 (0.23)	33 (0.18)	1.33 (0.67 - 2.64)
AGE (Years)			
< 30	5 (0.10)	19 (0.10)	1.05 (0.39 - 2.82)
30 - 60	22 (0.46)	63 (0.33)	1.40 (0.86 - 2.27)
> 60	3 (0.06)	14 (0.07)	0.86 (0.25 - 2.99)

Annexes - Table 15. Crude ORs for road-traffic accident in anxiolytic users, stratified by user type, half-life, sex, and age (Total population)

N05B ANXIOLYTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	19 (0.40)	41 (0.22)	1.86 (1.08 - 3.20)*
Chronic user	93 (1.94)	269 (1.43)	1.38 (1.09 - 1.76)*
HALF-LIFE			
Short half-life	0	0	-
Intermediate half-life	48 (1.00)	222 (1.18)	0.87 (0.63 - 1.18)
Long half-life	31 (0.65)	84 (0.45)	1.48 (0.98 - 2.23)
SEX			
Male	61 (1.28)	162 (0.86)	1.51 (1.12 - 2.03)*
Female	51 (1.07)	148 (0.79)	1.38 (1.00 - 1.90)
AGE (Years)			
< 30	9 (0.23)	19 (0.10)	1.90 (0.86 - 4.19)
30 - 60	73 (1.84)	185 (0.98)	1.58 (1.20 - 2.08)*
> 60	30 (0.76)	106 (0.56)	1.13 (0.75 - 1.70)

* Statistically significant

Annexes - Table 16. Crude ORs for road-traffic accident in hypnotic users, stratified by user type, half-life, sex, and age (Total population)

N05C HYPNOTICS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	9 (0.19)	21 (0.11)	1.72 (0.79 - 3.75)
Chronic user	84 (1.76)	252 (1.34)	1.33 (1.04 - 1.71)*
HALF-LIFE			
Short half-life	25 (0.52)	128 (0.68)	0.98 (0.51 - 1.20)
Intermediate half-life	6 (0.13)	4 (0.02)	6.00 (1.69 - 21.29)*
Long half-life	38 (0.79)	138 (0.73)	1.10 (0.77 - 1.58)
SEX			
Male	40 (0.84)	142 (0.75)	1.13 (0.79 - 1.60)
Female	53 (1.11)	131 (0.70)	1.62 (1.18 - 2.23)*
AGE (Years)			
< 30	3 (0.08)	11 (0.06)	1.09 (0.30 - 3.32)
30 - 60	46 (1.16)	123 (0.65)	1.50 (1.07 - 2.10)*
> 60	44 (1.11)	139 (0.74)	1.27 (0.90 - 1.78)

* Statistically significant

Annexes - Table 17. Crude ORs for road-traffic accident in antidepressant users (Antidepressants as a total group, sedative antidepressants, SSRIs), stratified by user type, sex, and age (Total population)

N06A ANTIDEPRESSANTS	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	12 (0.25)	23 (0.12)	2.09 (1.04 - 4.20)*
Chronic user	149 (3.11)	375 (1.99)	1.59 (1.31 - 1.93)*
SEX			
Male	70 (1.46)	188 (1.00)	1.49 (1.13 - 1.97)*
Female	91 (1.90)	210 (1.12)	1.74 (1.35 - 2.22)*
AGE (Years)			
< 30	22 (0.46)	43 (0.23)	2.05 (1.22 - 3.43)*
30 - 60	107 (2.24)	278 (1.48)	1.54 (1.23 - 1.93)*
> 60	32 (0.67)	77 (0.41)	1.66 (1.10 - 2.52)*

SEDATIVE ANTIDEPRESSANTS (TCAs, MAOs + Others)	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	4 (0.10)	7 (0.04)	2.29 (0.67 - 7.82)
Chronic user	45 (1.14)	139 (0.74)	1.30 (0.92 - 1.82)
SEX			
Male	20 (0.50)	66 (0.35)	1.21 (0.74 - 2.00)
Female	29 (0.73)	80 (0.42)	1.45 (0.95 - 2.22)
AGE (Years)			
< 30	3 (0.08)	13 (0.07)	0.93 (0.26 - 3.24)
30 - 60	34 (0.86)	95 (0.50)	1.43 (0.97 - 2.12)
> 60	12 (0.30)	38 (0.20)	1.26 (0.66 - 2.42)
SSRIs			
USER TYPE			
New user	11 (0.28)	16 (0.08)	2.75 (1.28 - 5.93)*
Chronic user	103 (2.60)	236 (1.25)	1.75 (1.38 - 2.21)*
SEX			
Male	52 (1.31)	122 (0.65)	1.71 (1.23 - 2.36)*
Female	62 (1.56)	130 (0.69)	1.91 (1.41 - 2.59)*
AGE (Years)			
< 30	19 (0.48)	30 (0.16)	2.54 (1.43 - 4.51)*
30 - 60	74 (1.87)	183 (0.97)	1.62 (1.23 - 2.13)*
> 60	21 (0.53)	39 (0.21)	2.16 (1.27 - 3.67)*

* Statistically significant

Annexes - Table 18. Crude ORs for road-traffic accident in antihistamine users, stratified by user type, sex, and age (Total population)

R06A ANTIHISTAMINES##	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
USER TYPE			
New user	8 (0.17)	50 (0.27)	0.64 (0.30 - 1.35)
Chronic user	50 (1.05)	254 (1.35)	0.79 (0.58 - 1.07)
SEX			
Male	30 (0.63)	140 (0.74)	0.86 (0.58 - 1.27)
Female	28 (0.59)	164 (0.87)	0.68 (0.46 - 1.02)
AGE (Years)			
< 30	11 (0.23)	101 (0.54)	0.44 (0.23 - 0.81)
30 - 60	38 (0.79)	165 (0.88)	0.92 (0.65 - 1.30)
> 60	9 (0.19)	38 (0.20)	0.95 (0.46 - 1.96)

2nd generation antihistamines account for approximately 90% of this medication group as used by the study population

Annexes - Table 19. Crude ORs for road-traffic accident in different medicine category users (Total population)

MEDICINE CATEGORY (Exposed to one medication)	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
CAT. I	119 (2.49)	422 (2.24)	1.13 (0.92 - 1.39)
CAT. II	44 (0.92)	152 (081)	1.16 (0.83 - 1.62)
CAT. III	121 (2.53)	388 (2.06)	1.25 (1.02 - 1.54)*

* Statistically significant

Annexes - Table 20. Crude ORs for road-traffic accident in different medicine category users, stratified by user type (Total population)

MEDICINE CATEGORY and USER TYPE (Exposed to one medication)	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)
CAT. I			
New user	11 (0.23)	51 (0.27)	0.86 (0.45 - 1.66)
Chronic user	108 (2.26)	371 (1.97)	1.17 (0.94 - 1.45)
CAT. II			
New user	2 (0.04)	12 (0.06)	0.67 (0.15 - 2.98)
Chronic user	42 (0.88)	140 (0.74)	1.20 (0.85 - 1.69)
CAT. III			
New user	15 (0.31)	46 (0.24)	1.31 (0.73 - 2.34)
Chronic user	106 (2.22)	342 (1.82)	1.24 (1.00 - 1.55)