Psychotropic medications and traffic safety

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PSYCHOTROPIC MEDICATIONS and TRAFFIC SAFETY

Contributions to risk assessment and risk communication

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Contributions to risk assessment and risk communication

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"La ricerca non dà mai risposte,
apre sempre interrogativi,
anche se interrogativi nuovi"

Vittorino Andreoli

Ai miei genitori

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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

Road traffic safety in Europe and the DRUID project

It was estimated that, every year, over 39000 people are killed and approximately 1.5 million people are injured on the European Union (EU) roads [1, 2]. For this reason, in 2003, the EU launched the 2003 - 2010 European Road Safety Action Programme and set the target of halving the number of road deaths by 2010 [2]. In October 2006 the EU launched the five-year Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project, which is part of the 2003 - 2010 European Road Safety Action Programme, and, specifically, belongs to the 6th EU Framework Programme [3]. The integrated project DRUID involves 19 European countries and aims to provide scientific support to the EU transport policy makers by suggesting guidelines and measures to combat impaired driving [3]. In particular, the DRUID project aims to understand how traffic safety is affected by the use of psychoactive substances (alcohol, illicit drugs, and medicines), to integrate the results of its research studies in common answers and to combine the knowledge from different problem areas in new practical approaches to reduce the danger of psychotropic substances in traffic and, therefore, decrease the number of road victims [3]. DRUID is structured in terms of 7 technical Work Packages (WPs); each WP has its own goals and methodology, but, at the same time, is strictly connected to the other WPs and, therefore, is part of a dynamic and interactive structure.

Table 1 describes the 7 DRUID WPs and their main objectives.

In summary, the DRUID project reflects the efforts and contribution of the EU with respect to traffic safety and, due to its broad spectrum studies, tries to combat the scourge of drink-driving, to find solutions to the issue of drug and medication use, and, therefore, to improve road transport in Europe [3].

Methodologies in medication use and traffic safety research

As it was pointed out in the EU 2001 White Paper on the Transport Policy as well as in the 2004 World Health Organization (WHO) report on road traffic injury prevention, it is universally recognized that exceeding speed limits or driving under the influence of alcohol plays a crucial role in traffic safety. However, it is important to point out that medications that affect the central nervous system (CNS) can also represent a hazard to traffic safety and, nowadays, they actually constitute a growing problem in motor vehicle accidents [1, 4].

Psychoactive medications principally act on the CNS and, consequently, can adversely affect driving related skills [5]. In particular, CNS medications can cause adverse effects (e.g., decreased vigilance, increased reaction time, reduced visual field and acuity, somnolence, confusion) that impair cognitive and psychomotor functions and, as a result, constitute a hazard to traffic safety [5-7].

Published data suggest that, at European level, the prevalence of medications in motor vehicle accidents is approximately 10%; however, it is often difficult to establish a

Table 1. The 7 DRUID Work Packages (WPs) and their main objectives.

WP 1 - Methodology and Experimental Studies: This WP aims to assess the effects of single and combined psychotropic active substances on driving performance by means of experimental studies. Furthermore, WP 1 also provides the theoretical structure and methodology for the integration of the outcomes of the different DRUID study designs.
WP 2 - Epidemiology: The aims of WP 2 are to assess the situation in Europe regarding the prevalence of alcohol and other psychoactive substances in drivers in the general traffic and drivers involved in injury accidents, to calculate the accident risk for drug impaired drivers and to identify characteristics of drug impaired drivers. These goals are carried out by means of epidemiological studies (e.g., prevalence studies, case-control studies, culpability studies).
WP 3 - Enforcement: The purpose of this WP is to develop a good practice approach for enforcement in order to be able to detect impaired drivers (psychoactive substances other than alcohol) in an efficient and effective way.
WP 4 - Classification: The main aim of WP 4 is to propose a European classification system for medications deteriorating mental and physical fitness to drive, based on European-wide consensus.
WP 5 - Rehabilitation: This WP aims to evaluate and propose best practices with respect to the rehabilitation of drivers addicted to alcohol and/or illicit drugs.
WP 6 - Withdrawal: The main goal of WP 6 is to review and assess the effect of the current strategies regarding driving licence withdrawal as well as sanctions for impaired driving, in the different EU member states.
WP 7 - Dissemination and Guidelines: WP 7 aims to develop guidelines and information materials for health care professionals (HPCs), patients and users of psychoactive substances and to communicate the traffic accident risks associated with the use of these substances.

direct causal link between medication use and road trauma, and, generally speaking, the evidence for the role of prescribed medicines in traffic safety is still uncertain [5, 7-9].

To date, two main methods have been used to investigate the alleged relationship between medication use and driving impairment: 1) Experimental studies and 2) Epidemiological studies.

Experimental studies include performance tests in laboratory settings, driving simulator tests and "real" driving tests. In these studies, the active substances are applied to volunteers under controlled conditions and the effects on their performance are measured and compared to placebo or a positive control (e.g., alcohol) [10, 11]. Experimental studies have a number of important scientific advantages. First, they can explore medication-specific effects in specific groups of users; second, they can provide information about the effects of rarely used active substances; third, their results can provide a strong evidence on the cause effect relation; fourth, they give the possibility to work on more differentiated questions and less frequently occurring risk factors compared to epidemiological research; finally, they might solve the problem of "confounding by indication" in situations where observational research

cannot [10-12]. On the other hand, several limitations of experimental studies have to be acknowledged: to a certain extent, these studies can be artificial because of their narrow inclusion and exclusion criteria (e.g., young volunteers, healthy subjects, small sample size); they can only identify potential risks since the risks demonstrated in these studies may not necessarily occur in real road traffic; their testing techniques may not be representative of "real-life" driving; their findings can be influenced by factors such as route of administration, dosage, delay between medication consumption and performance of the task; lastly, their sensitivity and specificity to detect medicine effects on performance may be reduced by inter-individual differences [10, 11].

Epidemiological studies include prevalence studies and roadside surveys, pharmacoepidemiological studies and responsibility studies [6, 9, 10]. The main aim of epidemiological research is to explore the use of medicines in different driving populations, assess the driving risks associated with medication use, and evaluate the association between driving under the influence of medications and the responsibility for a motor vehicle accident [10]. In contrast to experimental studies, epidemiological studies measure a real risk, better reflect "normal-life" situations, examine larger population samples, allow the quantification of the magnitude of the relationship between medication exposure and/or use and traffic accident hazards, and can also be used to establish legal concentration limits [11, 13]. However, as well as experimental research, epidemiological studies are not free from limitations. In particular, epidemiological research can be hampered by the absence of a reference group or inadequate comparison group, different types of bias and confounding (e.g., selection bias, information bias, confounding by indication, confounding by co-medications, etc.), use of different study designs and data analysis techniques which may lead to divergent results and result interpretations, lack of statistical power, and difficulties in establishing whether accidents occur as a direct result of medication consumption per se or as a result of other reasons [9-11].

Despite the large amount of published experimental and epidemiological studies, at the moment, it is still difficult to draw consistent conclusions on the actual prevalence of driving under in influence of medications in the general population, the effects of commonly prescribed medications on driving performance, and the risks associated with driving under the influence of medications [9]. Generally speaking, based on the present knowledge, it can be stated that hypnotics and anxiolytics (mainly benzodiazepines) constitute a major risk to traffic safety, followed by opioids, tricyclic antidepressants and first-generation antihistamines [5-7, 14, 15]. However, as mentioned before, a number of questions on the risks associated with driving under the influence of medications still remain unanswered, especially with respect to older and newer medications, different medication combinations (psychoactive and non-psychoactive poly-therapy), dosage, acute and chronic treatment, and the role of the disease combined with therapeutic treatment [6, 16].

OBJECTIVES OF THIS DISSERTATION

This PhD dissertation is focussed in part on the contributions to the EU project DRUID and, specifically, to DRUID WP 2 and WP 4. The main objectives of this thesis are to evaluate the dimension of the use of psychotropic medications in the general population, in Europe and in the Netherlands, to examine the effects of psychoactive medication exposure on the risk of experiencing a traffic accident, and to define the criteria and methodology for the development of a categorisation system for relevant therapeutic groups of medications that can impair driving fitness.

OUTLINE OF THIS DISSERTATION

Chapter 2 presents the results of a European survey estimating the use of frequently prescribed driving impairing medication groups in a non-hospitalised population, in 12 EU countries, in the years 2000 to 2005 (DRUID WP 2).

Chapter 3 describes a study investigating the prevalence, cumulative incidence, monotherapy versus combination therapy, and treatment duration of commonly prescribed psychotropic medicine groups that might have an influence on driving performance, in the Dutch population, over the period 2000 - 2005.

In **Chapter 4** a case-control study is presented. The main aim of this study was to examine the association between the exposure to commonly prescribed psychotropic medications and the risk of experiencing a road traffic accident. The role of factors that might contribute to driving impairment (i.e., recency of the prescription, medication half-life, gender, and age) was also investigated in this study (DRUID WP 2).

In **Chapter 5** the risk of having a road traffic accident while exposed to some psychotropic medication groups is evaluated by applying a case-crossover and a case-time-control design to the database used in the case-control study. The results of these three studies are compared in order to evaluate whether the outcomes of different pharmacoepidemiological designs could lead to comparable traffic accident risk estimations (DRUID WP 2).

Chapter 6 consists of an inventory of the existing literature on the role of selective serotonin reuptake inhibitors (SSRIs) in impaired driving and traffic accidents. Starting from the main outcomes of the case-control study, this chapter evaluates the current knowledge concerning SSRIs and traffic safety, and, in particular, it discusses the pharmacological profile of SSRIs, the results of experimental and pharmacoepidemiological studies on SSRI driving impairment, two existing categorisation systems for medications, and the European legislative scenario.

In **Chapter 7** the criteria and the development of the DRUID categorisation system are presented. This chapter summarizes the work that was done in WP 4 and it briefly discusses the strengths, limitations, and implications for health care professionals and patients related to the establishment of categorisation system for potentially driving impairing medications that are currently on the EU market.

Finally, **Chapter 8** summarizes and discusses the main findings of the previous Chapters. Additionally, in this chapter implications and recommendations for future research are proposed, as well.

REFERENCES

1. Commission of the European Communities - COM (2001) White Paper - European Transport policy for 2010 - Time to decide (COM (2001) 370 final):1-124. Available at: http://eur-lex.europa.eu. Accessed: 28 July 2011
2. Commission of the European Communities - COM. European road safety action programme - Halving the number of road accident victims in the European Union by 2010: A shared responsibility (COM/2003/0311 final). Available at: http://eur-lex.europa.eu. Accessed: 28 July 2011
3. Driving under the Influence of Drugs, Alcohol and Medicines - DRUID. Available at: http://www.druid-project.eu. Accessed: 28 July 2011
4. WHO (2004) World report on road traffic injury prevention. Geneva, World Health Organization (WHO)
5. Drummer OH (2008) The role of drugs in road safety. Australian Prescriber 31:33-35
6. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
7. Agence française de sécurité sanitaire des produits de santé - AFSSAPS (2009) Medicinal products and driving (02/07/2009). Available at: http://www.afssaps.fr/Afssaps-media/Publications/Information-in-English. Accessed: 28 July 2011
8. Berthelon C, Bocca ML, Denise P, Pottier A (2003) Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation? J Psychopharmacol 17:324-331
9. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA (1999) An inventory of literature on the relation between drug use, impaired driving and traffic accidents (CT.97.EP.14). Available at: www.drugsandalcohol.ie/5308/1/1366-1591.pdf. Accessed: 28 July 2011
10. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu.publications/insights/driving. Accessed: 28 July 2011
11. Berghaus G, Hilgers RD (2009) Measurement and methods to determine driving ability. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 59-82
12. Vandenbroucke JP (2008) Observational research, randomised trials, and two views of medical science. PLoS Med 5:e67
13. Hennekens CH, Buring JE (1987) Epidemiology in Medicine. Lippincott Williams and Wilkins, Philadelphia, USA
14. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
15. Morland J (2000) Driving under the influence of non-alcoholic drugs. Forensic Science Review 12:79-104
16. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658

PART 1

DRUG UTILIZATION

CHAPTER 2

THE USE OF DRIVING IMPAIRING MEDICINES: A EUROPEAN SURVEY

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ABSTRACT

Aim: To analyse the consumption of a number of medicines with a known potential for increasing the risk of road traffic accidents in the general population of Europe.

Methods: Questionnaires were distributed through the European Drug Utilization Research Group (EuroDURG) and Post-Innovation Learning through Life-events of drugs (PILLS) networks. A total of 30 countries (the current EU Member States, Iceland, Norway and Switzerland) were asked to supply data on the use of driving impairing medicines for the period 2000 - 2005, aggregated at the level of the active substance and presented in Defined Daily Doses (DDDs) per 1000 inhabitants per day.

Results: National utilization data were provided by 12 of the 30 countries. Based on these data, a considerable increase in consumption was only seen for the antidepressants and the selective serotonin reuptake inhibitors. A slight increase, decrease or no increase was seen for the rest of the drugs studied (i.e., opioids, antipsychotics, anxiolytics, hypnotics and sedatives, drugs that are used in addictive disorders and antihistamines). Limitations were encountered when data on driving impairing medicines were compared between countries (e.g., variation in the data sources and providers, population coverage, inclusion of hospital data, use of divergent ATC/DDD versions) and, therefore, a cross-national comparison could not be performed.

Conclusions: During the study period, trends within countries showed slight to no increase in the consumption of selected medicinal drug groups, with the exception of the antidepressants and the selective serotonin reuptake inhibitors: they showed a remarkable increased use during the study time-frame. Our results illustrate that it is still difficult to perform a valid and comprehensive collection of drug utilization data on driving impairing medicines. Therefore, efforts to harmonize data collection techniques are required and recommended.

INTRODUCTION

In the year 2000, more than 40000 people in the European Union (EU) were killed in road accidents and more than 1.7 million were injured [1]. An increasing proportion of these road accidents can be attributed to the use of psychoactive substances (i.e., alcohol, drugs and certain medicines), with the use of drugs and medicines increasing proportionally over the years [2]. Consequently, a number of active steps must be taken to gain better insight into this relevant societal problem and introduce appropriate countermeasures.

In 2001, the European Commission set the ambitious goal of halving the number of road deaths between 2003 and 2010 (EU Road Safety Target, White Paper) [3]. To meet this goal, the Commission launched the 4-year Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project in October 2006 [4]. The objective of this integrated European project is to provide scientific support to the EU transport policy of reaching the 2010 road safety target. However, critical information on the amount of driving impairing medicinal products that are consumed by the European population currently does not exist. Such information is crucial as input for the future planning and successful implementation of the DRUID project.

The aim of the study reported here was to describe the use of some psychotropic medicines and some frequently used medicines with Central Nervous System (CNS) side effects in a non-hospitalized EU population between 2000 and 2005. The consumption data were collected to detect trends that illustrate an increased or decreased utilization of the most relevant medicinal drug groups with known accident risk potentials in the individual countries.

METHODS

All current EU member states as well as other countries of the wider European region (i.e., Iceland, Norway and Switzerland) were invited to supply data on the use of medicines of interest in their country. These countries were approached through two international scientific networks - the Post-Innovation Learning through Life-events of drugs (PILLS) of Utrecht University, the Netherlands, and the European Drug Utilization Research Group (EuroDURG) [5] or directly via public websites when possible (i.e., Scandinavian countries and the Netherlands). The data were requested for the time period 2000 - 2005; however, if data were only available for part of the study period, responses were still included in the study. Drug consumption data were presented by the Anatomical Therapeutic Chemical (ATC) Classification System, as recommended by the World Health Organization (WHO) [6].

The included ATC sub-groups (Table 1) cover the most frequently used psychotropic medicines and medicines with CNS side effects that are known to be of relevance for traffic safety [7-12]. Glucose-lowering medicines and antiepileptic drugs, also known

to be potentially impairing, were excluded from the selection for this study because extensive procedures are in place for the regulation of driving while using these medicines [13].

Consumption was expressed in Defined Daily Doses (DDDs)[1] per 1000 inhabitants per day or as the total number of DDDs per year accompanied by the number of inhabitants for the matching periods and region(s). The DDD/1000 inhabitants per day measure was chosen since it is a common unit of measurement tools used to present drug utilization statistics, and it enables international comparisons of drug use and evaluations of trends in drug use over time [6]. Consumption data on hospital care were not requested. Information on the coverage of the data and the sources of the data were requested (e.g., wholesaler data, reimbursement data, pharmacy sale data, etc.) (Table 2).

The ACT code of a small number of the medicines of interest for this study was changed during the study period 2000 - 2005 (Table 1). Levoceterizine remained within the same therapeutic sub-group, while bupropion, levacetylmethadol and

Table 1. Selected groups of psychotropic medicines and medicines with CNS side effects.

ATC
N02A Opioids (total group) N02AC02 Methadone* N02AC06 Levacethylmethadol*
N05A Antipsychotics
N05B Anxiolytics
N05C Hypnotics and sedatives
N06A Antidepressants (total group) N06AA Non-selective monoamine reuptake inhibitors N06AB Selective serotonin reuptake inhibitors N06AX12 Bupropion*
N07B Drugs used in addictive disorders (total group) N07BA02 Bupropion* N07BC02 Methadone* N07BC03 Levacetylmethadol*
R06A Antihistamines for systemic use (total group) R06AE Piperazine derivatives R06AX Other antihistamines for systemic use

* These substances changed therapeutic sub-groups within the time frame of this research question. The old ATC codes are N06AX12, bupropion; N02AC06, levacethylmethadol; N02AC02, methadone.

[1] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and, therefore, it does not reflect precisely the recommended or prescribed daily dose [6].

methadone were changed to a different therapeutic sub-groups [14]. In order to avoid bias, we requested the consumption data on these three substances separately. Lastly, the DDDs of four substances (bezitramide, fentanyl, hydromorphone and oxycodone) changed during the time frame of this retrospective study. We were unable to correct for the impact of these DDD changes because specific information was lacking.

RESULTS

Thirty countries were approached through the PILLS and EuroDURG networks and public websites. Data from 13 countries were obtained (Bulgaria, Czech Republic, Denmark, Finland, Germany, Hungary, Iceland, Norway, Portugal, Serbia, Slovenia, Sweden and the Netherlands). The response rate was 57%. Data from Czech Republic were not included in this study as they did not meet the study criteria (i.e., the medicinal products were aggregated at a brand level, and consumption was expressed in number of sold packages). Consequently, all data referred to hereafter have been obtained from the remaining 12 EU data providers.

Data providers and type of data

An overview of the specific data providers per country is reported in Table 2. Data providers comprised national agencies of medicines, national institutes of public health, social insurance companies, ambulatory care data collected by organizations of community pharmacies, ministries of health, national health insurance companies and scientific institutes of health insurance companies. Seven countries (Bulgaria, Denmark, Finland, Germany, Norway, Sweden and the Netherlands) provided the data as DDD/1000 inhabitants per day; the remaining countries (Hungary, Iceland, Portugal, Serbia and Slovenia) provided the number of DDDs together with the estimated covered population.

Population coverage

Nine countries provided data covering 100% of their respective population, and three countries (Germany, Slovenia and the Netherlands) could not provide consumption data that covered 100% of their respective population.

Hospital data

Hospital consumption data were neither requested nor included in this study. However, for some countries (Finland, Iceland, Norway and Serbia), it was not possible to separate the total data from ambulatory and hospital care data.

Medicinal drug utilization trends

The data on the use of psychotropic medicines and medicines with CNS side effects are presented in Table 3. This table gives an overview of the use of the selected drug classes

Table 2. Specific data sources and providers on psychotropic medicines and medicines with CNS side effects consumption per country.

Country	Data provider	Data source	Covered period	Covered population	Hospital data	Drugs with a changed ATC code
Bulgaria	National agency of medicines (Bulgarian Drug Agency)	Wholesaler monthly reports concerning the saled products	2000-2001	100%	Not included	Consumption data on bupropion, methadone, and levacetylmethadol were not available
Denmark	National agency of medicines (the Danish Medicine Agency)	Pharmacy sale data	2000-2005	100%	Not included	Consumption data on levacetylmethadol were not available
Finland	National agency of medicines (National Agency for Medicines and Social Insurance Institution) (website)	Sales to pharmacies and hospitals by wholesalers	2000-2005	100%	Included	Consumption data on bupropion and methadone were available for the years 2003-2005. Consumption data on levacetylmethadol were not available
Germany	Scientific research institute sponsored by community pharmacies and professional pharmacists' organizations (DAPI)	Reimbursement data from community and hospital pharmacies	2000-2005	80%	Not included	Consumption data on levacetylmethadol were not available
Hungary	Social insurance company (Hungarian National Health Fund Administration)	Pharmacy sales data both for reimbursed and non-reimbursed drugs	2002-2005	100%	Not included	Consumption data on levacetylmethadol were not available
Iceland	National agency of medicines (Icelandic Medicine Controle Agency)	Unknown	2000-2005	100%	Included	Consumption data on bupropion and methadone were available for the years 2002-2005. Levacetylmethadol was not registered in Iceland; therefore, no consumption data were available

Table 2. Continued.

Country	Data provider	Data source	Covered period	Covered population	Hospital data	Drugs with a changed ATC code
Norway	Norwegian Institute of Public Health (website)	Sales of medicinal products from wholesalers to pharmacies, hospitals, non-pharmacy outlets, etc.	2000-2005	100%	Included	Consumption data on levacetylmethadol were not available
Portugal	Organization of community pharmacies (CEFAR database)	Pharmacy sale data	2002-2005	100%	Not included	Consumption data on methadone, and levacetylmethadol were not available
Serbia	National agency of medicines (Medicines and Medical Devices Agency of Serbia)	Manufacturers, representatives and distributors of medicinal products	2004-2005	100% (Serbia without Kosovo and Metohija)	Included	Consumption data on levacetylmethadol were not available
Slovenia	Ministry of Health/National Health Insurance Company	Unknown	2000-2005	99%	Not included	Consumption data on bupropion for the period 2000-2001 were not available. Consumption data on levacetylmethadol were not available
Sweden	Apoteket AB (website)	Unknown	2000-2005	Unknown	Unknown	Consumption data on bupropion and methadone for the period 2000-2003 were not available. Consumption data on levacetylmethadol were not available
The Netherlands	Scientific institute of health insurance company (Genees-en hulpmiddelen Informatie Project - GIP -)	Prescription-related data on drugs that are prescribed by general practitioners and specialists, and dispensed by pharmacists, dispensing general practitioners, and other outlets as well as being reimbursed under the Health Care Insurance Act	2000-2005	80%	Not included	Consumption data on bupropion and levacetylmethadol were not available. As for methadone, in the Netherlands, most of methadone is provided in special programs; that the delivered data do not include any consumption data referring to the above mentioned special programs

Table 3. Overview of the use of the selected drug classes in 2005 and an indication of the consumption trends in 2000-2005.

DRUG CLASSES (ATC code)	COUNTRY (DDD/1000 inhabitants/day in the year 2005 and general trend in the time-frame 2000-2005)											
	Bulgaria	**Denmark**	**Finland**	**Germany**	**Hungary**	**Iceland**	**Norway**	**Portugal**	**Serbia**	**Slovenia**	**Sweden**	**The Netherlands**
Opioids (N02A)	Data not available in 2005 (↑)	17.5 (↑)	15.1 (↑)	11.6 (↑)	0.3 (-)	17.4 (↑)	19.6 (↑)	3.3 (↑)	0.8 (-)	6.3 (↑)	20.8 (↓)	6.3 (↑)
Antipsychotics (N05A)	Data not available in 2005 (-)	11.4 (↑)	17.4 (↑)	9.8 (↑)	0.8 (-)	11.5 (↑)	10.6 (↑)	7.9 (↑)	18.3 (↑)	7.8 (↑)	9.2 (↑)	7.7 (↑)
Anxiolytics (N05B)	Data not available in 2005 (-)	19.0 (↓)	31.2 (-)	6.0 (↓)	4.7 (-)	25.8 (↑)	21.4 (↑)	89.0 (↑)	91.6 (↓)	22.2 (↓)	16.4 (↑)	18.1 (↓)
Hypnotics and sedatives (N05C)	Data not available in 2005 (-)	29.9 (↓)	54.4 (↑)	6.8 (↓)	1.4 (↓)	66.7 (↑↑)	41.4 (↑)	17.9 (↑)	2.8 (↑)	13.4 (↑)	51.6 (↑)	22.1 (-)
Antidepressants (N05A)	Data not available in 2005 (↑)	58.3 (↑↑)	52.1 (↑↑)	28.5 (↑↑)	2.4 (↑)	94.8 (↑↑)	51.6 (↑)	56.8 (↑↑)	7.0 (↑↑)	29.5 (↑↑)	65.7 (↑↑)	39.0 (↑↑)
Non-selective monoamine reuptake inhibitors (N06AA)	Data not available in 2005 (-)	4.2 (-)	4.2 (-)	10.7 (↑)	0.1 (-)	8.1 (-)	3.8 (↓)	5.4 (-)	2.3 (↑)	1.5 (↓)	3.8 (-)	5.6 (-)
Selective serotonin reupttake inhibitors (N06AB)	Data not available in 2005 (↑)	40.8 (↑)	35.3 (↑)	11.2 (↑)	1.7 (-)	64.8 (↑↑)	34.8 (-)	39.8 (↑)	3.8 (↑)	23.4 (↑)	48.4 (↑)	25.5 (↑)

Table 3. Continued.

DRUG CLASSES (ATC code)	COUNTRY (DDD/1000 inhabitants/day in the year 2005 and general trend in the time-frame 2000-2005)											
	Bulgaria	Denmark	Finland	Germany	Hungary	Iceland	Norway	Portugal	Serbia	Slovenia	Sweden	The Netherlands
Drugs that are used in addictive disorders (N07B)	Data not available in 2005 (no data)	11.8 (↑↑)	6.7 (↑↑)	0.3 (↑↑)	0.2 (-)	20.6 (↑)	8.0 (↑↑)	0.9 (↑↑)	0.5 (↑↑)	0.8 (-)	8.6 (↑↑)	0.9 (↑↑)
Bupropion (N07BA02)	Data not available in 2005 (no data)	0.3 (-)	0.1 (-)	No data	0.0 (-)	1.0 (-)	0.2 (↓)	0.1 (-)	0.1 (-)	0.0 (-)	0.2 (-)	0.0 (-)
Methadone (N07BC02)	Data not available in 2005 (no data)	2.6 (-)	0.4 (↑)	0.2* (↓)	0.0 (-)	0.0 (-)	3.5 (↑)	No data	0.2 (-)	0.7 (-)	0.4 (-)	0.5 (-)
Antihistamine for systemic use (R06A)	Data not available in 2005 (-)	19.9 (↑)	31.2 (↑)	4.6 (↓↓)	2.2 (-)	30.0 (↑)	54.8 (↑)	20.5 (↑)	8.8 (↑)	17.2 (↑)	30.8 (↑)	15.3 (↑)
Piperazine derivatives (R06AE)	Data not available in 2005 (-)	9.8 (↑)	20.4 (↑)	1.7 (↓↓)	0.9 (-)	5.7 (-)	23.0 (↑)	9.1 (↑)	0.0 (-)	3.8 (↑)	9.7 (↑)	5.9 (↑)
Other antihistamine for systemic use (R06AX)	Data not available in 2005 (-)	8.6 (↑)	10.8 (↓)	2.6 (↓↓)	1.0 (-)	14.1 (↑)	25.0 (↑)	10.8 (↑)	7.5 (↑)	13.0 (↓)	15.0 (↑)	7.6 (-)

* = together with levomethadone

Legend: ↑ = slight increase (1.5-10%); ↑↑ = considerable increase (>10%); - = stable trend (0-1.49%); ↓ = slight decrease (1.5-10%); ↓↓ = considerable decrease (>10%)

in 2005 and an indication of the consumption trends in 2000 - 2005. It can be seen that the consumption of these medicinal products varied across Europe. In general, a significative upward trend was only found for two of the medicinal product classes of interest, namely the antidepressants and the Selective Serotonin Reuptake Inhibitors (SSRIs).

The consumption data showed an increase in the use of antidepressants in 11 countries between 2000 and 2005. A stable trend in antidepressant use was observed in Hungary.

There was a remarkable increase in the consumption of SSRIs in six of the 12 countries that provided data, namely Denmark, Finland, Iceland, Portugal, Slovenia and Sweden. The remaining countries showed a slight increase in the use of these active substances, with the exception of Hungary where a stable trend was observed.

A slight increase, decrease or no increase at all in the use of the drugs studied was found for most of the countries for which data were obtained. Our analysis of German consumption data revealed a considerable decrease in the consumption of antihistamines.

Finally, some unusual patterns of methadone use were observed in Denmark, Norway and Slovenia in the form of an irregular consumption pattern. In general, there was a rather large variation in the consumption of this medicine in these countries over the period of interest.

DISCUSSION

To the best of our knowledge, this is the first study carried out on the general population of Europe that focuses on the consumption of a number of frequently used medicinal products with a known potential to increase the risk of road traffic accidents. Our results indicate that the overall utilization of psychotropic medicines and medicines with CNS side effects has slightly increased, decreased or not increased at all in Europe between 2000 and 2005.

Based on the national data that were made available to us, only the consumption of antidepressants and SSRIs showed a considerable increase during the study time interval. The increased use of antidepressants is probably associated to an increase in the consumption of SSRIs. This trend was detected in all countries, with the exception of Hungary, where a stable trend was registered during the years of interest. In some countries, the increase in the use of SSRIs may result from the current clinical practice guidelines that recommend SSRIs as the first-line treatment for panic and generalized anxiety disorders, instead of benzodiazepines [15-17]. However, it should be noted that our figures indicated that there had been no significant decline in benzodiazepine use between 2000 and 2005.

Our data also indicate an irregular pattern of methadone use in Denmark, Norway and Slovenia that deserves attention. These trends may be explained either by the

primary utilization of this drug (i.e., maintenance anti-addictive use in patients addicted to opioids) and the consequent difficulties in obtaining valid consumption data or by the various biases that could have potentially affected the data collection procedures.

Contrary to expectations, a reduction in the use of antihistamines was found in the German consumption data. This finding may be explained by the implementation of new legislation, the so-called GMG, in 2004 [18]. Part of this legislation involved a change in the reimbursement regulations for Over-The-Counter (OTC) pharmaceuticals and, for most indications, OTC products were no longer reimbursed by the respective health insurance system, but rather had to be paid by patients themselves. The consumption of a number of OTC products may have been slightly affected as a result.

An interesting result of our study is that, according to our figures, the consumption of the medicines of interest in the Scandinavian countries often appeared to be much higher than that in the other European countries. Considering that these countries are well known for their rational and conservative prescription practice [19] as well as the fact that they have a long history and experience in data collection [20], we suggest that the most probable reason for this is that Scandinavian countries are able to deliver more reliable and complete data on medicinal product consumption than some of the other countries.

A number of significant limitations to this study need to be considered. An important limitation may lie in the incompleteness of data and in the non-availability of information. In terms of the data collection process, the availability of a cross-national collection system based on the same data sources and data providers would provide more reliable and complete data. However, such a system does not exist, and, as a consequence, the differences in the collection and reporting of data may have compromised the validity of the drug utilization data.

Regarding the issue of incomplete data, it is interesting to observe that, for example, our findings on anxiolytic and antipsychotic drug use in Serbia do not support the findings of a previous study that showed a considerably lower consumption of these two drug classes [21]. This inconsistency may be related to the use of different data sources and providers. The same observations may also be valid for another drug utilization study conducted in Portugal that showed a lower use of hypnotics and sedatives than did our study [22]. However, it is important to emphasize that the discrepancies between the latter study and our study are less remarkable. Moreover, it is relevant to note that our findings on anxiolytic use in Portugal are consistent with those described by Furtado and Teixeira [22].

Another limitation may involve population coverage. Nine countries were able to provide consumption data that covered the whole population and three countries (Germany, Slovenia and the Netherlands) could not. However, even in data collection systems where 100% of the population is supposed to be covered, census bias cannot be completely ruled out. This bias may be due, for example, to underdetection in the case

of countries where the reimbursement system does not cover the whole population (in data collection systems based on reimbursement data), slight variations in the exact number of insured people (in data collection systems referring to consumption data from insurance companies), missing or incorrect information in the data source from which information on drug use is obtained, among others.

Drug coverage may also have compromised our drug utilization data. In countries where the drug of interest is obtainable OTC, consumption may have been underestimated, especially in the case of data collection systems based on reimbursement data. Underestimation may also have occurred in countries where some psychotropic medicines and medicines with CNS side effects are excluded from the reimbursement lists, but the data collection system of these countries is based on reimbursement data.

Another important point to be considered is the hospital data. As stated above, hospital consumption data were not intended to be included in this study. However, the drug utilization data delivered by Finland, Iceland, Norway and Serbia included hospital data. In Iceland, the hospital data covered approximately 30% of the total consumption data; in the other three countries, the percentage of coverage could not be assessed. Consequently, drug consumption in these countries may be overestimated.

Bias might also derive from the changes in the ATC or DDD classification of the medicinal drug between 2000 and 2005. Although the data referring to the active substances with a changed ATC code were requested separately, the majority of the countries were not able to provide complete data on the consumption of these substances. Therefore, we were unable to correct for the impact of these changes and, consequently, an underestimation of the use of these medications cannot be completely ruled out. For example, none of the 12 countries was able to provide data on the consumption of levacetylmethadol. This could be due to the fact that this active substance was not marketed or it was not registered in the country (e.g., Hungary and Iceland) or because of the withdrawal of Orlaam® (levacetylmethadol) from the EU market in 2002 by the European Medicines Agency (EMEA) [23]. The consumption of the four active substances whose DDD changed during the study period may also have been misclassified. No specific details on the calculation of the number of DDDs were reported and, therefore, we do not know whether the old or the new DDD was used for this calculation. Other possible sources of bias with respect to the ATC/DDD classification could be associated with the use of different ATC/DDD versions, different DDDs for combination products and the use of unofficial or national DDDs [24].

In light of the above considerations, we can assert that, despite highly developed administrative systems, it is still difficult to collect valid and exhaustive drug utilization data and, therefore, to perform a reliable cross-national comparison in Europe. These findings are consistent with the study carried out by Vander Stichele et al. [25], the rationale of the EUROMEDSTAT project [26] as well as the findings of other authors [24, 27-29].

Our results show that there are large differences in the number of psychotropic drug prescriptions in the 12 EU countries included in our study. Since the validity of the data could not be assessed, it seems reasonable to state that the above-mentioned variations may be due to the different biases which hampered our consumption data. Consequently, it is also possible to conclude that, in this study, patterns of the use of the medicinal products of interest could only be analysed on a national level.

Finally, it is important to highlight that this study did not investigate the correlation between drug utilization patterns and road traffic accidents trends within Europe between 2000 and 2005. However, a recent study of the use of benzodiazepines (BDZs) and driving in Finland may provide insight into this relationship [30]. BDZs are widely used as anxiolytics and hypnotics, and they are also commonly abused drugs [31]. Our findings show a stable use of anxiolytics, hypnotics and sedatives in the period 2000 - 2005, but, on the other hand, they also show a relatively high use of these drug classes, especially in Scandinavian countries. The Finnish study found an increased trend in driving under the influence of BDZs during the period 2000 - 2005 [30]. Hence, it could be hypothesized that the observed increase in the use of BDZs may be correlated to the outcomes of our study. Another recent study [32] found a correlation between the prevalence of BDZs among Norwegian drivers and the sales data for these drugs. Similar outcomes also emerged from another study [33] that found a relationship between the number of prescriptions for BDZs in different Norwegian provinces and the frequency of drivers testing positive for BDZs from the same region. One of the issues that emerges from these findings is that the consumption of a number of prescribed drugs as well as of illicit drugs and alcohol represent a real risk for road traffic safety. Consequently, we can conclude that more research is needed to investigate this association.

CONCLUSIONS

A slight increase in the use of psychotropic medicines and medicines with CNS side effects has been observed in an earlier study [34], and the results of our study partially confirm this increase. However, since our study did not focus on the association between the prevalence of medicinal products and road traffic accidents, further research is needed to gain a better understanding of the scale of medicinal drug utilization in the driving population and the relation between medicine use and driving. This study also emphasizes that a trustworthy, methodological approach is essential and necessary to ensure the validity, reliability, and homogeneity of the data and enable cross-national comparisons. Improvements should be made in order to obtain better data, and there should be more harmonization of the data collection techniques to establish a reliable epidemiological database. Last, but not least, international collaboration between different countries would be most welcome and is highly recommended.

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REFERENCES

1. Hedqvist Petersen E (2000) Report on the communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions on "Priorities in EU road safety - Progress report and ranking of actions" [COM (2000) 125-C5-0248/2000-2000/2136 (COS)]. Strasbourg. Adopted by Parliament on 18 January 2001
2. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu. publications/insights/driving. Accessed: 25 May 2009
3. Commission of the European Communities - COM (2001) White Paper - European Transport policy for 2010 - Time to decide (COM (2001) 370 final):1-124. Available at: http://eur-lex.europa.eu. Accessed: 28 July 2011
4. Driving under the Influence of Drugs, Alcohol and Medicines - DRUID. Available at: http://www.druid-project.eu. Accessed: 15 September 2008
5. European Drug Utilisation Ground - EuroDURG. Available at: http://www.eurodurg.com. Accessed: 15 September 2008
6. WHO Collaborating Centre for Drug Statistics Methodology - The purpose of the ATC/DDD system. Available at: http://www.whocc.no/atcddd. Accessed: 15 September 2008
7. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
8. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
9. del Río MC, Gómez J, Sancho M, Alvarez FJ (2002) Alcohol, illicit drugs and medicinal drugs in fatally injured drivers in Spain between 1991 and 2000. Forensic Sci Int 127:63-70
10. Hindmarch I (1986) The effect of psychoactive drugs on car handling and related psychomotor ability: a review. In: O'Hanlon JF, de Gier JJ (eds) Drugs and driving. Taylor & Francis Group, London, pp 71-82
11. Movig KLL, Mathijssen MPM, Nagel PHA, van Egmond T, de Gier JJ, Leufkens HGM, Egberts ACG (2004) Psychoactive substance use and the risk of motor vehicle accidents. Accident Anal Prev 36:631-636

12. Moskowitz H (2004) Antihistamine and driving related behavior: a review of the evidence for impairment. Report number DOT HS 809 073. Available at: http://www.nhtsa.dot.gov/people/injury/research. Accessed: 15 September 2008
13. Council Directive 91/439/EEC of 29 July 1991 on driving licences. Official Journal L. 237, 24/08/1991 1-24
14. WHO Collaborating Centre for Drug Statistics Methodology - Alterations in DDDs. Available at: http://www.whocc.no/atcddd. Accessed: 15 September 2008
15. Bruce SE, Vasile RG, Goisman RM, Salzman C, Spencer M, Machan JT, Keller MB (2003) Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? Am J Psychiatry 160:1432-1438
16. Kennedy SH, Lam RW, Cohen NL, Ravindran AV (2001) Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can J Psychiatry 46(1):38S-58S
17. Allgulander C, Bandelow B, Hollander E, Montgomery SA, Nutt DJ, Osaka A, Pollack MH, Stein DJ, Swinson RP (2003) WCA recommendations for the long-term treatment of generalized anxiety disorder. CNS Spectr 8(1):53-61
18. GKV-Modernisierungsgesetz (GMG) 2004 BGBl. I 2190 of 14 November 2003. Available at: http://www.buzer.de/gesetz/7332/index.htm. Accessed: 3 September 2008
19. Fuerst J, Kocmur M (2003) Use of psychiatric drugs in Slovenia in comparison to Scandinavian countries. Pharmacoepidemiol Drug Saf 12:399-403
20. World Health Organization - WHO (2004) The world medicine situation. Available at: http://apps.who.int/medicinedocs/en/d/Js6160e/10.html. Accessed: 26 May 2009
21. Divac N, Toševski DL, Babić D, Djurić D, Prostran M, Samardžić R (2006) Trends in consumption of psychiatric drugs in Serbia and Montenegro 2000-2004. Pharmacoepidemiol Drug Saf 15:835-838
22. Furtado C, Teixeira I (2006) Utilização de benzodiazepinas em Portugal continental (1999-2003). Acta Med Port 19:239-246
23. European Medicines Agency - EMA. Available at: www.ema.europa.eu. Accessed: 15 September 2008
24. Rønning M, Blix HS, Strøm H, Skovlund E, Andersen M, Vander Stichele RH (2003) Problems in collecting comparable national drug use data in Europe: The example of antibacterials. Eu J Clin Pharmacol 58:843-849
25. Vander Stichele RH, Elsevier MM, Ferech M, Blot S, Goossens H, SAC Project Group (2004) European surveillance of antimicrobial consumption (ESAC): Data collection performance and methodological approach. Br J Clin Pharmacol 58:419-428
26. The EUROMEDSTAT Project. Available at: http://www.euromedstat.cnr.it/default.asp. Accessed: 26 May 2009
27. Cooperstock R, Parnell P (1982) Research on psychotropic drug use. A review of findings and methods. Soc Sci Med 16:1179-1196
28. World Health Organization - WHO (1970) Consumption of drugs. Report on a Symposium convened by the Regional Office for Europe of the WHO. WHO, Copenhagen
29. Hamunen K, Laitinen-Parkkonen P, Paakkari P, Breivik H, Gordh T, Jensen NH, Kalso E (2002) What do different databases tell about the use of opioids in seven European countries in 2002? Eur J Pain 12:705-715
30. Ojaniemi K, Lintonen T, Impinen AO, Lillsunde PM, Ostamo AI (2009) Trends in driving under the influence of drugs: A register-based study of DUID suspects during 1977-2007. Accident Anal Prev 41:191-196
31. Bramness JG, Skurtveit S, Mørland J (2002) Clinical impairment of benzodiazepines - Relation between benzodiazepine concentrations and impairment in apprehended drivers. Drug Alcohol Depend 68:131-141
32. Gjerde H, Normann PT, Pettersen BS, Assum T, Aldrin M, Johansen U, Kristoffersen L, Øiestad E, Christophersen AS, Mørland J (2008) Prevalence of alcohol and drugs among Norwegian motor vehicle drivers: A roadside survey. Accident Anal Prev 40:1765-1772

33. Skurtveit S, Christophersen AS, Mørland J (1995) Driving under the influence of benzodiazepines: Provincial differences in sale are reflected in drivers suspected of driving under the influence of a drug. Tidsskr Norske Laegeforen 115(2):200-203
34. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA (2006) Annual report 2006: The state of the drugs problem in Europe 2006. Available at: http://www.emcdda.europa.eu/publications/searchresults?action=list&type=PUBLICATIONS&SERIES_PUB=w36. Accessed: 15 May 2009

CHAPTER 3

PREVALENCE, CUMULATIVE INCIDENCE, MONOTHERAPY AND COMBINATION THERAPY, AND TREATMENT DURATION OF FREQUENTLY PRESCRIBED PSYCHOACTIVE MEDICATIONS IN THE NETHERLANDS: RETROSPECTIVE DATABASE ANALYSIS FOR THE YEARS 2000 TO 2005

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ABSTRACT

Background: Psychoactive drugs have been reported to impair daily activities (e.g., driving), but data regarding the use of such drugs in the Netherlands are lacking.

Aim: The aim of this work was to examine the prevalence, cumulative incidence, use of monotherapy and combination therapy, and treatment duration of frequently prescribed psychoactive drug classes in the Netherlands.

Methods: Data for the years 2000 through 2005 were derived from IADB.nl, a database with pharmacy dispensing data from a population of approximately 500000 people in the northern region of the Netherlands. The following prescription psychotropic drug classes were considered: antidepressants (as a total group and the 2 sub-groups of non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors), antipsychotics, anxiolytics, and hypnotics and sedatives. Patients aged 18 to 89 years who received ≥ 1 prescription for a psychoactive medication of interest were selected, and prevalence and cumulative incidence were calculated per 1000 patients per year. The treatment duration was analysed by means of Kaplan-Meier survival analysis. Age, gender, and drug class stratifications were performed.

Results: There was a slight increase in the prevalence of antipsychotics [final median prevalence in 2000 vs. 2005: 16.9 (95% CI: 16.5 - 17.3) vs. 18.7 (95% CI: 18.3 - 19.1)] and antidepressants [60.4 (95% CI: 59.7 - 61.2) vs. 67.1 (95% CI: 66.4 - 67.9)], with selective serotonin reuptake inhibitors being the most frequently prescribed drugs in these classes [35.2 (95% CI: 34.6 - 35.7) vs. 37.5 (95% CI: 36.9 - 38.1) in 2000 and 2005, respectively]. At the same time, there was a slight decrease in the prevalence of anxiolytics [95.1 (95% CI: 94.2 - 96.0) vs. 83.2 (95% CI: 82.3 - 84.0)], hypnotics and sedatives [68.1 (95% CI: 67.3 - 68.9) vs. 60.9 (95% CI: 60.1 - 61.6)], and non-selective monoamine reuptake inhibitors [20.3 (95% CI: 19.8 - 20.7) vs. 19.2 (95% CI: 18.8 - 19.7)]. The data also suggested that women had more prescriptions for the psychoactive medications of interest than did men, although these observations were not assessed for statistical significance. The only increase from 2000 to 2005 in median incidence per 1000 people in prescriptions was for antipsychotics [4.1 (95% CI: 3.9 - 4.3) vs. 4.9 (95% CI: 4.6 - 5.0)]; a decrease was noted in the incidence of antidepressants [18.6 (95% CI: 18.2 - 19.1) vs. 16.2 (95% CI: 15.8 - 16.6)], non-selective monoamine reuptake inhibitors [7.1 (95% CI: 6.9 - 7.4) vs. 6.8 (95% CI: 6.6 - 7.1)], selective serotonin re-uptake inhibitors [12.0 (95% CI: 11.6 - 12.3) vs. 8.6 (95% CI: 8.3 - 8.9)], anxiolytics [34.6 (95% CI: 34.1 - 35.2) vs. 30.2 (95% CI: 29.7 - 30.7)], and hypnotics and sedatives [21.2 (95% CI: 20.8 - 21.7) vs. 18.4 (95% CI: 18.0 - 18.9)]. Combination therapy was most common among those aged 30 to 44 years (6.5%) and those aged 45 to 59 years (6.1%). The longest median treatment duration was noted for antipsychotic use [1781.8 days (95% CI: 1755.2 - 1808.4)]; the shortest was observed for anxiolytic use [617.4 days (95% CI: 608.9 - 625.9)].

Conclusions: From 2000 to 2005 in the Netherlands, the yearly prevalence and cumulative incidence of prescriptions for psychoactive drugs were relatively stable, although there were some changes within specific drug classes. Monotherapy was more prevalent than combination therapy. Antipsychotics had the longest median duration of use; anxiolytics had the shortest duration.

INTRODUCTION

The use of psychotropic drugs in the general population has increased in recent years, raising questions about the factors that contribute to the use of these medications, as well as the adverse events associated with some of them [1-4]. There has been a growing concern about the role of psychotropic drugs in traffic accidents and related injuries [5-11]. An ongoing European project, Driving under the Influence of Alcohol, Drugs and Medicines (DRUID), aims to explore the impact of psychoactive substances on motor vehicle accidents [12]. Ultimately, the data from DRUID's research will be used to formulate measures to prevent impaired driving.

A drug-utilization study was conducted as part of the DRUID project to investigate the use of psychotropic medicines in the general population of Europe [13].

Twelve of 30 European countries produced national utilization data, but there was great variation in data collection methods; consequently, the data from that study did not allow in-depth analysis of the actual prevalence of prescriptions for these medications.

The aim of the present study was to examine the prevalence, cumulative incidence, use of monotherapy and combination therapy, and treatment duration of frequently prescribed psychoactive drug classes in the Netherlands.

METHODS

Settings

This study was conducted using prescription data from IADB.nl, a database with information about approximately 500000 people in the northern region of the Netherlands [14]. The data in IADB.nl are derived from 55 community pharmacies. In the Netherlands, people commonly register with a single pharmacy and obtain all their medications from that pharmacy, so a complete medication history is available in the pharmacy dispensing records. Registration at a pharmacy does not require health insurance, so such data from the IADB.nl database are representative of the general population in the Netherlands. The data are stored anonymously, and they include all prescribed medicines, except those dispensed during hospitalization; they do not include over-the-counter drugs [14-16]. All medicines are coded in IADB.nl with the Anatomical Therapeutic Chemical (ATC) classification system [17].

Study Population and Design

The following psychotropic drug classes (which may be related to driving impairment [5-8, 18]) were considered: antidepressants [as a total group (ATC code: N06A) and the 2 sub-groups of non-selective monoamine reuptake inhibitors (ATC code: N06AA) and selective serotonin reuptake inhibitors (ATC code: N06AB)], antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), and hypnotics and sedatives (ATC code: N05C).

Patients aged 18 to 89 years who received ≥ 1 prescription for a psychoactive medication of interest between January 1, 2000, and December 31, 2005, were selected from the IADB.nl and divided into the following age categories, based on previously published studies that also focused on the use of psychoactive medications: 18 to 29 years, 30 to 44 years, 45 to 59 years, 60 to 74 years, and 75 to 89 years [1, 7].

Annual prevalence was defined as the number of individuals who received ≥ 1 prescription for a study medication in a given year, divided by the total population covered by the IADB.nl, and multiplied by 1000. *Cumulative incidence* was defined as the number of new users of the study drugs in that year, divided by the correspondent population in that year, and multiplied by 1000. *New users* were defined as individuals who did not receive any prescription in the previous 18 months. Ninety-five per cent CIs were calculated for both the prevalence and incidence rates. Annual prevalence and cumulative incidence were stratified by gender, age group, and drug class.

The prevalence of monotherapy and combination therapy was calculated analogously. *Combination therapy* was defined as the concomitant use of ≥ 2 study drug classes at the third ATC level (i.e., therapeutic/pharmacologic sub-group) during the same year. Three study years were considered for calculations of the prevalence of monotherapy and combination therapy: 2000, 2003, and 2005. Age-group stratifications were also performed (i.e., 18 - 29 years, 30 - 44 years, 45 - 59 years, 60 - 74 years, and 75 - 89 years).

Treatment duration was analysed by means of a Kaplan-Meier survival analysis (SPSS 14.0 for Windows, SPSS Inc., Chicago, Illinois). To maximize the sample size in the Kaplan-Meier curve, the study population was divided into 3 age groups: 18 to 41 years, 42 to 65 years, and 66 to 89 years. Therapy was considered to have started when a patient became a new user. Therapy was considered to have ended if ≥ 15 months had passed since the last day of use of a prescription. To determine the day on which therapy ended, the number of days of use of every prescription were calculated by looking at the daily dose and the prescribed number of units. The remaining cases were considered to be censored according to the Kaplan-Meier analysis. Treatment duration was also stratified by drug class, age group, and gender.

RESULTS

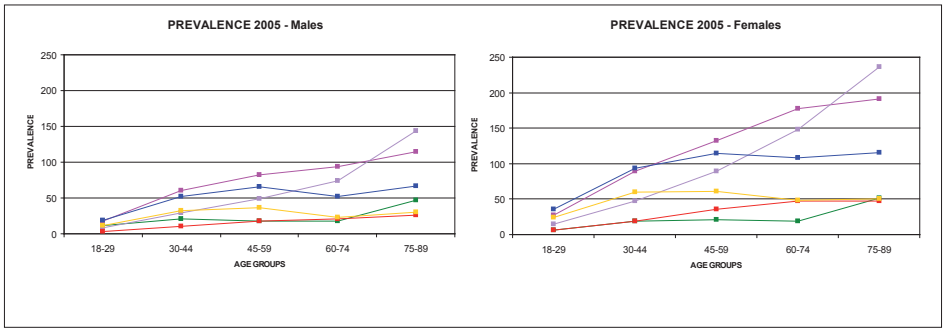
A general overview of the prevalence of the drug classes studied is presented in Table 1. The prevalence of prescriptions for the medications of interest remained relatively steady over the study period, but there were some variations. Overall, the results

indicate that there was a slight increase in the prevalence of antipsychotics [final median prevalence in 2000 vs. 2005: [16.9 (95% CI: 16.5 - 17.3) vs. 18.7 (95% CI: 18.3 - 19.1)] and antidepressants [60.4 (95% CI: 59.7 - 61.2) vs. 67.1 (95% CI: 66.4 - 67.9], with selective serotonin reuptake inhibitors being the most frequently prescribed drugs in these classes [35.2 (95% CI: 34.6 - 35.7) vs. 37.5 (95% CI: 36.9 - 38.1) in 2000 and 2005, respectively]. At the same time, there was a slight decrease in the prevalence of anxiolytics [95.1 (95% CI: 94.2 - 96.0) vs. 83.2 (95% CI: 82.3 - 84.0)], hypnotics and sedatives [68.1 (95% CI: 67.3 - 68.9) vs. 60.9 (95% CI: 60.1 - 61.6)], and non-selective monoamine reuptake inhibitors [20.3 (95% CI: 19.8 - 20.7) vs. 19.2 (95% CI: 18.8 - 19.7)]. These observations were true for all age groups and both genders. The data also suggested that women had more prescriptions for the psychoactive drug classes considered in this study than did men (Figure 1), although these findings were not assessed for statistical significance.

Table 2 provides a general overview of the cumulative incidence of the medicines of interest. The only increase noted from 2000 to 2005 in median incidence was for antipsychotics [4.1 (95% CI: 3.9 - 4.3) vs. 4.9 (95% CI: 4.6 - 5.0)]; a decrease was noted in the incidence of antidepressants [18.6 (95% CI: 18.2 - 19.1) vs. 16.2 (95% CI: 15.8

Table 1. Annual prevalence of use of selected psychoactive drugs for the years 2000 to 2005 in a retrospective analysis of prescription data from the IADB.nl database for the Netherlands, calculated as the number of individuals who received 1 prescription for a study medication in a given year, divided by the total number of individuals in that age group in the population covered by the IADB.nl in that year, and multiplied by 1000.

Drug classes (ATC Code)	**Prevalence (95% CI) 2000**	**Prevalence (95% CI) 2001**	**Prevalence (95% CI) 2002**	**Prevalence (95% CI) 2003**	**Prevalence (95% CI) 2004**	**Prevalence (95% CI) 2005**
Antipsychotics (N05A)	16.9 (16.5-17.3)	17.5 (17.3-17.7)	17.4 (17.2-17.6)	18.1 (17.9-18.3)	18.3 (18.1-18.5)	18.7 (18.3-19.1)
Anxiolytics (N05B)	95.1 (94.2-96.0)	94.3 (93.8-94.7)	92.8 (92.4-93.3)	90.7 (90.3-91.2)	88.3 (87.9-88.7)	83.2 (82.3-84.0)
Hypnotics and sedatives (N05C)	68.1 (67.3-68.9)	67.5 (65.8-67.9)	65.9 (65.5-66.3)	64.9 (64.5-65.5)	63.8 (64.3-64.5)	60.9 (60.1-61.6)
Antidepressants (N06A)	60.4 (59.7-61.2)	64.7 (64.3-65.0)	66.1 (65.7-66.5)	66.7 (66.3-67.1)	68.3 (67.9-68.7)	67.1 (66.4-67.9)
- Non-selective monoamine reuptake inhibitors (N06AA)	20.3 (19.8-20.7)	20.2 (20.0-20.4)	20.1 (19.9-20.3)	19.7 (19.5-19.9)	19.5 (19.3-19.7)	19.2 (18.8-19.7)
- Selective serotonin reuptake inhibitors (N06AB)	35.2 (34.6-35.7)	37.8 (37.5-38.1)	38.5 (38.1-38.8)	38.5 (38.2-38.8)	39.2 (38.8-39.5)	37.5 (36.9-38.1)



Legend: Green: Antipsychotics; Purple: Anxiolytics; Violet: Hypnotics and Sedatives; Blue: Antidepressants; Red: Non-selective monoamine reuptake inhibitors; Yellow: SSRIs

Figure 1. Prevalence per 1000 men (left) and per 1000 women (right) of prescriptions for antidepressants (as a whole and with non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors considered separately), antipsychotics, anxiolytics, and hypnotics and sedatives in the year 2005 in the Netherlands, in a retrospective analysis of prescription data from the IADB.nl database.

Table 2. Cumulative incidence per year of use of selected psychoactive drugs for the years 2000 to 2005 in a retrospective analysis of prescription data from the IADB.nl database for the Netherlands, calculated as the number of new users of the study drugs in a given year, divided by the correspondent population in that year, and multiplied by 1000.

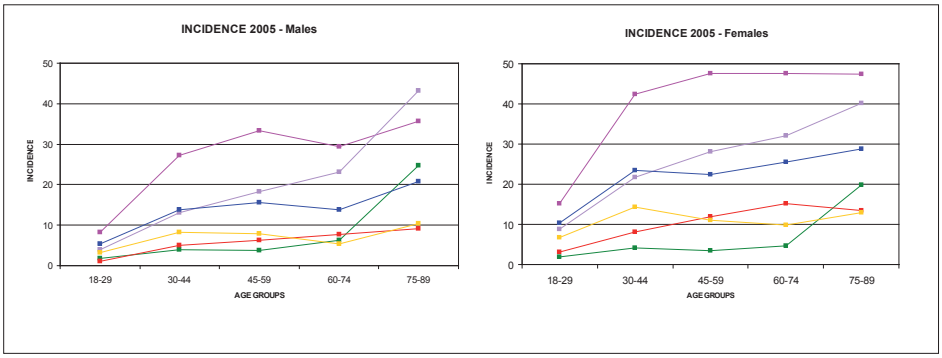
Drug classes (ATC Code)	Cum. Incidence (95% CI) 2000	Cum. Incidence (95% CI) 2001	Cum. Incidence (95% CI) 2002	Cum. Incidence (95% CI) 2003	Cum. Incidence (95% CI) 2004	Cum. Incidence (95% CI) 2005
Antipsychotics (N05A)	4.1 (3.9-4.3)	4.2 (4.0-4.4)	4.4 (4.2-4.6)	4.8 (4.6-5.0)	4.8 (4.5-5.0)	4.9 (4.6-5.0)
Anxiolytics (N05B)	34.6 (34.1-35.2)	34.3 (33.7-34.9)	33.8 (33.3-34.4)	33.4 (32.8-34.0)	33.3 (32.7-33.9)	30.2 (29.7-30.7)
Hypnotics and sedatives (N05C)	21.2 (20.8-21.7)	20.6 (20.2-21.1)	20.2 (19.8-20.7)	20.1 (19.7-20.6)	20.3 (19.9-20.8)	18.4 (18.0-18.9)
Antidepressants (N06A)	18.6 (18.2-19.1)	19.1 (18.7-19.6)	18.0 (17.6-18.4)	18.0 (17.6-18.4)	18.7 (18.3-19.1)	16.2 (15.8-16.6)
- Non-selective monoamine reuptake inhibitors (N06AA)	7.1 (6.9-7.4)	7.2 (7.0-7.5)	7.2 (6.9-7.5)	6.9 (6.7-7.2)	7.2 (7.0-7.5)	6.8 (6.6-7.1)
- Selective serotonin reuptake inhibitors (N06AB)	12.0 (11.6-12.3)	11.8 (11.5-12.2)	11.1 (10.8-11.4)	10.7 (10.4-11.0)	10.7 (10.3-11.0)	8.6 (8.3-8.9)

- 16.6)], non-selective monoamine reuptake inhibitors [7.1 (95% CI: 6.9 - 7.4) vs. 6.8 (95% CI: 6.6 - 7.1)], selective serotonin reuptake inhibitors [12.0 (95% CI: 11.6 - 12.3) vs. 8.6 (95% CI: 8.3 - 8.9)], anxiolytics [34.6 (95% CI: 34.1 - 35.2) vs. 30.2 (95% CI: 29.7 - 30.7)], and hypnotics and sedatives [21.2 (95% CI: 20.8 - 21.7) vs. 18.4 (95% CI: 18.0 - 18.9)].

Cumulative incidence per year of use of selected psychoactive drugs for the years 2000 to 2005 in a retrospective analysis of prescription data from the IADB.nl database for the Netherlands, calculated as the number of new users of the study drugs in a given year, divided by the correspondent population in that year, and multiplied by 1000.

Table 3 shows the use of monotherapy and combination therapy in the year 2005. Because these rates were comparable in the 3 years of interest, only data for the year 2005 are reported. Monotherapy was more common than combination therapy; the rates of combination therapy use were the highest among those aged 30 to 44 years (6.5%) and those aged 45 to 59 years (6.1%).

Regarding the duration of use, antipsychotics had the longest median treatment duration [1781.8 days (95% CI: 1755.2 - 1808.4)], and anxiolytics had the shortest [617.4 days (95% CI: 608.9 - 625.9)]. The median duration of use of antipsychotics by age was as follows: 18 to 41 years, 1604.7 days (95% CI: 1558.0 - 1651.5); 42 to 65 years, 1691.3 days (95% CI: 1643.0 - 1739.5); 66 to 89 years, 2002.0 days (95% CI: 1690.1 - 2043.9) (Figure 3A). By contrast, the median duration of use of anxiolytics by age was as follows: 18 to 41 years, 520.8 days (95% CI: 507.3 - 534.4); 42 to 65 years, 610.1 days (95% CI: 597.7 - 622.5); 66 to 89 years, 804.8 days (95% CI: 783.3 - 826.3) (Figure 3B).



Legend: Green: Antipsychotics; Purple: Anxiolytics; Violet: Hypnotics and Sedatives; Blue: Antidepressants; Red: Non-selective monoamine reuptake inhibitors; Yellow: SSRIs

Figure 2. Incidence per 1000 men (left) and per 1000 women (right) of prescriptions for antidepressants (as a whole, and with non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors considered separately), antipsychotics, anxiolytics, and hypnotics and sedatives in the year 2005 in the Netherlands, in a retrospective analysis of prescription data from the IADB.nl database.

Table 3. Monotherapy and combination therapy use, stratified by age group, in the year 2005 in a retrospective analysis of prescription data for antidepressants, antipsychotics, anxiolytics, and hypnotics and sedatives from the IADB.nl database for the Netherlands. Combination therapy was defined as the use of drugs from > 1 Anatomical Therapeutic Chemical (ATC) classification group*.

Age group	1 ATC group %	2 ATC groups %	3 ATC groups %	4 ATC groups %	Total Combination therapy %
18-29 N=6448	77.4	16.8	4.7	1.1	22.6
30-44 N=17304	71.1	21.1	6.5	1.3	28.9
45-59 N=21462	71.1	21.7	6.1	1.1	28.9
60-74 N=15353	72.2	21.8	5.3	0.7	27.8
75-89 N=12208	69.5	23.3	6.3	0.9	30.5

* Antidepressants (all) = ATC code: N06A; antipsychotics = ATC code: N05A; anxiolytics = ATC code: N05B; hypnotics and sedatives = ATC code: N05C.

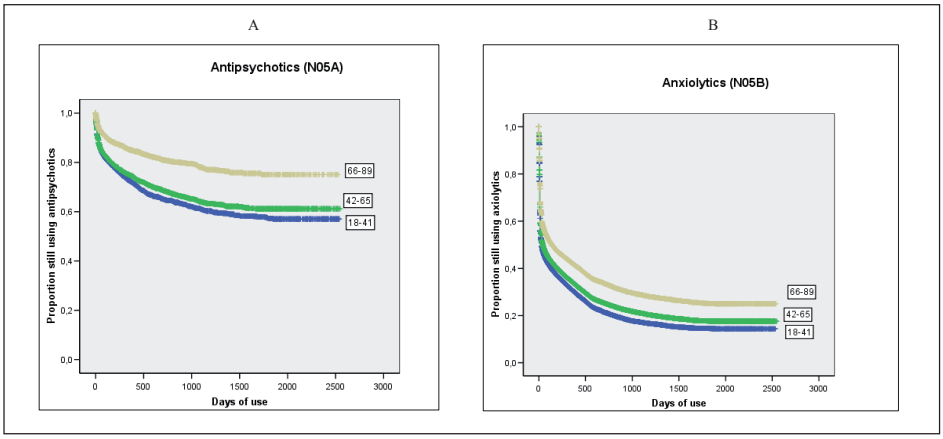


Figure 3. Kaplan-Meier survival curves for duration of prescriptions for antipsychotics (A) and anxiolytics (B) from 2000 to 2005 in the Netherlands, in a retrospective analysis of prescription data from the IADB.nl database.

DISCUSSION

In this study, there was no significant increase or decrease in the prevalence and cumulative incidence of the selected psychoactive medications from 2000 through 2005 in the Netherlands. The prevalence of antipsychotics, antidepressants, and selective serotonin reuptake inhibitors increased slightly, but not significantly; the prevalence of anxiolytics, hypnotics and sedatives, and non-selective monoamine re-uptake inhibitors decreased slightly, but not significantly. Similar slight (but not statistically significant) changes were observed regarding incidence, with the exception of antidepressants, for which a nonsignificant decrease in the number of new users was noted.

Regarding the observed nonsignificant changes in prevalence and cumulative incidence, it should be noted that the reasons for these small changes in the prescription of the studied drugs are not clear, but they may be related to slight changes in the attitudes and prescription practice of physicians, changes in treatment guidelines, or possible variations in reimbursement systems. Furthermore, these nonsignificant changes in the prevalence and incidence of prescriptions for these psychoactive drugs could be associated with scientific publications and warnings, or with the marketing efforts of pharmaceutical companies [19-23].

The higher prevalence and incidence of psychoactive drug prescriptions observed among female patients in the present study appear to support those of previously published reports [1, 24-27]. There could be several possible explanations for these findings, such as differences between the genders in the use of health care services, perceptions of physical symptoms, and attitudes about seeking help, but it would be difficult to determine definitively the reasons for these observed differences [24]. Previously published research has indicated greater prevalence and incidence of psychoactive medication use among older patients [1, 25-27]. Age-related differences could be explained by higher morbidity and, consequently, greater medication needs in an aging population.

Epidemiologic studies suggest that new users of some classes of psychoactive medications (especially anxiolytics, hypnotics and sedatives) could have elevated risk for adverse events that might affect the ability to drive [6, 28-31]. In this study, there was no significant change in the incidence of prescriptions for these drugs.

With regard to monotherapy versus combination therapy, combination therapy (i.e., the concomitant use of more than 2 ATC groups) was mainly observed among those aged 30 to 59 years. These findings could be attributable to a greater prevalence of psychiatric disorders in these age groups and, consequently, to the common practice of prescribing more than 1 antipsychotic medication to treat psychiatric diseases [32-35]. The concomitant use of medications can predispose patients to adverse events and undesirable drug interactions [35]; therefore, special attention should be directed to polypharmacy and combination therapy.

In this study, antipsychotics were the drug class with the longest median treatment duration of those considered, which may be explained by the fact that these drugs are used to treat chronic conditions (e.g., schizophrenia). Our survival analysis also indicated that the shortest median treatment duration was for anxiolytics. However, it is interesting to note that the observed treatment duration (approximately 1.7 years) was longer than that recommended, especially considering that the active substances of this drug class are mainly benzodiazepines [36]; recommendations for the use of anxiolytics indicate that prescriptions for them should be limited to occasional or intermittent use [36, 37].

The present study had several limitations. First, a dispensing database was used as the information source; thus, it was not possible to evaluate whether patients used their medications as prescribed. Second, this study only examined prescription patterns for some psychoactive drug classes and did not focus on medical and psychiatric conditions. Third, no information was included in this study regarding the use of over-the-counter medications during hospitalization; however, because the studied medicines were prescribed mainly to outpatients, this limitation probably is unlikely to have markedly affected the results. Finally, this study did not focus on specific medications, but rather on drug classes (i.e., the fourth level of the ATC classification system); therefore, it was not possible to evaluate dispensing trends for specific active substances.

Future research should investigate the impact of psychoactive medication use and related adverse events on the daily lives and activities of their users.

CONCLUSIONS

In this study, based on information from a prescribing database for the Netherlands, the yearly prevalence and cumulative incidence of the psychoactive medications of interest appeared to be relatively stable during the years 2000 through 2005, although there were some changes within drug classes. Monotherapy was more prevalent than combination therapy, and combination therapy was mainly noted among those aged 30 to 59 years. Finally, the median treatment duration was the longest with antipsychotics and shortest with anxiolytics.

REFERENCES

1. Alonso J, Angermeyer MC, Bernert S, et al., for the ESEMeD/ MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders Project (2004) Psychotropic drug utilization in Europe: Results from the European Study of Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 109(Suppl):55-64
2. Koenig W, Rüther E, Filipiak B (1987) Psychotropic drug utilization patterns in a metropolitan population. Eur J Clin Pharmacol 32:43-51
3. Riska E, Klaukka T (1984) Use of psychotropic drugs in Finland. Soc Sci Med 19:983-989
4. Cooperstock R, Parnell P (1982) Research on psychotropic drug use. A review of findings and methods. Soc Sci Med 16:1179-1196

5. Movig KLL, Mathijssen MPM, Nagel PHA, van Egmond T, de Gier JJ, Leufkens HGM, Egberts ACG. (2004) Psychoactive substance use and the risk of motor vehicle accidents. Accid Anal Prev 36:631-636
6. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prevent 5:241-253
7. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
8. Drummer OH (2008) The role of drugs in road safety. Aust Prescr 31:33-35
9. Commission of the European Communities - COM (2001) White Paper - European Transport policy for 2010 - Time to decide (COM (2001) 370 final):1-124. Available at: http://eur-lex.europa.eu. Accessed: 10 February 2010
10. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658
11. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu/publications/insights/driving. Accessed: 25 April 2010
12. Driving under the Influence of Drugs, Alcohol and Medicines - DRUID. Available at: http://www.druid-project.eu. Accessed: 24 February 2009
13. Ravera S, Hummel SA, Stolk P, Heerdink ER, de Jong-van den Berg LTW, de Gier JJ (2009) The use of driving impairing medicines: A European survey. Eur J Clin Pharmacol 65:1139-1147
14. IADB.nl database. Available at: http://www.iadb.nl. Accessed: 24 February 2009
15. Kalverdijk LJ, Tobi H, van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, de Jong-van den Berg LTW (2008) Use of antipsychotic drugs among Dutch youths between 1997 and 2005. Psychiatr Serv 59:554-560
16. Schirm E, Tobi H, de Vries TW, Choonara I, de Jong-van den Berg LTW (2003) Lack of appropriate formulations of medicines for children in the community. Acta Paediatr 92:1486-1489
17. WHO Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/atcddd. Accessed: 10 January 2009
18. Anonymous (2009) Driving under the influence (in Dutch). Pharm Weekblad 144:18. Available at: http://www.sfk.nl/publicaties/farmacie_in_cijfers/2009/2009-26.html. Accessed: 15 September 2009
19. Wagner AK, Ross-Degnan D, Gurwitz JH, Zhang F, Gilden DB, Cosler L, Soumerai SB (2007) Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. Ann Intern Med 146:96-103
20. Allery LA, Owen PA, Robling MR (1997) Why general practitioners and consultants change their clinical practice: A critical incident study. BMJ 314:870-874
21. Katz LY, Kozyrskyj AL, Prior HJ, Enns MW, Cox BJ, Sareen J. (2008) Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults (Published correction appeared in CMAJ 2008;178:1466). CMAJ 178:1005-1011
22. Moynihan R (2003) Who pays for the pizza? Redefining the relationships between doctors and drug companies - 1: Entanglement. BMJ 326:1189-1192
23. Wazana A (2000) Physicians and the pharmaceutical industry: Is a gift ever just a gift? JAMA 283:373-380
24. Neutel CI, Walop W (2005) Drug utilization by men and women: Why the differences? Drug Inform J 39:299-310
25. van Hulten R, Leufkens HG, Bakker A (1998) Usage patterns of benzodiazepines in a Dutch community: A 10-year follow-up. Pharm World Sci 20:78-82
26. del Rio MC, Alvarez FJ (1996) Medication use by the driving population. Pharmacoepidemiol Drug Saf 5:255-261

27. Vrublevska K, Rukmane J, Burmistrs R, Sipols J, Muceniece R (2008) Dispensing of psychotropic drugs to adults in community pharmacies in Latvia. Pharm World Sci 30:934-939
28. Verster JC, Mets MAJ, Leufkens TRM, Vermeeren A (2009) Insomnia, hypnotic drugs and traffic safety. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 233-244
29. Vermeeren A, Leufkens TM, Verster JC (2009) Effects of anxiolytics on driving. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 289-305
30. Neutel CI (1995) Risk of traffic accident injury after a prescription for a benzodiazepine. Ann Epidemiol 5:239-244
31. Engeland A, Skurtveit S, Mørland J (2007) Risk of road traffic accidents associated with the prescription of drugs: A registry-based cohort study. Ann Epidemiol 17:597-602
32. Vollebergh WAM, de Graaf R, ten Have M, Schoemaker C, van Dorsselaer S, Spijker J, Beekman A (2003) Mental Impairments in the Netherlands: Overview of the results of NEMESIS (in Dutch). Utrecht, the Netherlands: Trimbos-Instituut
33. Bijl RV, Ravelli A, van Zessen G (1998) Prevalence of psychiatric disorder in the general population: Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS) Soc Psychiatry Psychiatr Epidemiol 33:587-595
34. Karow A, Lambert M (2003) Polypharmacy in treatment with psychotropic drugs: The underestimated phenomenon. Curr Opin Psychiatry 16:713-718
35. Ananth J, Parameswaren S, Gunatilake S (2004) Antipsychotic polypharmacy. Curr Pharm Des 10:2231-2238
36. Ashton H (1994) Guidelines for rational use of benzodiazepines. When and what to use. Drugs 48:25-40
37. National Institute for Health and Clinical Excellence. Available at: http://www.nice.org.uk. Accessed: 15 October 2010

PART 2

RISK ASSESSMENT

CHAPTER 4

ROAD TRAFFIC ACCIDENTS AND PSYCHOTROPIC MEDICATION USE IN THE NETHERLANDS: A CASE-CONTROL STUDY

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ABSTRACT

Aim: To examine the association between the use of commonly prescribed psychotropic medications and road traffic accident risk.

Methods: A record-linkage database was used to perform a case-control study in the Netherlands. The data came from three sources: pharmacy prescription data, police traffic accident data and driving licence data. Cases were defined as drivers, who had a traffic accident that required medical assistance between 2000 and 2007. Controls were defined as adults, who had a driving licence and had no traffic accident during the study period. Four controls were matched for each case. The following psychotropic medicine groups were examined: antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants stratified in the two groups, SSRIs and other antidepressants. Various variables, such as age, gender, medicine half-life and alcohol use, were considered for the analysis.

Results: Three-thousand nine-hundred and sixty-three cases and 18828 controls were included in the case-control analysis. A significant association was found between traffic accident risk and exposure to anxiolytics [Adj. OR = 1.54 (95% CI: 1.11 - 2.15)], and SSRIs [Adj. OR = 2.03 (95% CI: 1.31 - 3.14)]. A statistically significant increased risk was also seen in chronic anxiolytic users, females and young users (18 to 29 years old), chronic SSRI users, females and middle-aged users (30 to 59 years old), and intermediate half-life hypnotic users.

Conclusions: The results of this study support previous findings and confirm that psychoactive medications can constitute a problem in traffic safety. Both health care providers and patients should be properly informed of the potential risks associated with the use of these medicines.

INTRODUCTION

Impaired driving involving alcohol, illegal and legal drugs causes, each year, a great number of traffic accidents all over the world [1-6]. Alcohol is a recognized leading contributor to road accidents and the association between alcohol and traffic accident risk has been extensively demonstrated [1-4], but, on the contrary, except for a few active substances (e.g., benzodiazepines, sedative antidepressants, opioids), the evidence of the role of medicine is still limited [4, 5].

Epidemiological studies have shown a positive association between psychotropic medication exposure and the risk of having a traffic accident [1-10]. A substantial number of studies have reported an increased traffic accident risk associated with the use of benzodiazepines [4, 5, 11-14]; however, there is still uncertainty on the traffic accident risk associated with the exposure to other psychoactive medications [3-5, 11]. Owing to methodological limitations and data availability, there is limited evidence of the association between road accidents and some commonly prescribed psychotropic medications (e.g., antipsychotics, antidepressants, anxiolytics, etc.), and, especially, the role of their dose regimen, first and new generations of medications, new and chronic users, and polypharmacy [3-5, 7, 8, 11, 15-17].

The current pharmacoepidemiological study examined the association between road traffic accidents and the exposure to different psychotropic medicine classes. In particular, it focused on the impact of factors contributing to driving impairment (i.e., recency of the prescription, medication half-life, gender and age) on the risk of experiencing a motor vehicle accident.

METHODS

We performed a case-control study, using three existing Dutch databases (i.e., PHARMO, DVS, RDW), and focusing on a 7 year period (2000 - 2007).

PHARMO is a pharmacy dispensing database which covers a population of more than 3 million Dutch residents [18]. In the Netherlands people commonly register with one pharmacy and obtain all their medications from that pharmacy so that an almost complete medication history is available. Registration is irrespective of health insurance and representative for the general population [19, 20]. Medicines are coded with the Anatomical Therapeutic Chemical (ATC) classification system [21], and, among others, the dispensing date, the prescribed dosage, the dispensed quantity and the estimated duration of use are available. PHARMO only contains de-identified information. 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, gender, etc.) that is used to perform probabilistic linkages [18].

The Dienst Verkeer en Scheepvaart (DVS) is the Dutch Traffic and Navigation Authority [22]. 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, gender, etc.) as well as traffic accident details such as the date of accident, day of the week, weather conditions, light conditions, severity of injuries incurred and breath test for alcohol excess.

The Rijks Dienst Wegverkeer (RDW) is the Dutch Road Transport Authority [23]. Its database contains all the available data on registered vehicles, their owners, vehicle registration numbers and driving licence numbers.

Database linkage

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

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 licence numbers belonging to those subjects who were involved in a traffic accident, and, consequently, stored in both databases. In the second phase of the linking process, the DVS + RDW database was linked to the PHARMO database. This phase was based on a probabilistic record linkage technology which is a purely statistical methodology [24]. This technology is widely used to perform database linkages and has been described in detail elsewhere [24, 25].

Approximately 3% of the car accidents that occurred in the Netherlands, in the study time frame, could be included in the database linkage process.

Inclusion and exclusion criteria

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. Based on the police data, at the time of the accident, the subjects were driving, and, after their traffic accident, medical assistance was received and the seriousness of the accident was assessed. Cases were restricted to those subjects who were found negative for alcohol use.

Controls were defined as adults (18 years or older), who had a driving licence and had no traffic accident during the study period. Four controls were matched for each case; the matching was by gender, age within 5 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 and exposure definitions

The following psychotropic medications, known to be of relevance for traffic safety, were included: antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics and sedatives (N05C), antidepressants stratified in selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants [i.e., non-selective monoamine re-uptake inhibitors; monoamine oxidase A inhibitors (MAOs); other antidepressants].

Anxiolytic and hypnotic benzodiazepines were stratified according to their half-life (short: 12 h; intermediate: >12 h and 24 h; long: >24 h) [26].

Cases and controls were considered to be exposed if the medication was used during the week before the accident date (i.e., index date) (Figure 1). The day after the dispensing date was considered as the start of the therapy. If the therapy ended 2 days before the index date, the subjects were still considered as exposed (Figure 1). Medications dispensed 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.

New users were defined as 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 receive any prescriptions for this medication in the 6 months before the initiation of the therapy. Chronic users were defined as 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 (Figure 1).

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

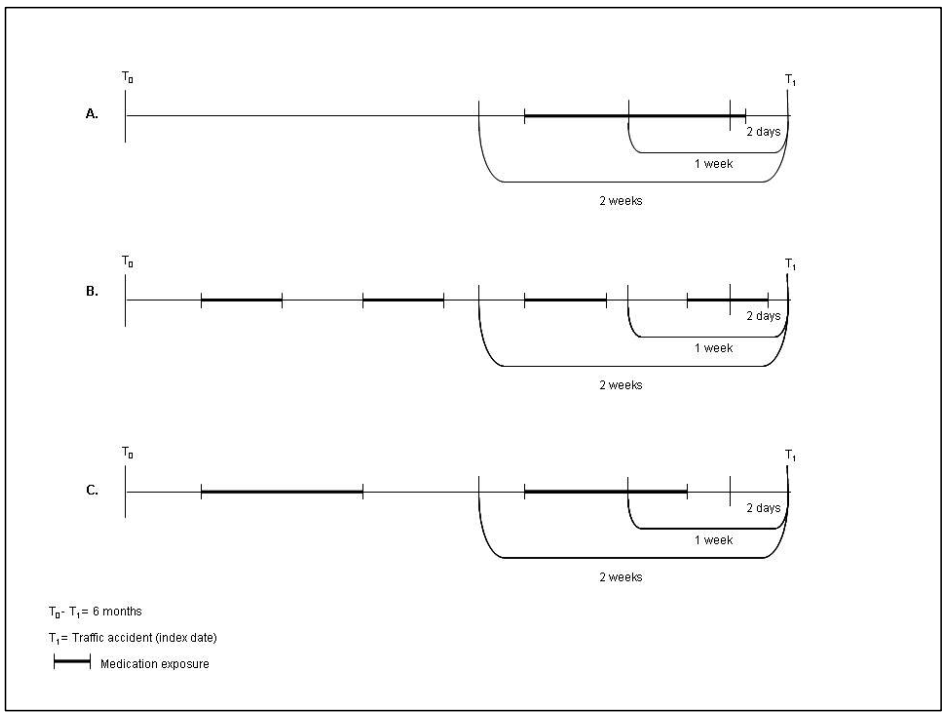

Figure 1. Medication exposure (cases and controls). A. New user - Exposed, B. Chronic user - Exposed, and C. Chronic user - Not exposed.

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.

Logistic regression analysis was used to calculate the odds ratios (ORs) of a traffic accident after exposure to the study medications. The case-control status was used as a dependent variable. The analysis compared the odds of exposure to the study medications among the cases with the odds of exposure among the controls. Exposure to one of the study ATC groups (e.g., SSRIs) was compared with the absence of exposure to the ATC groups of interest. Driver and medication characteristic stratifications were performed (i.e., medication user type; gender, age and benzodiazepine half-life) and adjusted ORs were computed (combination therapy adjustment). ORs were adjusted for psychotropic drug polypharmacy because it is well known that the concomitant use of medications can increase the risk of adverse effects, medicine interactions and, consequently, lead to an increased risk of traffic accidents [11, 14, 20].

95% confidence intervals (CIs) were calculated for all ORs to establish whether the findings were statistically significant.

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.

RESULTS

Data on 155470 traffic accidents were available in the DVS database whereas 64937 licence numbers were associated with 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. After this second phase, 3963 traffic accidents that satisfied the study inclusion criteria were available.

With respect to the control selection, in the first phase of the linking process, 6916598 driving licence holders who did not have a traffic accident in the years 2000 - 2007 were selected from the RDW database. After the second phase of the linking process, a database consisting of 858039 subjects was available to perform the final control selection. This led to the selection of 18828 controls corresponding to the inclusion criteria.

Therefore, our final study population consisted of 3963 cases and 18828 controls.

Eight-hundred and twenty-one cases were excluded because they were either positive for alcohol (485 cases) or had no data on alcohol use (336 cases).

Cases were mainly males (males = 62.5%) and they mostly belonged to the age group 30 - 60 years (< 30 years = 28.7%; 30 - 60 years = 53.9%; > 60 years = 17.4%).

Table 1 presents the accident characteristics of the cases. From this table it can be seen that accidents were equally distributed during the four seasons, they mainly occurred on week days, with dry weather conditions, at daylight, and between 13.00 h and 19.00 h. According to the police report, the majority of the accidents were classified as either serious or moderately serious and, consequently, the subjects were transported to the hospital to receive further medical assistance.

Table 1. Accident characteristics (cases only).

ACCIDENT CHARACTERISTICS (N = 3963)	**N (%)**
SEASON	
Winter	963 (24.3)
Spring	1019 (25.7)
Summer	881 (22.2)
Autumn	1100 (27.8)
WEATHER	
Dry	3199 (80.7)
Rain	635 (16.0)
Snow/Hail	49 (1.2)
Fog	52 (1.3)
Hard wind	3 (0.1)
Missing	25 (0.6)
WEEK/WEEKEND	
Week day	3044 (73.8)
TIME	
1 a.m. - 7 a.m.	249 (6.3)
7 a.m. - 1 p.m.	1245 (31.4)
1 p.m. - 7 p.m.	1803 (45.5)
7 p.m. - 1 a.m.	666 (16.8)
LIGHT	
Daylight	2865 (72.3)
Dark	872 (22.0)
Dawn	226 (5.7)
SERIOUSNESS	
Fatal	24 (0.6)
Seriously injured (Hospitalization > 24 hours)	1365 (34.4)
Moderately injured (1st aid point or hospitalization < 24 hours)	1486 (37.5)
Slightly injured (Treated on scene)	1088 (27.5)

Two-hundred and thirty-seven cases and 967 controls were exposed to monotherapy of one of the study medications, and 76 cases and 236 controls were exposed to combination therapy.

Table 2 shows in detail the medication exposure of cases and controls. It can be seen that anxiolytics were the most represented psychoactive medications, in both cases and controls, followed by SSRIs, and hypnotics and sedatives.

Table 2 also presents the crude and adjusted ORs for road traffic accidents related to psychoactive medication use, stratified by user-type, gender and age.

A significant increased traffic accident risk was seen for anxiolytics and SSRIs.

The data also illustrate that new users were associated with a higher traffic accident risk compared with no use, except for the SSRIs. However, this association was not statistically significant.

In relation to the gender stratifications, it can be seen from Table 2 that there was a statistically significant association between the risk of having a traffic accident and female anxiolytic, and SSRI users. On the contrary, no statistically significant association was found between male users of the study medications and traffic accident risk.

Lastly, analyses of medication exposure by age groups indicated that only young anxiolytic and middle-aged SSRI users were positively associated with a higher traffic accident risk.

Table 3 illustrates the crude and adjusted ORs for road traffic accident in anxiolytic and hypnotic benzodiazepine users, stratified by half-life. As can be seen from this table, a statistically significant association was only found in the case of exposure to intermediate half-life hypnotics.

Table 2. Exposed subjects [cases (N=3963) and controls (N=18828)], crude and adjusted ORs* for road-traffic accident in different psychotropic medicine group users, stratified user type, gender, and age.

MEDICINE GROUP	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)	Adj. ORs (95% CI)
Antipsychotics				
All exposed individuals	20 (0.50)	96 (0.51)	1.01 (0.62-1.63)	1.31 (0.71-2.42)
New users	1 (0.03)	3 (0.02)	1.61 (0.17-15.48)	1.61 (0.17-15.48)
Chronic users	19 (0.48)	93 (0.49)	0.99 (0.60-1.62)	1.29 (0.68-2.44)
Males	12 (0.30)	63 (0.33)	0.92 (0.50-1.71)	1.00 (0.41-2.41)
Females	8 (0.20)	33 (0.18)	1.17 (0.54-2.54)	1.78 (0.75-4.24)
< 30 yrs	3 (0.08)	19 (0.10)	0.76 (0.23-2.58)	2.41 (0.60-9.66)
30 - 60 yrs	15 (0.38)	63 (0.33)	1.15 (0.65-2.02)	1.32 (0.63-2.75)
> 60 yrs	2 (0.05)	14 (0.07)	0.69 (0.16-3.04)	0.54 (0.10-4.24)
Anxiolytics				
All exposed individuals	94 (2.37)	310 (1.65)	**1.46 (1.16-1.85)**	**1.54 (1.11-2.15)**
New users	15 (0.38)	41 (0.22)	1.77 (0.98-3.20)	1.81 (0.71-4.63)
Chronic users	79 (1.99)	269 (1.43)	**1.41 (1.01-1.83)**	**1.51 (1.06-2.16)**
Males	49 (1.24)	162 (0.86)	**1.46 (1.06-2.01)**	1.22 (0.74-2.03)
Females	45 (1.14)	148 (0.79)	**1.47 (1.05-2.05)**	**1.89 (1.21-2.95)**
< 30 yrs	8 (0.20)	19 (0.10)	2.03 (0.89-4.65)	**4.02 (1.23-13.19)**
30 - 60 yrs	58 (1.46)	185 (0.98)	**1.51 (1.12-2.04)**	1.51 (1.00-2.28)
> 60 yrs	28 (0.71)	106 (0.56)	1.28 (0.84-1.94)	1.27 (0.65-2.46)
Hypnotics				
All exposed individuals	76 (1.92)	273 (1.45)	**1.34 (1.04-1.74)**	1.39 (0.94-2.07)
New users	6 (0.15)	21 (0.11)	1.38 (0.56-3.42)	2.76 (0.81-9.43)
Chronic users	70 (1.77)	252 (1.34)	**1.34 (1.03-1.75)**	1.30 (0.86-1.98)
Males	33 (0.83)	142 (0.75)	1.12 (0.77-1.64)	1.21 (0.64-2.28)
Females	43 (1.09)	131 (0.70)	**1.59 (1.12-2.24)**	1.53 (0.93-2.54)
< 30 yrs	2 (0.05)	11 (0.06)	0.88 (0.20-3.96)	0.97 (0.11-8.27)
30 - 60 yrs	33 (0.83)	123 (0.65)	1.30 (0.88-1.91)	1.40 (0.83-2.37)
> 60 yrs	41 (1.03)	139 (0.74)	1.42 (1.00-2.02)	1.43 (0.77-2.65)
SSRIs				
All exposed individuals	92 (2.32)	252 (1.34)	**1.76 (1.38-2.24)**	**2.03 (1.31-3.14)**
New users	7 (0.18)	16 (0.08)	2.11 (0.87-5.14)	1.81 (0.48-6.83)
Chronic users	85 (2.14)	236 (1.25)	**1.74 (1.35-2.23)**	**2.06 (1.30-3.26)**
Males	40 (1.01)	122 (0.65)	**1.58 (1.11-2.27)**	1.46 (0.72-2.97)
Females	52 (1.31)	130 (0.69)	**1.93 (1.40-2.67)**	**2.55 (1.46-4.45)**
< 30 yrs	16 (0.40)	30 (0.16)	**2.58 (1.40-4.73)**	3.02 (0.99-9.23)
30 - 60 yrs	57 (1.44)	183 (0.97)	**1.50 (1.12-2.03)**	**1.74 (1.01-2.98)**
> 60 yrs	19 (0.48)	39 (0.21)	**2.35 (1.36-4.08)**	2.63 (0.97-7.13)

* ORs adjusted for combination therapy
Bold = Statistically significant

Table 2. Continued.

MEDICINE GROUP	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)	Adj. ORs (95% CI)
Other antidepressants				
All exposed individuals	40 (1.01)	146 (0.78)	1.32 (0.93-1.88)	1.45 (0.81-2.58)
New users	3 (0.08)	7 (0.04)	2.07 (0.54-8.00)	2.41 (0.22-26.63)
Chronic users	37 (0.93)	139 (0.74)	1.29 (0.89-1.85)	1.41 (0.78-2.56)
Males	16 (0.40)	66 (0.35)	1.17 (0.68-2.02)	1.61 (0.72-3.59)
Females	24 (0.61)	80 (0.42)	1.45 (0.92-2.29)	1.30 (0.56-3.00)
< 30 yrs	2 (0.05)	13 (0.07)	0.74 (0.17-3.29)	4.83 (0.32-77.21)
30 - 60 yrs	28 (0.71)	95 (0.50)	1.42 (0.93-2.17)	1.48 (0.75-2.90)
> 60 yrs	10 (0.25)	38 (0.20)	1.27 (0.63-2.55)	1.11 (0.32-3.91)

* ORs adjusted for combination therapy
Bold = Statistically significant

Table 3. Crude and adjusted ORs* for road-traffic accidents in anxiolytic and hypnotic benzodiazepine users, stratified by half-life.

MEDICINE GROUP	CASES (Exposed) (%)	CONTROLS (Exposed) (%)	Crude ORs (95% CI)	Adj. ORs (95% CI)
ANXIOLYTIC BENZODIAZEPINES				
Short half-life	0	0	-	-
Intermediate half-life	42 (1.06)	222 (1.18)	0.91 (0.66-1.27)	1.13 (0.73-1.75)
Long half-life	26 (0.66)	84 (0.45)	1.50 (0.96-2.32)	1.57 (0.82-3.01)
HYPNOTIC BENZODIAZEPINES				
Short half-life	20 (0.50)	128 (0.68)	0.75 (0.47-1.21)	0.79 (0.39-1.60)
Intermediate half-life	6 (0.15)	4 (0.02)	**7.24 (2.04-25.68)**	**6.44 (1.44-28.78)**
Long half-life	31 (0.78)	138 (0.73)	1.10 (0.73-1.60)	1.42 (0.80-2.53)

* ORs adjusted for combination therapy
Bold = Statistically significant

DISCUSSION

The outcomes of this study showed that the use of psychotropic medications could place drivers at a higher risk for a traffic accident. In particular, the current study indicated that there was a statistically significant association between the risk of having a motor vehicle accident and the exposure to anxiolytics and SSRIs. The results of our research also showed a significantly increased traffic accident risk in case of chronic SSRI users, intermediate half-life hypnotic users, female anxiolytic and SSRI users and young to middle-aged drivers (this latter association was statistically significant only for users of anxiolytics and SSRIs).

Contrary to expectations, our study revealed a significant association between the risk of being involved in an accident as a driver and the exposure to SSRIs [Adj. OR = 2.03 (95% CI: 1.31 - 3.14)]. Although these findings differ from previous studies which showed no increased risk of road traffic accidents in SSRI users [4, 5, 7, 8, 11, 27], they are in line with those of Rapoport *et al.* and Hooper *et al.* who, however, focused on very specific populations (i.e., patients with dementia and military population, respectively) [28, 29]. Our results are also consistent with those of Orriols *et al.* who, however, did not specifically focus on SSRIs but on psychoanaleptics as a total group [10]. A possible explanation for our SSRI 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 [30, 31] or with not properly diagnosed or treated depression which is well-known to play a causal role in suicidal deaths [32-34]. 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 [28, 35-37]. 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 [38]. Another possible explanation is that the side effects of a single SSRI could have accounted for the increased ORs of SSRIs [8] or it is also possible that these results are due to lack of therapy adherence which has been often seen in depressed patients and might result in more severe adverse drug events and treatment failure [39, 40]. Lastly, the observed increase in traffic accident risk could 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 during their course of treatment, exposing themselves to a greater risk of being involved in a traffic accident.

Surprisingly, our study did not find a strong association between road traffic accidents and anxiolytics, and hypnotics and sedatives [anxiolytics: Adj. OR = 1.54 (95% CI: 1.11 - 2.15); hypnotics and sedatives: Adj. OR = 1.39 (95% CI: 0.94 - 2.07), not statistically significant], which are both well-known driving impairing medication groups [4, 5, 7, 8, 11-13]. It is difficult to explain these results, but they could be related to the fact that these medicines can be often taken at subtherapeutic doses for different indications (anxiolytics) [41] or at night (hypnotics) [12], 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 and sedative 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 [42].

With regard to the user type, our research showed that the risk associated with psychotropic medication users was the highest among new users, even though this association was not found to be statistically significant in any of the selected medication groups. On the contrary, our results showed a significant increased risk in chronic SSRI users [Adj. OR = 2.06 (95% CI: 1.30 - 3.26)]. Very little was found in the literature on

these latter findings. Nevertheless, the observed increased risk in chronic users of SSRIs could be explained by residual depressive symptoms [27, 43] or it could be attributed to a not fully achieved clinical remission by antidepressant treatment.

On the question of medicine half-life, the current study found a strong association between the exposure to intermediate half-life hypnotics and traffic accident risk [Adj. OR = 6.44 (95% CI: 1.44 - 28.78)], and a positive, but not statistically significant, association in case of long half-life anxiolytic exposure [Adj. OR = 1.57 (95% CI: 0.82 - 3.01)]. These ORs confirm previous research [7, 8, 12, 44-47] and might be due to 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, consequently, have an extended negative effect on driving performance [8, 44, 45, 48].

The current study also indicated that female patients were more often significantly associated with the risk of having a traffic accident than male patients. These findings do not support previously published studies which showed an increased accident risk in male patients [29, 46, 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 [44, 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 attributed 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, generally speaking, 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 related 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 [12, 57]. These findings are in agreement with earlier findings [12, 13, 46, 47, 49, 55] and are also reflected in the descriptive statistics of our study.

To conclude, a number of limitations need to be considered. First, a pharmacy 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, both cases and controls mainly used their medications either on a low or regular dosage. Therefore, it was not possible to examine the role of high medication dosage which is also known to be related to an increased risk of road traffic accidents [12, 44, 58]. Third, there was no possibility to obtain information on medications prescribed during recent hospitalization or the concomitant use of over

the counter medicines which could also have played a role in endangering traffic safety. Fourth, no information was available on what medical condition the psychotropic medications were prescribed for or on patients' comorbidities which both might have biased our outcomes [5, 13, 47]. Fifth, it was assumed that cases and controls regularly drove a car. This was a rough assumption, based on that fact that both cases and controls had a driving licence, 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 (e.g., illicit drug use among cases and controls, alcohol use among controls, speeding, etc.), 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 [29]. 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 thus fully reliable outcomes (e.g., user type and age stratifications).

Despite of these limitations, it is important to underline that, to our knowledge, this matched case-control study is one of the first studies to examine the risk of having a traffic accident associated with exposure to a large and comprehensive set of different driving impairing medications and to investigate the role of other influential predictors such as user type, gender, age and medication half-life. Furthermore, 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 also focused on a broad time frame.

In conclusion, the results of this study confirmed previous findings and those of a recent French study [10] on prescription medicines and road traffic crash risk and contributed additional evidence that psychotropic medications can constitute a considerable danger for traffic safety, especially for patients with no medicine use experience, female, and young psychoactive medication 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 safer alternatives, monitoring their patients' driving experience with the medication, and, if needed, advising them not to drive until they are fit to drive.

It is recommended that more research should be undertaken to investigate further the effect of SSRIs in traffic accidents in order to understand better the extent to which these antidepressants can cause or contribute to accidents. Moreover, more work needs to be done to determine the role of medication dose and dose changes, non-psychoactive medicines, and medical conditions.

COMPETING INTERESTS

There are no competing interests to declare.

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REFERENCES

1. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, Swann P (2004) The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accident Anal Prev 36:239-248
2. European Commission. Road Safety - Fitness to Drive. Available at: http://ec.europa.eu/transport/road_safety/topics/behaviour/fitness_to_drive/index_en.htm. Accessed: 15 October 2010
3. Canadian Traffic Injury Research Foundation and Palmer SA. Drugs and driving: A compendium of research studies. Available at: http://www.justice.gc.ca/eng/pi/rs/rep-rap/2006/rr06_8/p1.html. Accessed: 15 October 2010
4. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
5. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658
6. del Río MC, Gómez J, Sancho M, Alvarez FJ (2002) Alcohol, illicit drugs and medicinal drugs in fatally injured drivers in Spain between 1991 and 2000. Forensic Sci Int 127:63-70
7. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu/publications/insights/driving. Accessed: 15 October 2010
8. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA (1999) An inventory of literature on the relation between drug use, impaired driving and traffic accidents (CT.97.EP.14). Available at: www.drugsandalcohol.ie/5308/1/1366-1591.pdf. Accessed: 19 October 2010
9. Anonymous (2009) Driving under the influence (in Dutch). Pharm Weekblad 144:18. Available at: http://www.sfk.nl/publicaties/farmacie_in_cijfers/2009/2009-26.html. Accessed: 12 October 2010
10. Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B, Laumon B, Salmi LR. Lagarde E, and the CESIR research group (2010) Prescription medicines and the risk of road traffic crashes: a French registry-based study. PLoS Med 7: e1000366
11. Drummer OH (2008) The role of drugs in road safety. Aust Prescr 31:33-35

12. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
13. Engeland A, Skurtveit S, Mørland J (2007) Risk of road traffic accidents associated with the prescription of drugs: A registry-based cohort study. Ann Epidemiol 17:597-602
14. Movig KLL, Mathijssen MPM, Nagel PHA, van Egmond T, de Gier JJ, Leufkens HGM, Egberts ACG (2004) Psychoactive substance use and the risk of motor vehicle accidents. Accident Anal Prev 36:631-636
15. Berghaus G, Hilgers RD (2009) Measurement and methods to determine driving ability. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 59-74
16. Houwing S, Mathijssen R, Brookhuis KA (2009) Case-control studies. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 107-120
17. Bramness JG, Skurtveit S, Neutel CI, Mørland J, Engeland A (2008) Minor increase in risk of road traffic accidents after prescriptions of antidepressants: A study of population registry data in Norway. J Clin Psychiat 69:1099-1103
18. PHARMO Institute. Available at: http://www.pharmo.nl. Accessed: 6 October 2010
19. Kalverdijk LJ, Tobi H, van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, de Jong-van den Berg LTW (2008) Use of antipsychotics drugs among Dutch youth between 1997 and 2005. Psychiatr Serv 59:554-560
20. Ravera S, Visser ST, de Gier JJ, de Jong-van den Berg LTW (2010) Prevalence, cumulative incidence, monotherapy and combination therapy, and treatment duration of frequently prescribed psychoactive medications in the Netherlands: Retrospective database analysis for the years 2000 to 2005. Clin Ther 32:2457-2466
21. WHO Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/atcddd. Accessed: 6 October 2010
22. Dienst Verkeer en Scheepvaart - DVS. Available at: http://www.rijkswaterstaat.nl. Accessed: 12 October 2010
23. Rijks Dienst Wegverkeer - RDW. Available at: http://www.rdw.nl/nl/particulier/Pages/default.aspx. Accessed: 12 October 2010
24. van Herk-Sukel MPP, van de Poll-Franse LV, Lemmens VEPP, Vreugdenhil G, Pruijt JFM, Coebergh JWW, Herings RMC (2010) New opportunities for drug outcomes research in cancer patients: The linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer 46:395-404
25. Herings RMC (1993) PHARMO: A record linkage system for postmarketing surveillance of prescription drugs in the Netherlands. Thesis (Doctorate). Utrecht University (The Netherlands)
26. Trevor AJ, Way WL (2001) Sedative-hypnotic drugs. In: Basic and Clinical Pharmacology, Eighth edn. Katzung BG. New York: Lange Medical Books/McGraw-Hill, pp 364-381
27. Verster JC, Ramaekers JG (2009) Antidepressants and traffic safety. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 307-314
28. Rapoport MJ, Molnar F, Rochon PA, Juurlink DN, Zagorski B, Seitz D, Morris JC, Redelmeier DA (2008) Psychotropic medications and motor vehicle collisions in patients with dementia. J Am Geriatr Soc 56:1968-1969
29. Hooper TI, DeBakey SF, Pearse L, Pratt S, Hoffman KJ (2010) The use of electronic pharmacy data to investigate prescribed medications and fatal motor vehicle crashes in a military population, 2000-2006. Accident Anal Prev 42:261-268
30. Hampton T (2004) Suicide caution stamped on antidepressants. JAMA 291:2060-2061
31. Teicher MH, Glod CA, Cole OJ (1998) Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf 8:186-212
32. American Psychiatric Association (2000). In: Diagnostic and Statistical Manual of Mental Disorders, 4th eds. Text Revision (DSM-IV-TR). Washington, DC: APA, USA

33. Wessely S, Kerwin R (2004) Suicide risk and the SSRIs. JAMA 292:379-381
34. Neutel CI, Patten SB (1997) Risk of suicide attempts after benzodiazepine and/or antidepressant use. Ann Epidemiol 7:568-574
35. Leveille SG, Buchner DM, Koepsell TD, McCloskey LW, Wolf ME, Wagner EH (1994) Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 5:591-598
36. Agence française de sécurité sanitaire des produits de santé - AFSSAPS (2009) Medicinal products and driving (02/07/2009). Available at: http://www.afssaps.fr/Afssaps-media/Publications/Information-in-English. Accessed: 15 October 2010
37. Rapoport MJ, Baniña MC (2007) Impact of psychotropic medications on simulated driving - A critical review. CNS Drugs 21:503-519
38. Noël PH, Williams JW, Unützer J, Worchel J, Lee S, Cornell J, Katon W, Harpole LH, Hunkeler E (2004) Depression and comorbid illness in elderly primary care patients: Impact on multiple domains of health status and well-being. Ann Fam Med 2:555-562
39. Hansen HV, Kessing LV (2007) Adherence to antidepressant treatment. Expert Rev Neurother 7:57-62
40. Bulloch AG, Patten SB (2010) Non-adherence with psychotropic medications in the general population. Soc Psychiatry Psychiatr Epidemiol 45:47-56
41. Farmacotherapeutisch Kompas (in Dutch). Available at: http://www.fk.cvz.nl. Accessed: 15 October 2010
42. de Gier JJ, Alvarez FJ, Mercier-Guyon C, Verstraete AG (2009) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 121-134
43. Wingen M, Ramaekers JG, Schmitt JAJ (2006) Driving impairment in depressed patients receiving long-term antidepressant treatment. Psychopharmacology 188:84-91
44. Verster JC, Mets MAJ, Leufkens TRM, Vermeeren A (2009) Insomnia, hypnotic drugs and traffic safety. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 233-244
45. Hemmelgarn B, Suissa S, Huang A, Boivin JF, Pinard G (1997) Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 278:27-31
46. Neutel CI (1998) Benzodiazepine-related traffic accidents in young and elderly drivers. Hum Psychopharmacol 13:S115-123
47. Dubois S, Bédard M, Weaver B (2008) The impact of benzodiazepines on safe driving. Traffic Inj Prev 9:404-413
48. van Laar MW, Volkerts ER (1998) Driving and benzodiazepine use - Evidence that they do not mix. CNS Drugs 10:383-396
49. Neutel CI (1995) Risk of traffic accident injury after a prescription for a benzodiazepine. Ann Epidemiol 5:239-244
50. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF (2004) Sex differences and pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol 44:499-523
51. Rademaker M (2001) Do women have more adverse drug reactions? Am J Clin Dermatol 2:349-351
52. Li G, Baker SP, Langlois JA, Kelen GD (1998) Are female drivers safer? An application of the decomposition method. Epidemiology 9:379-384
53. Massie DL, Campbell KL, Williams AF (1995) Traffic accident involvement rates by driver age and gender. Accident Anal Prev 27:73-87
54. Deffenbacher JL, Lynch RS, Filetti LB, Dahlen ER, Oetting ER (2003) Anger, aggression, risky behaviour, and crash related outcomes in three groups of drivers. Behav Res Ther 41:333-349
55. Vermeeren A, Leufkens TRM, Verster JC (2009) Effects of anxiolytics on driving. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 289-306

56. Tavris DR, Kuhn EM, Layde PM (2001) Age and gender patterns in motor vehicle crash injuries: Importance of type of crash and occupant role. Accident Anal Prev 33:167-172
57. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J (2008) Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. Sleep Med 9:818-822
58. Bramness JG, Skurtveit S, Mørland J (2002) Clinical impairment of benzodiazepines - Relation between benzodiazepine concentrations and impairment in apprehended drivers. Drug Alcohol Depen 68:131-141

CHAPTER 5

A COMPARISON OF PHARMACOEPIDEMIOLOGICAL STUDY DESIGNS IN MEDICATION USE AND TRAFFIC SAFETY RESEARCH

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ABSTRACT

Aim: To evaluate the risk of having a motor vehicle accident while exposed to some psychotropic medication groups by means of a case-crossover and a case-time-control study, and to compare the results of these two pharmacoepidemiological designs to those of our recent case-control study, which also evaluated the association between the exposure to psychotropic medications and the risk of experiencing a road-traffic accident.

Methods: A record-linkage database was used to perform a case-crossover and a case-time-control study. The outcomes of these two studies were compared to those of a case-control study that was performed using the same database. The following psychotropic medicine groups were examined: antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants stratified in the two groups selective serotonin reuptake inhibitors (SSRIs) and other antidepressants. The data were stratified according to the type of user (i.e., all users and acute users), number of days of medication use, and number of defined daily doses received in the previous year.

Results: 3786 cases and 18089 controls were identified between the time-frame 2000 - 2007 and included in the case-crossover and case-time-control analyses. The case-crossover design did not show any statistically significant association between psychotropic medication exposure and motor vehicle accident risk [e.g., SSRIs - Adj. OR = 1.00 (95% CI: 0.69 - 1.46); Anxiolytics - Adj. OR = 0.95 (95% CI: 0.68 - 1.31)]. The case-time-control design only showed a statistically significant increased traffic accident risk in SSRI users [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)].

Conclusions: This study found that case-crossover and case-time-control analyses produced different results than those of our recent case-control study, which showed an increased traffic accident risk in anxiolytic and SSRI users. These divergent results can probably be explained by the differences in the study designs. Given that the case-crossover design is only appropriate for short-term exposures and the case-time-control design is an elaboration of this latter, it can be concluded that these two approaches are probably not the most suitable ones to investigate the relation between traffic accident risk and psychotropic medications, which are often use chronically.

INTRODUCTION and AIM

Driving a motor vehicle is a complex task that involves several psychomotor and cognitive skills [1]. Some commonly prescribed medications can influence cognitive and psychomotor functions and, therefore, impair the ability to drive safely [1, 2].

The risk of experiencing a road traffic accident while exposed to psychotropic medications has often been estimated by means of pharmacoepidemiological studies, and, in particular, mainly by case-control and case-crossover studies [3]. The results of these studies have frequently shown a positive association between the risk of having a motor vehicle crash (MVC) and the exposure to some groups of psychoactive medications (e.g., benzodiazepines, benzodiazepine-like substances such as zopiclone and zolpidem, tricyclic antidepressants) [3-5], but, in some cases, their findings have been rather controversial. For instance, in 1997, Hemmelgarn *et al.* performed a case-control study which showed that elderly drivers exposed to long half-life benzodiazepines (BZDs) were significantly associated to the risk of having an MVC within the first week of benzodiazepine use [6], but, on the contrary, in 1998, the case-crossover study of Barbone *et al.* found no increased traffic accident risk associated to benzodiazepine use in individuals ≥ 65 years old [7]. A similar discrepancy was also described in the study of Hebert *et al.* which showed an increased MVC in case of long half-life BZD elderly users by applying a case-control approach, but no association was found by using a case-crossover analysis [8]. Another example is a recent Dutch case-control study [9] which reported a statistically significant association between the risk of experiencing a traffic accident and the exposure to selective serotonin reuptake inhibitors (SSRIs); however, these results differed from those of Barbone's case-crossover study which found no increased MVC risk in SSRI users [7].

The divergences in the outcomes of these pharmacoepidemiological studies could be explained by the use of different study designs. Generally speaking, case-control studies compare cases with an event to controls without the event, looking for differences in the antecedent exposures [10]. Case-control studies can be useful when assessing a wide range of possible causes of a single event as well as the evaluation of relatively rare events [10, 11]. However, one of the limitations that are often encountered while using this study design is the selection of the controls which can lead to selection bias and, consequently, incorrect conclusions [10, 11]. One possible alternative to the case-control design is the case-crossover design. The case-crossover design is an adaptation of the case-control design in which cases serve as their own controls [12-14]. Because of this peculiarity, the case-crossover design is immune to the control-selection bias, which, as stated above, could hamper case-control studies, and it also controls for stable subject-specific covariates [12, 14, 15]. However, the case-crossover design is only appropriate to investigate the effects of incidental exposures on the event of interest and, therefore, is not suitable to estimate the risk in people exposed to long-term treatments [7, 11]. If properly designed and performed, both study designs are valuable research

tools; nevertheless, due to their assumptions, strengths and limitations, caution has to be applied when interpreting and comparing their results [11].

The aim of this study was to evaluate the risk of having an MVC while exposed to some psychotropic medication groups by applying a case-crossover design to the database used in our recent case-control study [9], and to compare these results to those of the case-control study in order to evaluate whether the outcomes of these two different pharmacoepidemiological designs would lead to analogous traffic accident risk estimations. Lastly, in order to account for the potential time trends in psychotropic medication use in the case and control window [16, 17], a case-time-control analysis was also performed using the same control group that was used in the case-control study mentioned above.

METHODS

The case-crossover study, linking police traffic accident and pharmacy prescription databases, was performed in the Netherlands, from 1st January 2000 to 31st December 2007.

The data sources, inclusion and exclusion criteria, and exposure definition have been described in detail elsewhere [9]. In brief, a Trusted Third Party (TTP) performed the linkage between the PHARMO [18], Dutch Traffic and Navigation Authority (DVS) [19], and Dutch Road Transport Authority (RDW) [20] databases, which provided pharmacy prescription data, traffic accident data, and driving licence records, respectively. Cases were defined as drivers who had an MVC attended by the Dutch police during the study time-frame. Subjects were excluded if they were ≤ 18 years old at the time of the accident (i.e., index date) and if they tested positive for alcohol or no alcohol test data were available.

The following medication groups were evaluated: antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics and sedatives (ATC code: N05C), antidepressants stratified in selective serotonin reuptake inhibitors (SSRIs) (ATC code: N06AB), and other antidepressants [i.e., non-selective monoamine reuptake inhibitors (ATC code: N06AA), monoamine oxidase A inhibitors (MAOs) (ATC code: N06AG), other antidepressants (ATC code: N06AX)].

The case window was defined as the week before the index date whereas the control window was defined as the same week one year before the index date, to control for possible seasonal and weather variations which could play a causal role in traffic accidents.

Exposure was considered to start the day after the dispensing date. Medications dispensed on the MVC day were not included because it was not possible to determine whether, in the case window, exposure occurred before or after the traffic accident. Subjects were considered to be exposed if the medication was used during the week before the index date; if the medication exposure ended 2 days before the index date, the subjects were still considered as exposed.

In order to evaluate the effects of the user type on the results of the case-crossover design, the study population was stratified as follows: 1) All users: subjects who were exposed to a driving impairing medication in the week before the index date, but possibly also used this medication in the 6 months before the index date; 2) Acute users: subjects who used a driving impairing medication in the week before the index date, but did not received any prescriptions for this medication in the 6 months before the initiation of the therapy. In this analysis, subjects were excluded if their medication history in the 18 months preceding the index date was not available.

In order to further investigate the effects of frequency of psychoactive medication exposure on the outcomes of the case-crossover analysis, subjects were also stratified by the number of defined daily doses (DDDs) and days of medication use in the 12 months before the index date, with the purpose of having a broader overview of the subjects' medication exposures preceding their traffic accidents. As a consequence, in this analysis, cases were excluded if their medication history in the 2 years preceding the index date was not available.

For the case-time-control study, a control group of 18089 subjects was used. This group was derived from the same database that was used in the case-control study [9]. In brief, the selected controls had to be ≥ 19 years or older, be in possession of a driving licence and have had no traffic accident during the study period. Four controls were matched for each case; the matching was by gender, age within five years, zip code, and date of the accident of the correspondent case. The definitions of the case and control windows and exposure were the same as reported above.

Descriptive statistics was used to describe the characteristics of the cases and controls as well as the accident characteristics of the cases.

For the case-crossover and case-time-control designs, logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). The standard method for matched case-control studies was used in order to calculate the ORs. The ORs were the measure of the odds of exposure in the case window versus the control window; specifically, medication exposure in the week before the MVC (case window) was compared with medication exposure during the same week of the control window, 1 year earlier.

Adjusted ORs were calculated by including exposure to combination therapy (i.e., concomitant use of at least two medicines) in the model.

A "control-crossover" analysis was performed similarly for the selected control group.

The case-time-control ORs were estimated by dividing the case-crossover ORs from the cases by "control-crossover" ORs from the controls.

All statistical analyses were performed by using the statistical package PASW Statistics Version 18.

RESULTS

Three-thousand seven-hundred eighty-six cases were included in the first part of the case-crossover analysis.

The characteristics of the cases included the case-crossover study are presented in Table 1. As shown in this table, the majority of case population was male (62.3%) and the age group 30 - 60 was the most represented one (54.2%).

Table 1. Characteristics of the cases.

CASES CHARACTERISTICS (N=3786)	**N (%)**
Gender	
Male	2360 (62.3)
Female	1426 (37.7)
Age (years)	
< 30	1062 (28.1)
30 - 60	2050 (54.2)
≥ 61	673 (17.8)

Table 2 illustrates the characteristics of the case accidents. Accidents were almost equally distributed during the four seasons, mainly occurred during week days, with dry weather conditions, at daylight, between 1 p.m. and 7 p.m., and were mostly either serious or moderately serious.

Table 3 presents the medication exposure of the cases (all users and acute users) and controls (all users and acute users), in the case and control windows, and the case-crossover and case-time-control crude and adjusted ORs for road traffic accidents related to the exposure to the selected psychoactive medication groups.

From this table it can be seen that, in the case group, anxiolytics and SSRIs were the two most used medication classes, with the exception of the control window of acute users (in this case, hypnotics and anxiolytics were the most represented classes). On the contrary, in the control group, the two most represented medication classes were anxiolytics and hypnotics, in both case and control windows.

With respect to the crude and adjusted ORs for road traffic accidents related to the exposure to the selected psychoactive medication groups, it can be seen that the case-crossover analysis did not show any statistically significant association between MVC risk and the exposure to the selected medications.

After dividing the ORs in the cases by the ORs in the controls (case-time-control analysis), a significant increased traffic accident risk was obtained for the SSRIs, if all users were taken into consideration, whereas a statistically significant association was found between other antidepressants and MVC risk, if the analysis was restricted to acute users (Table 3).

Table 2. Characteristics of the accidents (cases).

ACCIDENT CHARACTERISTICS (N = 3786)	N (%)
SEASON	
Winter	916 (24.2)
Spring	969 (25.6)
Summer	850 (22.5)
Autumn	1051 (27.8)
WEATHER	
Dry	3067 (81.0)
Rain	599 (15.8)
Snow/Hail	45 (1.2)
Fog	49 (1.3)
Hard wind	2 (0.1)
Unknown	24 (0.6)
WEEK/WEEKEND	
Week day	2911 (76.9)
TIME	
1 a.m. - 7 a.m.	239 (6.3)
7 a.m. - 1 p.m.	1203 (31.8)
1 p.m. - 7 p.m.	1714 (45.3)
7 p.m. - 1 a.m.	630 (16.6)
LIGHT	
Daylight	2741 (72.4)
Dark	826 (21.8)
Dawn	219 (5.8)
SERIOUSNESS	
Fatal	24 (0.6)
Seriously injured (Hospitalization > 24 hours)	1321 (34.9)
Moderately injured (1st aid point or hospitalization < 24 hours)	1421 (37.5)
Slightly injured (Treated on scene)	1020 (26.9)

Three-thousand seven-hundred fifty-two cases were included in the second part of the case-crossover analysis (stratifications by the number of DDDs and days of medication use in the year before the traffic accident) (Table 4). As can be seen from the Table 4, our analyses showed no increased traffic accident risk associated with the exposure to the selected medication groups stratified by days of use and DDDs in the year preceding the index date.

Table 3. Case-crossover and case-time-control crude and adjusted ORs* for road-traffic accident in different psychotropic medicine group users, stratified by all users and acute users.

MEDICINE GROUP	Exposed in CASE window (%)	Exposed in CONTROL window (%)	CASE-CROSSOVER Crude ORs (95% CI)	CASE-CROSSOVER Adj. ORs* (95% CI)	CASE-TIME-CONTROL Crude ORs (95% CI)	CASE-TIME-CONTROL Adj. ORs* (95% CI)
ANTIPSYCHOTICS (N05A)						
Cases (N=3786)						
All users	18 (0.50)	23 (0.60)	0.76 (0.41 - 1.41)	0.68 (0.34 - 1.35)	0.94 (0.67 - 1.32)	0.86 (0.61 - 1.23)
Acute users	1 (0.02)	1 (0.02)	0.97 (0.06 - 15.52)	0.97 (0.06 - 15.52)	1.01 (0.43 - 2.27)	0.50 (0.33 - 0.73)
Controls (N=18089)						
All users	91 (0.50)	108 (0.60)	0.81 (0.61 - 1.07)	0.79 (0.56 - 1.10)	-	-
Acute users	2 (0.01)	2 (0.01)	0.96 (0.14 - 6.84)	1.93 (0.18 - 21.26)	-	-
ANXIOLITICS (N05A)						
Cases (N=3786)						
All users	92 (2.40)	94 (2.50)	0.95 (0.71 - 1.27)	0.95 (0.68 - 1.31)	1.09 (0.95 - 1.25)	1.10 (0.94 - 1.27)
Acute users	13 (0.34)	11 (0.29)	1.15 (0.51 - 2.56)	0.97 (0.40 - 2.33)	1.28 (0.88 - 1.86)	1.04 (0.70 - 1.52)
Controls (N=18089)						
All users	303 (1.70)	335 (1.90)	0.87 (0.75 - 1.02)	0.86 (0.72 - 1.03)	-	-
Acute users	40 (0.22)	43 (0.24)	0.90 (0.58 - 1.38)	0.93 (0.57 - 1.53)	-	-
HYPNOTICS (N05C)						
Cases (N=3786)						
All users	75 (2.00)	85 (2.20)	0.86 (0.63 - 1.17)	0.89 (0.63 - 1.25)	0.98 (0.84 - 1.13)	0.95 (0.81 - 1.12)
Acute users	6 (0.16)	11 (0.29)	0.53 (0.20 - 1.43)	0.39 (0.12 - 1.24)	0.88 (0.59 - 1.36)	0.49 (0.28 - 0.85)
Controls (N=18089)						
All users	268 (1.50)	293 (1.60)	0.88 (0.75 - 1.04)	0.94 (0.78 - 1.12)	-	-
Acute users	20 (0.11)	32 (0.18)	0.60 (0.34 - 1.05)	0.80 (0.43 - 1.46)	-	-

* Combination therapy
Bold = Statistically significant

Table 3. Continued.

MEDICINE GROUP	Exposed in CASE window (%)	Exposed in CONTROL window (%)	CASE-CROSSOVER Crude ORs (95% CI)	CASE-CROSSOVER Adj. ORs* (95% CI)	CASE-TIME-CONTROL Crude ORs (95% CI)	CASE-TIME-CONTROL Adj. ORs* (95% CI)
SSRIs (N06AB)						
Cases (N=3786)						
All users	92 (2.40)	87 (2.30)	1.03 (0.76 - 1.38)	1.00 (0.69 - 1.46)	**1.26 (1.10 - 1.41)**	**1.16 (1.01 - 1.34)**
Acute users	7 (0.18)	5 (0.13)	1.36 (0.43 - 4.28)	1.29 (0.29 - 5.79)	1.19 (0.84 - 1.69)	1.07 (0.60 - 1.90)
Controls (N=18089)						
All users	240 (1.30)	281 (1.60)	0.82 (0.69 - 0.98)	0.86 (0.68 - 1.09)	-	-
Acute users	13 (0.07)	11 (0.06)	1.14 (0.51 - 2.54)	1.21 (0.48 - 3.05)	-	-
OTHER ANTIDEPRESSANTS						
Cases (N=3786)						
All users	40 (1.10)	45 (1.20)	0.86 (0.56 - 1.33)	0.88 (0.53 - 1.46)	1.10 (0.90 - 1.37)	1.24 (0.98 - 1.55)
Acute users	3 (0.08)	3 (0.08)	0.97 (0.20 - 4.81)	0.97 (0.20 - 4.81)	**2.37 (1.25 - 4.45)**	**1.76 (1.11 - 3.01)**
Controls (N=18089)						
All users	143 (0.80)	177 (1.00)	0.78 (0.62 - 0.97)	0.71 (0.54 - 0.94)	-	-
Acute users	6 (0.03)	14 (0.08)	0.41 (0.16 - 1.08)	0.55 (0.18 - 1.60)	-	-

* Combination therapy
Bold = Statistically significant

Table 4. Case-crossover crude and adjusted ORs* for road-traffic accident in different medication group users, stratified per number of days of use and number of DDDs in the year before the index date (N=3752).

MEDICINE GROUP	Exposed in CASE window (%)	Exposed in CONTROL window (%)	CASE-CROSSOVER Crude ORs (95% CI)	CASE-CROSSOVER Adj. ORs* (95% CI)
ANTIPSYC. (N05A)				
1 - 15 days	0	1	-	-
16 - 150 days	1	3	0.32 (0.03 - 3.11)	0.32 (0.03 - 3.11)
≥ 151 days	17	19	0.87 (0.45 - 1.67)	0.79 (0.38 - 1.64)
< 20 DDDs	1	2	0.48 (0.04 - 5.35)	0.48 (0.04 - 5.35)
21 - 150 DDDs	6	9	0.66 (0.23 - 1.82)	0.48 (0.15 - 1.61)
≥ 151 DDDs	11	12	0.89 (0.39 - 2.02)	0.87 (0.35 - 2.15)
ANXIOLYTICS (N05B)				
1 - 15 days	11	8	1.33 (0.54 - 3.32)	1.45 (0.52 - 4.09)
16 - 150 days	26	37	0.68 (0.41 - 1.13)	0.59 (0.34 - 1.05)
≥ 151 days	54	49	1.07 (0.72 - 1.58)	1.12 (0.73 - 1.72)
< 20 DDDs	22	27	0.79 (0.45 - 1.39)	0.78 (0.41 - 1.49)
21 - 150 DDDs	40	40	0.97 (0.62 - 1.51)	0.94 (0.59 - 1.51)
≥ 151 DDDs	29	27	1.04 (0.61 - 1.76)	1.07 (0.58 - 1.96)
HYPNOTICS (N05C)				
1 - 15 days	5	7	0.69 (0.22 - 2.18)	0.65 (0.18 - 2.29)
16 - 150 days	15	28	0.52 (0.28 - 0.97)	0.57 (0.29 - 1.14)
≥ 151 days	55	50	1.07 (0.72 - 1.57)	1.08 (0.71 - 1.64)
< 20 DDDs	6	10	0.58 (0.21 - 1.60)	0.61 (0.20 - 1.85)
21 - 150 DDDs	15	28	0.52 (0.28 - 0.97)	0.53 (0.27 - 1.03)
≥ 151 DDDs	54	47	1.11 (0.75 - 1.65)	1.16 (0.76 - 1.79)
SSRIs (N06AB)				
1 - 15 days	4	4	0.97 (0.24 - 3.88)	0.65 (0.11 - 3.87)
16 - 150 days	13	25	0.50 (0.26 - 0.99)	0.55 (0.24 - 1.24)
≥ 151 days	75	58	1.25 (0.89 - 1.77)	1.23 (0.80 - 1.92)
< 20 DDDs	4	4	0.97 (0.24 - 3.88)	0.65 (0.11 - 3.87)
21 - 150 DDDs	13	24	0.53 (0.27 - 1.03)	0.58 (0.25 - 1.33)
≥ 151 DDDs	75	59	1.23 (0.87 - 1.74)	1.20 (0.78 - 1.86)
OTHER ANTIDEPR.				
1 - 15 days	1	2	0.48 (0.04 - 5.35)	0.97 (0.06 - 15.50)
16 - 150 days	7	7	0.97 (0.34 - 2.77)	0.65 (0.18 - 2.29)
≥ 151 days	31	34	0.88 (0.54 - 1.44)	0.93 (0.52 - 1.65)
< 20 DDDs	2	4	0.48 (0.09 - 2.65)	0.65 (0.11 - 3.87)
21 - 150 DDDs	20	19	1.02 (0.53 - 1.92)	1.04 (0.50 - 2.15)
≥ 151 DDDs	17	20	0.82 (0.43 - 1.58)	0.76 (0.35 - 1.68)

*Combination therapy

DISCUSSION and CONCLUSIONS

The results of the current case-crossover study did not show any significant increase in MVC risk associated with the exposure to the selected psychotropic medication groups [e.g., All user stratification: Anxiolytics: Adj. OR = 0.95 (95% CI: 0.68 - 1.31); SSRIs: Adj. OR = 1.00 (95% CI: 0.69 - 1.46)]. Stratifications according to the number of days and DDDs used in the previous year were consistent with the above-mentioned findings, and, in particular, did not show any effects of exposure frequency on the risk of experiencing an MVC [e.g., 1-15 day stratification: Anxiolytics: Adj. OR = 1.45 (95% CI: 0.52 - 4.09); SSRIs: Adj. OR = 0.65 (95% CI: 0.11 - 3.87)]. Therefore, if compared to our recent pharmacoepidemiological study [9], it can be observed that the current case-crossover analysis produced different results than those of the case-control analysis, which actually found a statistically significant association between traffic accident risk and exposure to anxiolytics and SSRIs [Anxiolytics: Adj. OR = 1.54 (95% CI: 1.11 - 2.15); SSRIs: Adj. OR = 2.03 (95% CI: 1.31 - 3.14) - all exposed individuals].

Lastly, the outcomes of the case-time-control analysis showed a statistically significant increased risk only in SSRI users, in the stratification referred to all users [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)], whereas the acute user stratification only showed a statistically significant association between MVC risk and other antidepressant users [Adj. OR = 1.76 (95% CI: 1.11 - 3.01)]. Therefore, it can be speculated that, in this case, the findings of the case-time-control analysis only partially supported the outcomes of the case-control one.

The discrepancies between the outcomes of the case-control and case-crossover studies could be attributed to the choice of study design. The case-crossover design is a commonly used scientific method to investigate whether a certain event was triggered by something unusual that happened just before the event itself [14]. The case-crossover is a matched case-control study, but it only involves cases and each case serves as its own control [14]. Because of this peculiarity, the case-crossover design controls for stable subject-specific covariates and it overcomes control selection bias [13]. However, this type of design requires that the exposures are brief and their effects transient [10, 13]. Considering that psychotropic medications are often used on a regular and chronic basis [8, 21, 22], it can be speculated that, in the present study, one of the most important assumptions of the case-crossover design was not met, and, therefore, the choice of this study design was probably not appropriate. On the contrary, it could be conceivably hypothesised that the case-crossover analysis should be limited to intermittent users of the selected medication groups. However, it is important to note that, in the current study, this restriction led to a consistent loss of cases and, even if the ORs calculated for this specific group of users were more similar to the ORs obtained by the case-control technique, it can be speculated that our study did not have adequate statistical power to detect reliably the association between incidental psychotropic medication users and MVC risks [10, 11].

Stratifying the data according to the number of DDDs and days of use in the previous year did not support the associations that were shown in the case-control study either. With respect to the DDD, a possible explanation for this might be that, since the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose [23], the actual doses used by our study population could have been considerably different from the DDD, and, therefore, perhaps this stratification was not appropriate and led to a misclassification of our medication users.

With respect to the days of use, it is difficult to explain the study outcomes, but, as stated above, they could be related to the low sample size in the infrequent user groups which might have resulted in a lack of statistical power to address the issue of the association between the risk of experiencing an MVC while incidentally exposed to psychoactive medications [10, 11].

Besides the points reported above, there could also be other possible explanations for the discrepancies among the findings from the two designs that were used. As some authors have also pointed out [8, 13, 16, 24, 25], possible reasons for different results between case-crossover and case-control studies may be related to selection bias of the control-person time (i.e., our selected control person-time did not properly represent the population-time that generated the cases due to, for example, possible divergences in the driving patterns between the case and control times), confounding by indication, different effects of the medication at different points in time (e.g., different estimates in relation to therapy duration and/or prior exposures [26]), time-varying within-subject confounding factors (e.g., fluctuations in disease severity, co-morbidities, etc.), and time trend bias (i.e., changes in the prescribing patterns of the medications of interest).

With regard to the case-time-control analysis, our study only showed a positive association between MVC risk and SSRI users [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)], in the all user group, and other antidepressant users [Adj. OR = 1.76 (95% CI: 1.11 - 3.01)], in the acute user stratification, but, in contrast to our earlier findings, no evidence of an increased traffic accident risk associated with anxiolytics was detected [Adj. OR = 1.10 (95% CI: 0.94 - 1.27)]. The reason for the discrepant outcomes of this analysis is not clear, but it might also be related to the choice of the study design. The current case-time-control study was performed to remove bias due to time trends from the case-crossover estimate [16, 17], and, as suggested by Suissa [27], to possibly control for confounding by indication. However, since the case-time-control design can be seen as an elaboration of the case-crossover design [25], our findings could have been limited by the same shortcomings as those of the case-crossover approach (e.g., selection bias in the control-time window, within-person confounding, applicability restricted to transient exposures only, etc.). Moreover, since the case-time-control design requires a traditional control group, our study, and, consequently, its results could have been hampered by the same limitations as the case-control design, as well (e.g., selection bias in the collection process of the control group, between-person

confounding, higher complexity due to the necessity of a control group, etc.) [16, 25, 27]. Lastly, as Greenland argued [28], on the one hand, our case-time-control design could have been a helpful tool to adjust for time trends in measured exposures, but, on the other hand, if unmeasured confounders and/or carryover effects were present, new bias could have been introduced. As a consequence, the problem of confounding by indication would not have been solved and our final results could have been either more or less confounded than those obtained by the case-control and case-crossover analyses.

Our study supports the observations of Hebert *et al.*, who also compared the results of a case-control study to those of a case-crossover study using the same database to determine the association between BZDs and the risk of MVCs [8]. In that study, the case-control approach demonstrated an increased MVC risk associated with the use of long-acting BZDs whereas the case-crossover approach applied to all cases did not show any association. The authors concluded that the differences among the findings of these studies could have derived from intrinsic differences between the two designs, and that, in particular, a lack of intermittency of exposure could have altered the point estimates of their case-crossover analysis.

Although the differences between the study populations should be considered as a possible cause of divergent findings, the previously mentioned assumption could also clarify the discrepancies between the outcomes of Hemmelgarn *et al.*'s case-control study [6] and those of Barbone *et al.*'s case-crossover study [7] which, respectively, showed a statistically significant association between BZD exposure and traffic accident in older adults and no evidence that BZDs increased traffic accident risks in elderly patients.

Lastly, this hypothesis could also explain the contradictory findings between our case-control study on SSRIs and increased MVC risk [9] and Barbone's case-crossover outcomes which, in contrast to our research, found no increased risk of road traffic accidents in users of SSRIs [7].

In conclusion, our investigation has shown that different study designs seemed to give different answers to the same research hypothesis, in the same population. Considering that every study design has different design-specific assumptions, and strengths and limitations, it could be assumed that our three analyses actually tested distinctive causal hypotheses and focused on different aspects of psychoactive medication use and MVC risk [8, 16, 24]. As a consequence, it seems reasonable to conclude that each pharmacoepidemiological design may be appropriate only in certain settings and under specific assumptions [16], and, therefore, if possible, multiple designs and analyses should be used to investigate the different aspects of factors that can play a role in traffic safety while driving under the influence of psychotropic medications.

DISCLAIMER

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REFERENCES

1. de Gier JJ, Alvarez FJ, Mercier-Guyon C, Verstraete AG (2009) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 121-134
2. Drummer OH (2008) The role of drugs in road safety. Australian Prescriber 31:33-35
3. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658
4. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu/publications/insights/driving. Accessed: 25 July 2011
5. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
6. Hemmelgarn B, Suissa S, Huang A, Boivin JF, Pinard G (1997) Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 278:27-31
7. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
8. Hebert C, Delaney JA, Hemmelgarn B, Levesque LE, Suissa S (2007) Benzodiazepines and elderly drivers: A comparison of pharmacoepidemiological study designs. Pharmacoepidemiol Drug Saf 16:845-849
9. Ravera S, van Rein N, de Gier JJ, de Jong - van den Berg, L.T.W. (2011) Road traffic accidents and psychotropic medication use in the Netherlands: A case-control study. Br J Clin Pharmacol 72(3):505-513
10. Strom BL (1994) Pharmacoepidemiology. John Wiley and Sons Ltd, Chichester - West Sussex
11. Hennekens CH, Buring JE (1987) Epidemiology in Medicine. Lippincott Williams and Wilkins, Philadelphia, USA
12. Neas LM, Schwartz J, Dockery D (1999) A case-crossover analysis of air pollution and mortality in Philadelphia. Environ Health Perspect 107:629-631
13. Maclure M (1991) The case-crossover design: A method for studying transient effects on the risk of acute events. Am J Epidemiol 133:144-153
14. Maclure M, Mittleman MA (2000) Should we use a case-crossover design? Annu Rev Public Health 21:193-221
15. Maclure M, Mittleman MA (2008) Case-crossover designs compared with dynamic follow-up designs. Epidemiol 19(2):176-178
16. Hernandez-Diaz S, Hernan MA, Meyer K, Werler MM, Mitchell AA (2003) Case-crossover and case-time-control designs in birth defects epidemiology. Am J Epidemiol 158:385-391
17. Toh S, Mitchell AA, Anderka M, de Jong-van den Berg LT, Hernandez-Diaz S, National Birth Defects Prevention Study (2011) Antibiotics and oral contraceptive failure - A case-crossover study. Contraception 83:418-425

18. PHARMO Institute. Available at: http://www.pharmo.nl. Accessed: 24July 2011
19. Dienst Verkeer en Scheepvaart - DVS. Available at: http://www.rijkswaterstaat.nl/dvs. Accessed: 24 July 2011
20. Rijks Dienst Wegverkeer - RDW. Available at: http://www.rdw.nl. Accessed: 24 July 2011
21. Ravera S, Visser ST, de Gier JJ, de Jong-van den Berg LT (2010) Prevalence, cumulative incidence, monotherapy and combination therapy, and treatment duration of frequently prescribed psychoactive medications in the Netherlands: Retrospective database analysis for the years 2000 to 2005. Clin Ther 32:2457-2466
22. del Rio MC, Alvarez FJ (1996) Medication use by the driving population. Pharmacoepidemiol Drug Saf 5:255-261
23. WHO Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/ddd/definition_and_general_considera. Accessed: 24 July 2011
24. Maclure M (2007) 'Why me?' versus 'why now?' - Differences between operational hypotheses in case-control versus case-crossover studies. Pharmacoepidemiol Drug Saf 16:850-853
25. Schneeweiss S, Sturmer T, Maclure M (1997) Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf 6 Suppl 3:S51-9
26. Guess HA (2006) Exposure-time-varying hazard function ratios in case-control studies of drug effects. Pharmacoepidemiol Drug Saf 15:81-92
27. Suissa S (1995) The case-time-control design. Epidemiology 6:248-253
28. Greenland S (1996) Confounding and exposure trends in case-crossover and case-time-control designs. Epidemiology 7:231-239

CHAPTER 6

ARE SSRIS SAFE FOR DRIVERS? WHAT IS THE EVIDENCE?

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are widely used medications to treat several psychiatric diseases, and, above all, depression. SSRIs seem to be as effective as older antidepressants, but have less adverse effects. In spite of their favourable safety profile, little is known about their influence on traffic safety.

Aim: To evaluate, by means of a selective literature review, possible undesirable effects related to fitness to drive, experimental and pharmacoepidemiological studies on driving impairment, two existing categorisation systems for driving impairing medications (i.e., the French and the ICADTS systems), and the European legislative procedures for assessing fitness to drive before issuing a driving licence and driving under the influence of medicines.

Methods: English language scientific literature was searched using key-words such as SSRIs and psychomotor performance, car crash or traffic accident, and adverse effects. For inclusion in this review, papers had to be full-text articles, referred to possibly driving related side effects and to experimental and pharmacoepidemiological studies on SSRIs and traffic accident risks. No restrictions concerning the publication year were applied.

Results: Ten articles were selected as background information on driving related side effects and 14 articles were selected with regard to experimental and pharmacoepidemiological work. In respect to SSRI side effects, these were the most reported undesirable effects referred to driving impairment: anxiety, agitation, sleep disturbances, headache, therapy cessation reactions, increased risk of suicidal behaviour, and deliberate self-harm. In respect to the remaining issues addressed in this paper, inconsistencies were found between the outcomes of the selected experimental and epidemiological studies as well as between the two existing categorisation systems of interest. Briefly, experimental studies showed no effects on cognitive and psychomotor skills whereas the majority of the epidemiological papers under evaluation showed an increased traffic accident risk associated with the use of SSRIs. With regard to the categorisation systems, the French categorisation list stated that SSRIs "could affect the ability to drive" whereas the ICDATS system labelled these medications as "presumed to be safe or unlikely to produce an effect". Lastly, some pitfalls of the current legislative scenario were identified, as well. In particular, it was observed that European countries have regulations against driving under the influence of illicit drugs and medications, but, conversely, there are no clear and consistent definitions of the different types of drugs (licit or illicit), their legal limits of use, or their influence on fitness to drive.

Conclusions: Based on the current evidence, it was concluded that more experimental and epidemiological research was needed to elucidate the relationship between SSRI use and traffic safety. Furthermore, a revision of the existing categorisation systems and a harmonized European legislation in the field of medication use and driving were highly recommended.

INTRODUCTION

Depression is a common psychiatric disease and it is estimated that up to 15% of the population of most developed countries can suffer from depression during their lives [1, 2]. The two most common depression treatments are psychotherapy and pharmacotherapy [3]. Pharmacotherapeutic interventions for the treatment of depressed patients include, among others, the use of selective serotonin reuptake inhibitors (SSRIs).

Although SSRIs are associated with less adverse effects than other antidepressant medications (e.g., tricyclic antidepressants - TCAs) [4, 5], they can affect psychomotor and cognitive functions and, consequently, have the potential to impair fitness to drive [1, 6].

The relationship between SSRI use and traffic safety has often been studied by means of experimental and epidemiological studies. In general, experimental studies evaluate the volunteers' performance, after intake of a single dose or multiple doses of the study medication, by using laboratory tests, driving simulator tasks, and on-the-road experiments [7]. Epidemiological studies usually compare the frequency of prior medication use by drivers who sustained injuries (i.e., cases) with that by drivers who were not involved in accidents (i.e., controls). Afterwards, odds ratios (ORs) are calculated to estimate the risk of being involved in a traffic accident while under the influence of a certain medication [8, 9].

To date, several experimental and epidemiological studies have been carried out, investigating the role of SSRIs in traffic safety, but, at first sight, their outcomes seem to be inconsistent. In general, experimental studies showed no impairment of cognitive and psychomotor skills whereas epidemiological research frequently showed an increased traffic accident risk associated with the use of SSRIs.

In addition to the above-mentioned discrepancy, incongruities have also emerged from existing categorisation systems of driving impairing medications. Within the European Union (EU), it is mandatory to carry out studies to assess the effect of a medication on fitness to drive prior to its commercialisation. The outcomes of these studies have to be used to write the medication summary of product characteristics (SmPC) and the package insert, mentioning its possible effects on fitness to drive [10]. As reported in the most recent SmPC guideline, a medicinal product can be classified according to four levels of impairment, ranging from no influence to major influence on fitness to drive [11]. Following the aforementioned guideline, in the last decades several categorisation systems of potentially driving impairing medicines have been developed and/or implemented at national level, in Europe. To our knowledge, no standardized and harmonized criteria were used to categorise commonly used medications; therefore, the currently available categorisation systems differ significantly from each other, and, in particular, divergent categories are sometimes assigned to the same active substance, especially with reference to the SSRIs [10].

In 2006 the European Union (EU) launched the project Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) with the purpose of obtaining scientific support to the European transport policy and establishing guidelines and measures that combat impaired driving [12]. The DRUID Work Package (WP) 4 was assigned the task of establishing standardized and harmonized criteria for a European classification system, and developing a categorisation system for relevant therapeutic groups of medications with respect to their impact on driving skills [12]. WP4 partners decided to adopt a step-by-step procedure, and, more specifically, to evaluate different types of available information and data, such as pharmacodynamic and pharmacokinetic data, pharmacovigilance data, and experimental and epidemiological data [13]. Furthermore, WP4 partners decided to address the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) with a request to participate in the discussions on the DRUID categorisation system, since patient safety affected by medicines' adverse reactions was WP4's primary focus. In 2011, consensus was reached that a basic 2 level framework would be developed as the basis for warnings to the patient in the patient information leaflet. For medicines without a potential relevant influence on driving (no or negligible, or minor influence) and for medicines with a potential relevant influence on driving (moderate influence, or major influence), warnings for the patient have been proposed. Since the current SmPC guideline shows four descriptions of potential levels of impairment of fitness to drive, an update of the evidence based approach for supporting the warnings for medicines, such as SSRIs, is needed [10].

In view of the discrepancies between experimental and epidemiological data as well as the inconsistencies between the existing categorisation systems concerning the SSRIs, it was decided to perform a selective review with the intention of summarizing the current evidence on the role of SSRIs in traffic safety. In particular, it was decided to examine the following issues: the mechanism of action of SSRIs, and their adverse effects related to fitness to drive; experimental and pharmacoepidemiological findings on SSRIs and traffic safety; the discrepancies between two well-known categorisation systems for medicines and driving, and the European legislation on driving under the influence of medications. Finally, it was decided to include some general recommendations for future research and concluding remarks.

METHODS

Article selection

The article search was performed in the following electronic databases: MEDLINE, PsycINFO, ScienceDirect, and SafetyLit. The following search terms were used: SSRIs and psychomotor performance, driving skills, car crash or traffic accident, traffic accident risk, and side or adverse effects. In addition, the reference list of relevant articles and books was checked in order to retrieve other potentially relevant papers.

Due to the large amount of literature published on undesirable effects of SSRIs, the manuscript selection was limited to full-text articles (not abstracts), published in English, and referred to possibly driving related side effects and to experimental and pharmacoepidemiological studies on SSRIs and the risk of traffic accidents. No restrictions concerning the publication year were applied. References concerning the categorisation systems and European legislative scenario were retrieved by examining specific websites reporting detailed information on these two topics.

RESULTS

In total 2650 references were retrieved. After a title, key-word, and abstract screening, 10 articles were selected as background information on driving related side effects and 14 articles were selected with regard to experimental and pharmacoepidemiological work.

Mechanism of action, driving related side effects and clinical use of SSRIs

Six SSRIs are currently marketed in Europe: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline [14]. Despite the structural diversity among the SSRIs, which results in clear variations in their pharmacodynamic and pharmacokinetic profiles [15], the above mentioned active substances have similar mechanism of action and undesired effects [16]. In brief, SSRIs selectively block the reuptake of serotonin (5-hydroxy-tryptamine or 5-HT) at central synapses. Because reuptake is the primary mechanism of serotonin inactivation, inhibition of the serotonin reuptake carrier raises the level of this neurotransmitter in the synapse [15, 17]. Serotonin binds to serotonin receptors which are located in the central and peripheral nervous system and affect various functions such as sleep, pain perception, blood vessel regulation, anxiety, mood, and depression [2, 16]. The SSRIs have lower binding affinities for other neurotransmitter receptors (e.g., dopaminergic, histaminergic, muscarinic receptors), and, therefore, are considered safer and better tolerated than TCAs and monoamine oxidase inhibitors (MAOs) [16, 18].

After oral administration, SSRIs are well-absorbed, have a high protein binding, and a large volume of distribution. They are metabolized in the liver and their metabolites are mainly eliminated in the urine. The half-life of SSRIs varies from 16 hours (fluvoxamine) to 72 hours (fluoxetine) [16, 19]; SSRIs with longer half-lives need more time to reach the steady-state concentration and to washout after discontinuation [16, 20].

In general, SSRIs have less side effects than older antidepressants and their side effects are often dose related and transient [18, 21, 22]. These are the most commonly reported undesired effects, which can also play a role in traffic safety: anxiety, agitation, sleep disturbances, headache, and therapy cessation reactions (e.g., dizziness, fatigue, anxiety) [16, 21-23]. Lastly, although this issue has been rather controversial, it has also been reported that SSRIs might increase the risk of suicidal behavior and deliberate self-

harm, even if these side effects seem to be limited to special patient populations (e.g., patients with a history of suicide-related events, children and adolescents under the age of 18 years) [24-27]. Because of their efficacy and safety, SSRIs are commonly used to treat a variety of psychiatric illnesses, such as depression, generalized anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, eating disorders, and premestrual dysphoric disorder [14, 16, 28].

Experimental studies

Experimental studies usually assess the performance of healthy or diseased subjects by conducting either laboratory tests that evaluate cognitive and psychomotor functions [e.g., critical tracking test (CTT) where the subject is asked to control the position of a light bar on a display screen using a steering wheel or joystick] or driving simulator tests (in this case, subjects perform a computer simulation of a driving task) and on-the-road tests that measure the ability to drive (these tests can be performed either in presence or absence of normal traffic) [9, 29].

Currently available experimental studies on SSRIs either focused on single active substances or on SSRIs as a total group, and were mainly performed on healthy volunteers (see Table 1).

Experimental studies in healthy volunteers

Acute treatment (laboratory and driving simulator tests)

Iwamoto and colleagues performed a study involving healthy volunteers who received acute doses (i.e., administration of a single dose of the active substance of interest) of paroxetine, amitriptyline, and placebo. The subjects' cognitive and driving skills were tested by means of computers tasks and a driving simulator test, respectively. The study showed that acute doses of paroxetine and placebo did not affect cognitive function nor driving performance whereas amytriptyline significantly impaired driving performance, and caused somnolence [30].

Acute and sub-chronic treatment (laboratory and on-the-road tests)

One study used attention tests and the Groningen Sleep Quality Questionnaire to evaluate vigilance performance in sertraline, paroxetine, and placebo users. From this study it was apparent that sub-chronic administration (i.e., daily administration of the active substance during a well-defined time-frame) of paroxetine decreased vigilance performance whereas sertraline did not produce any vigilance impairment. Further on, paroxetine reduced sleep quality in female volunteers whereas male volunteers' sleep quality remained unchanged; sertraline did not have any influence on sleep quality [31].

The acute and sub-chronic effects of escitalopram, mirtazapine and placebo on driving and psychomotor performance and on the quality of sleep were evaluated in a Dutch experimental study. The investigators found that escitalopram did not impair driving and psychomotor skills after single and repeated doses, but they found a significantly reduced sleep duration [32].

Experimental studies in depressed patients

Antidepressant monotherapy (laboratory tests)

Brunnauer and colleagues examined the psychomotor function of 100 depressed patients using TCA, SSRI, mirtazapine, and venlafaxine monotherapy. Computerized psychomotor tests revealed that SSRI and mirtazapine users had better test performances than TCA users. However, the study also showed that 16% of the sample was unfit to drive and 60% of the subjects were mildly to moderately impaired [33].

Antidepressant monotherapy in depressed patients compared to healthy controls (laboratory and on-the-road tests)

Wingen *et al.* also investigated driving performance and cognition in depressed patients treated with SSRIs or venlafaxine and in healthy controls. Standardised on-the-road tests, laboratory cognition tests and subjective measures were performed. These tests revealed a statistically significant impairment of the driving performance in depressed patients compared to their healthy controls [34].

Antidepressants in combination with other CNS medications (laboratory tests)

Similar results were also shown in a German study. The influence of 3 antidepressant types and common co-medications were evaluated in 44 depressed inpatients. The computer-based tests that were performed demonstrated that 88.6% of the subjects failed to pass all the tests. No remarkable differences were seen in the users of the 3 types of antidepressants, even if there was a non-statistically significant tendency to perform better on time and error parameters in case of SSRI users [35].

Review articles focusing on experimental studies in healthy volunteers

Acute treatment (laboratory tests)

A review by Hindmarch, focusing on critical flicker fusion threshold (CFFT) and choice reaction time (CRT) tests, showed that sertraline and paroxetine produced a dose-related elevation of CFFT whereas fluvoxamine was comparable to placebo. Fluvoxamine also had a better effect on CRT than placebo while no difference on CRT was noted between placebo users and the rest of SSRIs studied [36].

Analogous results were also presented in another review where SSRIs were considered comparable to placebo with respect to CFFT, CRT and compensatory tracking task (CTT) tests; additionally, the paper pointed out that paroxetine and sertraline increased the CNS activation and excitation, as well [37].

Acute and sub-chronic treatment, in combination with benzodiazepines (on-the-road tests)

In 2003 Ramaekers published a review that compiled the outcomes of standard on-the-road tests performed in the years 1983 - 2000. The manuscript reported that non-sedating antidepressants (among which fluoxetine and paroxetine) did not impair the ability to drive if administered at therapeutic doses, in acute doses or after repeated doses. However, caution had to be applied in case these medications were combined

Table 1. Experimental studies on SSRIs and driving impairment.

STUDY COUNTRY PERIOD	TYPE of STUDY METHODOLOGY	POPULATION MEDICATIONS	MAIN OUTCOMES (Referred to SSRIs)
Dumont D.J.H. et al. [39]	Literature review on CNS tests (171 variants of neuropsychological tests)	- Healthy subjects - **SSRIs (56 single doses and 22 multiple doses)** - Amitriptyline (if used as a positive control)	1) SSRI low single doses: attention and memory stimulation 2) SSRI high doses: impairment of visual/auditory and visuomotor system and subjective performance, but acceleration of motor functions
Hindmarch I. [36]	Literature review on CFFT and CRT tests	- TCAs - **SSRIs**	1) SSRIs not associated with an increased accident risk 2) CFFT - Sertraline and paroxetine > excitatory effect - Fluvoxamine > comparable to placebo 3) CRT - Fluvoxamine > better reaction time than placebo - Rest of SSRIs > comparable to placebo
Ramaekers J.G. [38] From 1983 to 2000	Literature review on driving studies (Standard on-the-road driving tests)	- Mainly healthy subjects - Sedating antidepressants **- Nonsedating antidepressants (among which SSRIs)**	1) Therapeutic doses of fluoxetine and paroxetine: no influence on driving performance after acute or repeated doses 2) Interactions between antidepressants and co-medications > driving impairment
Brunnauer A. et al. [33] Germany Jan. 2004 - March 2005	- Act and React Testsystem (ART-90) - Wiener Testsystem - Hamilton Rating Scale for Depression (HDRS)	- 100 depressive inpatients - Mean age 46.8 years - Mono-therapy regime: TCAs; **SSRIs (25 users)**; Mirtazapine; Venlafaxine	1) SSRIs and mirtazapine: better performance than TCAs 2) 76% of study population mildly to severely impaired
Grabe H.J. et al. [35] Germany 1998	- ART-90 - HDRS - Clinical Global Impression (CGI)	- 44 depressive inpatients - Mean age 44.4 years - Combination therapy regime: MAOs; **SSRIs (15 users)**; Tricyclic and tetracyclic antidepressant	1) No differences in performance in the 3 antidepressant groups 2) 88.6% of study population failed to pass all the tests

Bold: SSRIs

Table 1. Continued.

STUDY COUNTRY PERIOD	TYPE of STUDY METHODOLOGY	POPULATION MEDICATIONS	MAIN OUTCOMES (Referred to SSRIs)
Iwamoto K. et al. [30] Japan 2008	- Double-blind trial - Driving tests (driving simulator) + cognitive tests (computer tests) + Stanford Sleepiness Scale	- 17 healthy males - Mean age 35.8 years - Acute doses of: **Paroxetine**; Amitriptyline; Placebo	Paroxetine and placebo: no significant impairment of driving performance and cognitive function
Schmitt J.A.J. et al. [31] NL 2002	- RCT Attentions tests + Groningen Sleep Quality Scale (GSQS)	- 21 healthy volunteers - Mean age 37.8 years **- Paroxetine (2 different dosages) - Sertraline (2 different dosages)** - Placebo	1) Paroxetine - Subchronic administration > negative effect on vigilance performance - Reduction of women's sleep quality 2) Sertraline - No impairment of vigilance performance - Possible increase of response speed - No influence on sleep quality
Sherwood N. [37] United Kingdom (Human Psychopharmacology Research Unit) Before 1995	Overview of CFFT, CRT tests and subjective ratings of sedation (SED)	- Healthy volunteers **- Different SSRIs** - TCAs (amitriptyline and dothiepin) Placebo	1) CFFT - Fluvoxamine and fluoxetine > no effects - Zilmenidine, paroxetine and sertraline > increased scores 2) CRT: SSRIs > performances comparable to placebo 3) SED: Sertraline (100mg) > sedation sensation
Wingen M. et al. [32] NL 2004	- RCT - Driving test (on the road) - Psychometric tests (computer tests) - Subjective mood measurement - GSQS	- 18 healthy subjects - Mean age 31.4 years **- Escitalopram (2 different dosages)** - Mirtazapine (2 different dosages) - Placebo	Escitalopram: no influence on driving performance, psychomotor function, subjective mood; decrease of sleep duration
Wingen M. et al. [34] NL 2006	- Driving tests (on the road) - Cognitive tests (computer tests) - HDRS - Beck's Depression Inventory (BDI) - GSQS - Subjective rating of driving performance	- 24 depressed patients treated with antidepressants (Mean age 42.2 years) - 24 healthy volunteers (Mean age 41.8 years) **- Citalopram (4 users) - Paroxetine (8 users) - Sertraline (4 users)** - Venlafaxine (8 users)	Depressed patient: - Significant impairment of driving performance - Significant reduction of CFFT - No significant difference between SSRIs and venlafaxine in terms of cognitive impairment - Higher HDRS and BDI scores - Statistically significant reduction of sleep quality - Driving ability rated worse than healthy controls

Bold: SSRIs

with benzodiazepines or with other medicines with incompatible pharmacokinetic profiles [38].

Low and high dosage (laboratory tests)

Another Dutch research group also performed a literature review covering all SSRI studies carried out on healthy volunteers. Seventy-eight studies were identified, reporting 171 neuropsychological tests, and published since 1983. These studies showed that, at low single doses, SSRIs caused a slight stimulation of the CNS functions; however, at high doses, SSRIs seemed to impair visual/auditory and visuomotor skills and subjective performance [39].

Based on the above mentioned studies, it could be argued that experimental studies showed that SSRIs do not constitute a high risk to traffic safety, unless used at high dosages or combined with other psychotropic substances. However, caution must be applied as these findings might not be transferable to depressed patients who, according to some other experimental studies [33-35], showed impaired driving performance.

Finally, it is important to underline that experimental studies are not free from limitations. Firstly, these studies are usually performed on healthy and young volunteers who can differ from the actual patients. Secondly, tests are often carried out on alcohol, smoke and drug free population which can be different from the real population and everyday life situations. Thirdly, the frequent use of small numbers of subjects could result in the non-detection of existing effects as well as a lack of statistical power. Fourthly, experimental studies often evaluate the acute effect of the medication; for this reason, there is often a lack of information on the effects of a medicine after its chronic use. Lastly, it can be questioned whether the tests actually represent facets of real driving which is a much more complex and multifactorial task [7, 9, 40].

Pharmacoepidemiological studies

Few pharmacoepidemiological data are currently available on SSRI use and the risk of having a traffic accident and the results of these studies are not always consistent (see Table 2) [6, 9].

Barbone *et al.* carried out a case-crossover study to investigate the risk of having a road-traffic accident if exposed to psychotropic medications, among which SSRIs. This study did not find any association between SSRI exposure and the risk of experiencing a traffic accident [41]. Bramness *et al.* performed a study of population-based registry data in Norway and found that there was a slightly increased traffic accident risk for drivers who received a newer, nonsedating antidepressants (including SSRIs) [42].

In contrast to the preceding studies, a Canadian study investigated the association between road traffic accidents and psychotropic medications in drivers with dementia. The study outcomes revealed that later-generation antidepressants (i.e., SSRIs and other newer antidepressants) were associated with a higher risk of motor vehicle crashes than

Table 2. Pharmacoepidemiological studies on SSRIs and driving impairment.

STUDY COUNTRY PERIOD	TYPE of STUDY METHODOLOGY	POPULATION MEDICATIONS	MAIN OUTCOMES (Referred to SSRIs)
Barbone F. et al. [41] United Kingdom Aug. 1992 - June 1995	Case-crossover	- ≥ 18 years old - 19386 accidents - Benzodiazepines - Tricyclic and related antidepressants **- SSRIs as a total group (84 users)** - Other psychoactive drugs	SSRIs: OR = 0.85 [95% CI: 0.55 - 1.33]
Bramness J.G et al. [42] Norway April 2004 - Sept. 2006	Cohort	- 18-69 years old - 20494 accidents - Cyclic sedating antidepressants **- Newer antidepressants (including SSRIs - 884 users)**	Newer antidepressants: SIR = 1.6 [95% CI: 1.5 - 1.7]
Rapoport M.J. et al. [43] Canada April 1997 - March 2005	Case-crossover	- Adults with dementia, ≥ 65 years old - 8690 accidents - Benzodiazepines - Antidepressants (among which SSRIs) - Antipsychotics	Later generation antidepressants (SSRIs and newer agents): OR = 2.15 [95% CI: 1.78 - 2.60]
Ravera S. et al. [44] NL Jan. 2000 - Dec. 2007	Case-control	- ≥ 18 years old - 3963 accidents - Antipsychotics - Anxiolytics - Hypnotics and sedatives **- SSRIs (344 users)** - Other antidepressants	SSRIs: OR = 2.03 [95% CI: 1.31 - 3.14]

Bold: SSRIs

older antidepressants (i.e., cyclic antidepressants and irreversible monoamine oxidase A inhibitors) [43].

Lastly, in a case-control study, performed in the Netherlands, a statistically significant association was found between the exposure to SSRIs and road traffic accident risk. As well as in the previously mentioned study, the traffic accident risk was also found to be higher in case of SSRI exposure than in case of older antidepressant exposure [44].

The outcomes of the above mentioned studies are rather contradictory and, as a consequence, their generalizability is problematic. These inconsistencies could be attributed to both methodological differences between the studies and their limitations. With respect to the study methodologies, the following divergences can be noted: 1) Study design: two studies used a case-crossover design [41, 43], one a

case-control design [44], and one was a cohort study in which standardized incidence ratios (SIRs) were calculated [42]. Besides the differences in the design, it is also important to mention the diversity of logistic regression models and stratifications that were performed, which could have also led to divergent findings. 2) Study population: three studies focused on the general driving population [41, 42, 44] whereas one was restricted to drivers with dementia [43]. Furthermore, different population ages were taken into consideration, namely drivers aged 18 years and over, drivers between the ages 18-69, and adults aged 65 and older. 3) Medication exposure: distinctive SSRIs groups were tested and specific definitions of medication exposure were probably used in these four studies, leading to different risk estimations.

With regard to study limitations, the following shortcomings can be mentioned, which are also the main limitations of pharmacoepidemiological studies: 1) Selection bias in the collection process of cases and controls. 2) The role of multiple risk factors (e.g., alcohol use, illicit drug use, concomitant use of other driving impairing medications). 3) Therapy adherence and proper use of the prescribed medications. 4) Confounding by indication, given the possible hazards of depression to traffic safety [45-47].

In light of the above considerations, it seems reasonable to conclude that these studies can provide valuable information on the risk of experiencing a traffic accident while exposed to SSRIs, but, since every investigation has its unique nuances, caution must be applied while interpreting the outcomes of each research paper because they might not be directly comparable [47].

Categorisation systems for medications and driving: The discrepancies between the ICADTS and the French system

In 1993 the European Commission developed the first action programme on road safety and, in an official communication, highlighted the influence of medicines on road safety [48]. The EU action programmes that followed also underlined the role of medicines in traffic safety and, in particular, in 2003, the European Commission welcomed "the idea of introducing compulsory harmonised pictograms on medical packaging, based on the European classification of drugs according to their effects" and the establishment of "an appropriate classification and labelling of medicines which affect driving ability" [49]. As previously mentioned, at this moment, no standard European classification and labelling system is available, but there are several examples of categorisations systems which were mainly developed at national levels [50, 51].

With respect to the classification of SSRIs, it is interesting to examine the discrepancies between two existing categorisation systems, namely the French system and the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) one. In 2005 the "Journal Officiel de la République Française" published a classification system for medications according to their influence on driving performance. This system is legally binding and it was developed by a group of experts, following the request of

the French Director General of Health to the French Agency for the Safety of Health Products (AFSSAPS) [52, 53].

Three levels of impairment were proposed and three different pictograms were associated to the medication level of impairment:

- Level 1: These medicinal products do not generally question the ability to drive, but require patient information. Patients have to read the leaflet carefully before driving;
- Level 2: These medicinal products could affect the ability to drive and require medical advice, from a physician or a pharmacist, before use;
- Level 3: These medicinal products affect the ability to drive during their use. Patients should not drive. Before starting to drive again, patients have to seek medical advice.

According to this system, level 2 is assigned to SSRIs and no distinction is made between older and newer antidepressants.

In 2006 the ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance also published a list with a categorisation of medications according to their driving impairment [54]. This list was based on the Belgian, Spanish and French categorisation lists, and three categories were proposed to define the level of impairment of commonly prescribed medications:

- Category I: Presumed to be safe or unlikely to produce an effect;
- Category II: Likely to produce minor or moderate adverse effects;
- Category III: Likely to produce severe effects or presumed to be potentially dangerous.

In the ICADTS list, SSRIs are categorized as category I, and, generally speaking, there is a distinction between newer and older antidepressants, these latter belonging either to category II or III. It is difficult to explain the discrepancies between these two categorisation systems, but they could be related to the fact that the French experts might have also taken the role of depression into consideration whereas the ICADTS Working Group solely focused on the medication effects and on the outcomes of the experimental research.

Considering that categorisation systems should serve as a tool for both health care professionals (HCPs) and patients, allowing them to take the right decision, it seems clear that the previously mentioned inconsistencies can lead to confusion and lose their important role and validity.

Legislation in EU

The EU Council Directive 91/439/EEC of July 1991 on driving licences establishes that "Driving licences shall not be issued to, or renewed for, applicants or drivers who regularly use psychotropic substances, in whatever form, which can hamper the ability to drive safely where the quantities absorbed are such as to have an adverse effect on driving. This shall apply to all other medicinal products or combinations of medicinal products which affect the ability to drive" [55]. The application of this directive is

mandatory for all European Union Member States, but there are differences in its implementation across the EU countries [56].

It is noteworthy to point out that, on the one hand, the EU directive clearly indicates that driving under the influence of psychotropic medications can hamper traffic safety and, consequently, subjects using these medications should not be allowed to drive a car. However, on the other hand, the current legislation is very general and it does not refer to any specific psychoactive substances that can impair the ability of driving safely. Finally, it is also important to underline that there is still no general consensus on factors that are strictly related to the application of the directive enforcement such as the identification of impaired drivers, the method/device to be used to detect the presence of medications, the concentration thresholds, the impact of the medication of the subject's ability to drive, the subject's liability [57-59].

With respect to the driving impairment related to SSRI use, it is interesting to mention that, in literature, there are a few case-reports focusing on the relationship between SSRIs and cognitive impairment [60, 61]. Rohrig and his colleague reported a case of car accident after sertraline intoxication. The medication was probably taken alone, at a high dosage, and it caused confusion, eye disorders, sleepiness, which could have played a role in the accident involvement [60]. Another example of possible impairment caused by SSRI use was examined in an American study which investigated the presence of these antidepressants in fatal civil aircraft accidents. The number of SSRI-involved accident was low, but the possible contributory role of these medicines (alone or in combination with alcohol and/or other medications) could not be ruled out [61]. Taken together, these two examples suggest that there could be a connection between the use of SSRIs and accident involvement. Therefore, we can conclude that, in Europe as well as in other developed countries, there is a definite need for specific legislation, covering the above-mentioned issue and, in general, the subject's liability in case of driving under the influence of SSRIs.

CONCLUSIONS

Recommendations and concluding remarks

This paper indicated that, based on available knowledge, the role of SSRIs in traffic safety is still not clear, and the results of experimental and pharmacoepidemiological studies were often contradictory. Furthermore, discrepancies were also found in two existing categorisation systems which should support prescribers choosing a safe medication with respect to its hazard potential for driving. Finally, with regard to the current EU legislation, our manuscript highlighted that, to date, the issue of driving under the influence of medications is not clearly and fully covered, yet.

Further epidemiological work needs to be done to investigate the effects of these active substances on the ability to drive, in different types of users (e.g., new and chronic users, young and old subjects, depressed patients, anxious patients), and in

combination with other illegal and legal substances (i.e., drugs, alcohol, and medicines) [62]. Moreover, additional experimental investigations, focusing on larger and representative groups of healthy and depressed subjects, are needed to determine the impact of each SSRI on psychomotor and cognitive functions, and to better understand the different levels of impairment of available SSRIs. In addition, future research should also concentrate on the role of the co-morbidities and the diseases that are treated with SSRIs which can also affect cognitive and psychomotor skills, if not properly managed [1, 6, 9]. Last but not least, harmonization of epidemiological and experimental studies on driving under the influence of medications is also required in order enable better comparisons between their results as well as a proper estimation of the risks associated with driving under the influence of SSRIs.

The current research also suggests that physicians and, in general, HCPs have to be aware of the possible risks associated with SSRI treatment and the ability to drive. Consequently, HCPs should individually counsel their patients and monitor them during their therapy, considering the potential side effects, the patient's response to the treatment, the subject's medical conditions and the disease, and the concomitant use of other medications. Lastly, patients should be adequately informed about their therapy and, if needed, be able to evaluate, alone or with their HCPs, their clinical conditions with respect to driving [6, 51]. In this respect, a consensus-based revision of the existing categorisation systems would be highly recommended in order to provide both HCPs and patients with consistent information on SSRIs and their impact on fitness to drive as well as a trustworthy tool for a correct use of driving impairing medications.

Finally, our work also supports the need of harmonized and clear regulations against driving under the influence of impairing medications. Specifically, more effective methods for identifying and measuring medication impairment are indispensable as well as detailed directives on medical assessment of fitness to drive in case of psychotropic medication users.

Conclusively, joint efforts of different key stakeholders (e.g., experts in the field of medications and driving, HCPs, policy-makers, etc.) are of fundamental importance in order to fully understand the role of SSRIs in traffic safety and avoid the occurrence of those traffic accidents that could be caused by these medications.

DISCLAIMER

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REFERENCES

1. Verster JC, Ramaekers JG (2009) Antidepressants and traffic safety. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 307-313
2. Katzung BG (2001) Basic and Clinical Pharmacology. Lange Medical Books/McGraw-Hill, New York
3. Trindade E, Menon D, Topfer LA, Coloma C (1998) Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: A meta-analysis. CMAJ 159:1245-1252
4. Wadsworth EJ, Moss SC, Simpson SA, Smith AP (2005) Psychotropic medication use and accidents, injuries and cognitive failures. Hum Psychopharmacol 20:391-400
5. Walinder J (1996) Comparative efficacy and safety of selective serotonin reuptake inhibitors in the short- and medium-term treatment of major depressive disorders. Nord J Psychiatry 50:55-59
6. Sansone RA, Sansone LA (2009) Driving on antidepressants: Cruising for a crash? Psychiatry 6:13-16
7. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA (1999) An inventory of literature on the relation between drug use, impaired driving and traffic accidents (CT.97.EP.14). Available at: www.drugsandalcohol.ie/5308/1/1366-1591.pdf. Accessed: 10 September 2011
8. Ramaekers JG (2003) Pitfalls in estimating drug-related crash risk. Trends Pharmacol Sci 24:114-115
9. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu/publications/insights/driving. Accessed: 26 September 2011
10. de Gier JJ, Ravera S, Monteiro SP, DRUID Work Package 4 Partners (2011) Establishment of criteria for a European categorization system for medicines and driving - DRUID Deliverable 4.2.1. Available at: http://www.druid-project.eu. Accessed: 10 October 2011
11. European Commission - Enterprise and Industry Directorate - General (2009) A guideline on summary of product characteristics (SmPC). Available at: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm. Accessed: 10 October 2011
12. Driving under the Influence of Drugs, Alcohol and Medicines - DRUID. Available at: http://www.druid-project.eu. Accessed: 10 October 2011
13. Gómez-Talegón T, Fierro I, Del Río MC, Alvarez FJ (2011) Establishment of framework for classification/categorisation and labelling of medicinal drugs and driving - DRUID Deliverable 4.3.1. Available at: http://www.druid-project.eu. Accessed: 10 October 2011
14. Ables AZ, Baughman OL (2003) Antidepressants: Update on new agents and indications. Am Fam Physician 67:547-554
15. Goodnick PJ, Goldstein BJ (1998) Selective serotonin reuptake inhibitors in affective disorders - I. Basic pharmacology. J Psychopharmacol 12:S5-20
16. Masand PS, Gupta S (1999) Selective serotonin-reuptake inhibitors: An update. Harvard Rev Psychiatry 7:69-84
17. Masand PS, Gupta S (2002) Long-term side effects of newer-generation antidepressants: SSRIS, venlafaxine, nefazodone, bupropion, and mirtazapine. Ann Clin Psychiatry 14:175-182
18. Peretti S, Judge R, Hindmarch I (2000) Safety and tolerability considerations: Tricyclic antidepressants vs. selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 403:17-25
19. Downie G, Mackenzie J, Williams A (2003) Pharmacology and medicines management for nurses. Churchill Livingstone, Edinburgh
20. Williams DA (2008) Antidepressants. In: Foye WO, Lemke TL, Williams DA (eds) Foye's principles of medicinal chemistry, Sixth edn. Lippincott Williams and Wilkins, Philadelphia, PA, pp 547-600

21. Kasper S, Hoeflich G, Scholl HP, Moeller HJ (1994) Safety and antidepressants efficacy of selective serotonin re-uptake inhibitors. Hum Psychopharmacol 9:1-12
22. Ferguson JM (2001) SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry 3:22-27
23. Moret C, Isaac M, Briley M (2009) Problems associated with long-term treatment with selective serotonin reuptake inhibitors. J Psychopharmacol 23:967-974
24. Hampton T (2004) Suicide caution stamped on antidepressants. JAMA 291:2060-2061
25. Moller HJ, Baldwin DS, Goodwin G, Kasper S, Okasha A, Stein DJ, Tandon R, Versiani M, WPA Section on Pharmacopsychiatry (2008) Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: consensus statement. Eur Arch Psychiatry Clin Neurosci 258 Suppl 3:3-23
26. Neutel CI, Patten SB (1997) Risk of suicide attempts after benzodiazepine and/or antidepressant use. Ann Epidemiol 7:568-574
27. Wessely S, Kerwin R (2004) Suicide risk and the SSRIs. JAMA 292:379-381
28. Schatzberg AF (2000) New indications for antidepressants. J Clin Psychiatry 61 Suppl 11:9-17
29. Verster JC, Ramaekers JG (2009) The on-the-road driving test. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 83-91
30. Iwamoto K, Takahashi M, Nakamura Y, Kawamura Y, Ishihara R, Uchiyama Y, Ebe K, Noda A, Noda Y, Yoshida K, Iidaka T, Ozaki N (2008) The effects of acute treatment with paroxetine, amitriptyline, and placebo on driving performance and cognitive function in healthy Japanese subjects: A double-blind crossover trial. Hum Psychopharmacol 23:399-407
31. Schmitt JA, Ramaekers JG, Kruizinga MJ, van Boxtel MP, Vuurman EF, Riedel WJ (2002) Additional dopamine reuptake inhibition attenuates vigilance impairment induced by serotonin reuptake inhibition in man. J Psychopharmacol 16:207-214
32. Wingen M, Bothmer J, Langer S, Ramaekers JG (2005) Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: A crossover trial. J Clin Psychiatry 66:436-443
33. Brunnauer A, Laux G, Geiger E, Soyka M, Moller HJ (2006) Antidepressants and driving ability: Results from a clinical study. J Clin Psychiatry 67:1776-1781
34. Wingen M, Ramaekers JG, Schmitt JA (2006) Driving impairment in depressed patients receiving long-term antidepressant treatment. Psychopharmacology 188:84-91
35. Grabe HJ, Wolf T, Gratz S, Laux G (1998) The influence of polypharmacological antidepressive treatment on central nervous information processing of depressed patients: Implications for fitness to drive. Neuropsychobiology 37:200-204
36. Hindmarch I (1995) The behavioural toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 9 Suppl 4:13-17
37. Sherwood N (1995) Comparative behavioural toxicity of the selective serotonin reuptake inhibitors. Human Psychopharmacology 10:S159-S162
38. Ramaekers JG (2003) Antidepressants and driver impairment: Empirical evidence from a standard on-the-road test. J Clin Psychiatry 64:20-29
39. Dumont GJ, de Visser SJ, Cohen AF, van Gerven JM, Biomarker Working Group of the German Association for Applied Human Pharmacology (2005) Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. Br J Clin Pharmacol 59:495-510
40. Walsh JM, Verstraete AG, Huestis MA, Morland J (2008) Guidelines for research on drugged driving. Addiction 103:1258-1268
41. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
42. Bramness JG, Skurtveit S, Neutel CI, Morland J, Engeland A (2008) Minor increase in risk of road traffic accidents after prescriptions of antidepressants: A study of population registry data in Norway. J Clin Psychiatry 69:1099-1103

43. Rapoport MJ, Herrmann N, Molnar F, Rochon PA, Juurlink DN, Zagorski B, Seitz D, Morris JC, Redelmeier DA (2008) Psychotropic medications and motor vehicle collisions in patients with dementia. J Am Geriatr Soc 56:1968-1970
44. Ravera S, van Rein N, de Gier JJ, de Jong - van den Berg LTW (2011) Road traffic accidents and psychotropic medication use in the Netherlands: A case-control study. Br J Clin Pharmacol 72(3):505-513
45. Strom BL (1994) Pharmacoepidemiology. John Wiley and Sons Ltd, Chichester - West Sussex
46. Houwing S, Mathijssen R, Brookhuis KA (2009) Case-control studies. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 107-120
47. Hennekens CH, Buring JE (1987) Epidemiology in Medicine. Lippincott Williams and Wilkins, Philadelphia, USA
48. Commission of the European Communities - COM. Communication from the Commission to the council for an action programme on road safety. Available at: http://eur-lex.europa.eu. Accessed: 18 October 2011
49. Commission of the European Communities - COM. European road safety action programme - Halving the number of road accident victims in the European Union by 2010: A shared responsibility (COM/2003/0311 final). Available at: http://eur-lex.europa.eu. Accessed: 18 October 2011
50. EU project ROSITA - Roadside Testing Assessment (Web page). Available at: http://www.rosita.org. Accessed: 15 September 2011
51. de Gier JJ, Alvarez FJ, Mercier-Guyon C, Verstraete AG (2009) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 121-134
52. Arrêté du 18 juillet 2005 pris pour l'application de l'article R. 5121-139 du code de la santé publique et relatif l'apposition d'un pictogramme sur le conditionnement extérieur de certains médicaments et produit. Available at: http://admi.net/jo/20050802/SANP0522726A.html. Accessed: 12 October 2011
53. Agence française de sécurité sanitaire des produits de santé - AFSSAPS (2009) Medicinal products and driving (02/07/2009). Available at: http://www.afssaps.fr/Afssaps-media/Publications/Information-in-English. Accessed: 12 September 2011
54. ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance. The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) categorization list. Available at: http://www.icadts.nl/medicinal.html. Accessed: 12 September 2011
55. Council Directive 91/439/EEC of 29 July 1991 on driving licences (1991). Available at: http://eur-lex.europa.eu/en/index.htm. Accessed: 12 September 2011
56. Alvarez FJ, Fierro I, Vicondoa A, Ozcoidi M, Gomez-Talegon T (2007) Assessment of fitness to drive and cardiovascular diseases at the Spanish medical traffic centres. Circ J 71:1800-1804
57. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA. Legal approaches to drugs and driving. Available at: http://www.emcdda.europa.eu/html.cfm/index19034EN.html. Accessed: 13 October 2011
58. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
59. Alvarez FJ, del Rio MC (2002) Medicinal drugs and driving: From research to clinical practice. Trends Pharmacol Sci 23(9):441-443
60. Rohrig TP, Goodson LJ (2004) A sertraline-intoxicated driver. J Anal Toxicol 28:689-691
61. Akin A, Chaturvedi AK (2003) Selective serotonin reuptake inhibitors in pilot fatalities of civil aviation accidents, 1990-2001. Aviat Space Environ Med 74:1169-1176
62. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658

PART 3

RISK COMMUNICATION

CHAPTER 7

A EUROPEAN APPROACH TO CATEGORIZING MEDICINES FOR FITNESS TO DRIVE: OUTCOMES OF THE DRUID PROJECT

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ABSTRACT

Aim: To illustrate: a) The criteria and the development of the DRUID categorisation system; b) The number of medicines that have currently been categorised; c) The added value of the DRUID categorisation system; d) The next steps in the implementation of the DRUID system.

Methods: The development of the DRUID categorisation system was based on several criteria. The following steps were considered: 1) Conditions of use of the medicine; 2) Pharmacodynamic and pharmacokinetic data; 3) Pharmacovigilance data, including prevalence of undesirable effects; 4) Experimental and epidemiological data; 5) Additional data derived from the Patient Information Leaflet, existing categorisation systems; and 6) Final categorisation. DRUID proposed 4 tiered categories for medicines and driving.

Results: In total, 3054 medicines were reviewed, and over 1541 medicines were categorised (the rest were no longer on the EU market). Nearly half of the 1541 medicines were categorised 0 (no or negligible influence on fitness to drive), about 26% placed in category I (minor influence on fitness to drive), and 17% were categorised as II or III (moderate or severe influence on fitness to drive).

Conclusions: The current DRUID categorisation system established and defined standardized and harmonized criteria to categorise commonly used medications, based on their influence on fitness to drive. Further efforts are needed to implement the DRUID categorisation system at a European level and further activities should be undertaken in order to reinforce the awareness of health care professionals and patients on the effects of medicines on fitness to drive.

INTRODUCTION

Driving a motor vehicle is a multifaceted task and it requires appropriate cognitive and psychomotor skills (e.g., alertness, concentration, reaction time, visual acuity) [1-3]. Medication can adversely affect these driving-related skills, and, consequently, be a hazard to traffic safety [4, 5].

The European Council Directive 83/570/EEC of October 1983 established that the summary of product characteristics (SmPC) has to contain information on medicines' "effects on the ability to drive and to use machines" [6]. In October 1991 the European Committee for Medicinal Products for Human Use (CHMP) provided a Note for Guidance for the SmPC in which it was stated that section 4.7 of medications registered from 1st January 1992 had to indicate, on the basis of the pharmacodynamic profile, reported adverse drug reactions (ADRs) and/or impairment of driving performance or performance related to driving based on 3 different levels of impairment with respect to the ability to drive and/or operate machines [7, 8]. However, this rule has never been implemented [9].

In September 2009, a new SmPC guideline was issued, which established that "on the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has: a) No or negligible influence; b) Minor influence; c) Moderate influence; d) Major influence on these abilities" [10]. These new guidelines were partly based on the proposal sent to the European Medicines Agency (EMA) by DRUID Work Package (WP) 4 partners during the consultation phase for the revision of the SmPC guidelines, in March 2008.

Despite the above-mentioned regulations, at this moment, a European categorisation system has not yet been established, and warning systems for potentially driving impairing medicines have mainly been developed and/or implemented at national levels [8, 11].

Existing categorisation systems on medicines and driving

A review of the existing classification/categorisation and labelling systems for medicines and driving was performed in 2008 and 15 different approaches were identified [12]. The categorisation/labelling systems differed significantly and were not standardized, making them difficult to understand. In most cases [13-17], the categorisation systems were developed by different and unrelated bodies, societies, or researchers, and were, in general, aimed at improving the prescription and dispensation of medicines to the patients and drivers. The identified categorisation systems often included a limited number of medicines belonging to a few different therapeutic groups (e.g., antihistamines, anxiolytics, etc.) and were not legally binding. However, the review also identified a couple categorisation/labelling systems that were developed by regulatory bodies, included the use of pictograms, and were legally binding [18, 19].

In 1973, the Netherlands became the first country to introduce a list of medications that can impair driving abilities. Besides the list, the use of a yellow warning sticker on medication boxes was established and implemented [20]. In 1981, Denmark, Finland, Iceland, Norway, and Sweden adopted a warning label. The label consisted of a red triangle printed on packages of "especially dangerous" medications, and it is currently still in use in Denmark, Finland, and Norway. Most recently, France [18] and Spain [19] developed a categorisation/labelling of all available medicines using technical interdisciplinary groups formed from their respective national medicines regulatory agency [21, 22]. The introduction of pictograms (3-tier labelling system in France and 2-tier in Spain) to be added on the packages of certain medicines became legally binding in both countries.

It is important to point out that although different categorisation systems are currently available across Europe, the criteria for the establishment of a categorisation system for potentially impairing medications has neither been clearly described or published nor been officially adopted at European level [12].

The DRUID project and its categorisation system on medicines and driving

The Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) project is an integrated project funded by the European Commission. The main aim of DRUID is to give scientific support to European Union (EU) transport policy by establishing guidelines and measures that combat impaired driving [23].

The DRUID WP4 aims to provide the basis and the methodology for the development of a European classification/labelling system for medications with respect to their impact on fitness to drive. Furthermore, it also focuses on the development of a classification of relevant therapeutic groups that are currently on the market in Europe as well as new medications approved by the European Medicines Agency (EMA) in the years 2007 - 2009 [23].

Aims of the study

This paper illustrates: a) The criteria and the development of the DRUID categorisation system; b) The number of medicines that have currently been categorised and the distribution of the DRUID categories across the Anatomical Therapeutic Chemical (ATC) index; c) The importance of this system, its implications for health care professionals (HCPs) and patients, and its strengths and limitations; d) The next steps in the implementation of the DRUID system and some general recommendations.

METHODS

The development of the DRUID categorisation system was based on the criteria that were established by a group of experts in the field of medicines and driving, involved in the DRUID WP4, and based on their consensus [24].

The 4 DRUID categories on medicines and driving

In 2006, the DRUID group established and agreed that, according to its influence on fitness to drive, a medicine could be categorised as follows:

- Category 0 (no or negligible influence on fitness to drive);
- Category I (minor influence on fitness to drive);
- Category II (moderate influence on fitness to drive);
- Category III (severe influence on fitness to drive).

The proposed categorisation is in line with the recently approved SmPC guidelines, which were adopted in September 2009 by the EMA [10].

Furthermore, the DRUID experts decided to develop, for each category, practical information to be used by HCPs for patient counselling purposes as well as simple warning labels that could be easily understood by patients (labelling).

The DRUID categorisation of medicines and driving

The ATC classification list [25] was used as a starting point for the selection of the relevant groups of medicines to be categorised. The aim was to categorise all available medicines on the European Union market for each selected ATC group.

Figure 1 shows the process that was followed in order to identify all those medications that are currently available on the European Union market. In general, a medicine was considered available on the EU market if it was commercialised in at least two of the following European countries: Belgium, France, Germany, Greece, the Netherlands, Spain, United Kingdom and Ireland. If the above-mentioned criterion was not fulfilled, the medication was not included in the categorisation process.

Figure 2 summarizes the methodology that was followed in order to assign a category to a selected medicine.

The conditions of use of the medicine, pharmacodynamic and pharmacokinetic data, and pharmacovigilance data (including prevalence of undesirable effects) were derived from the SmPC [10], whereas step 4 (experimental and epidemiological data) was based on a scientific literature search.

The SmPC and Patient Information Leaflet (PIL) of the selected medications were found online, in one of the following websites: Medicines and Healthcare products Regulatory Agency (MHRA) [26], Electronic Medicines Compendium (eMC) [27], or Irish Medicines Board (IMB) [28], or retrieved from national medicines regulatory agencies as needed. In case of recently approved active substances, the SmPC was found on the EMA website [29]. The selection of the above mentioned medicines regulatory affairs agencies was simply based on the fact that the required information had to be available either in English or in a language that could be fully understood by DRUID WP4 partners.

Specific sections of the SmPC and PIL were used to retrieve details on the active substance presentations and strength, indications, posology, route of administration

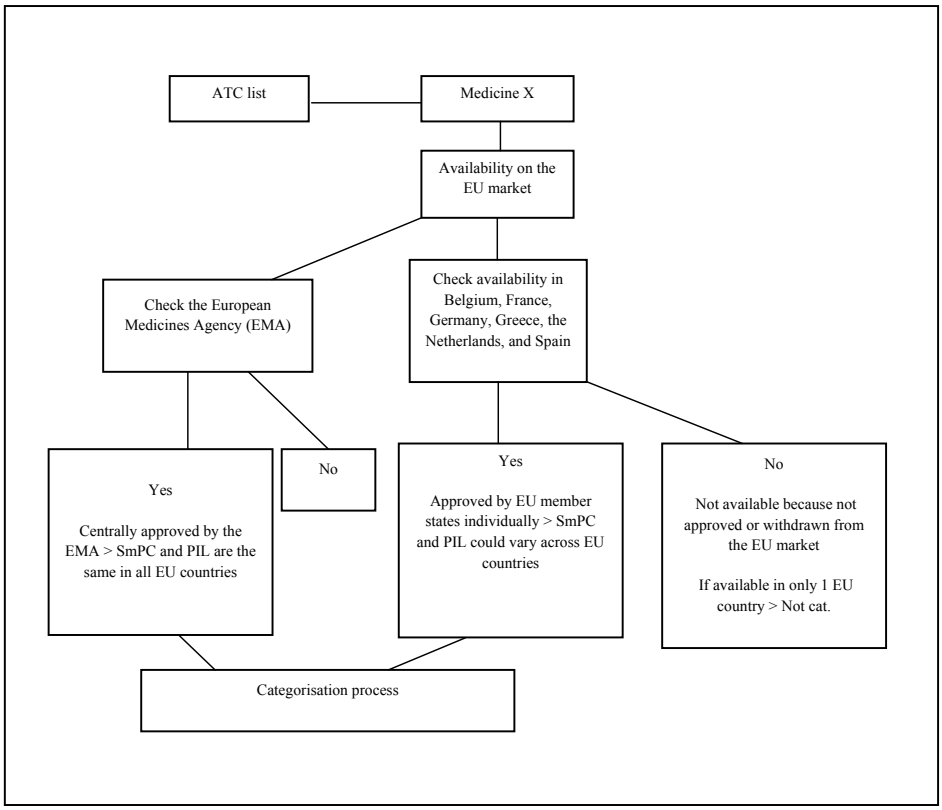

Figure 1. Identification process of medicines available on the EU market.

(Step 1), pharmacodynamic and pharmacokinetic profile (Step 2), effects on the ability to drive and use machines (Step 5), and undesirable effects related to driving and operating machines (Step 3).

With respect to the undesirable effects, their occurrence was considered as a key point, especially if experimental and epidemiological data were lacking or limited. This type of information was found in section 4.8 of the SmPC and, when not available, was retrieved from the available literature.

Generally speaking, only those adverse reactions that could affect the ability to drive and that were reported as common (>1/100, <1/10) or very common (>1/10) were considered to be relevant, as in accordance with the most recent EMA categorisation on frequency of undesirable effects, side effects or adverse reactions. In cases of rare or very rare undesirable effects, or if certain severely impairing effects occur, for example sudden sleep attacks, DRUID partners recommend that this should be mentioned in the PIL.

Table 1 reports the criteria used for assigning a medicine to a specific category whenever experimental or epidemiological data were lacking or limited.

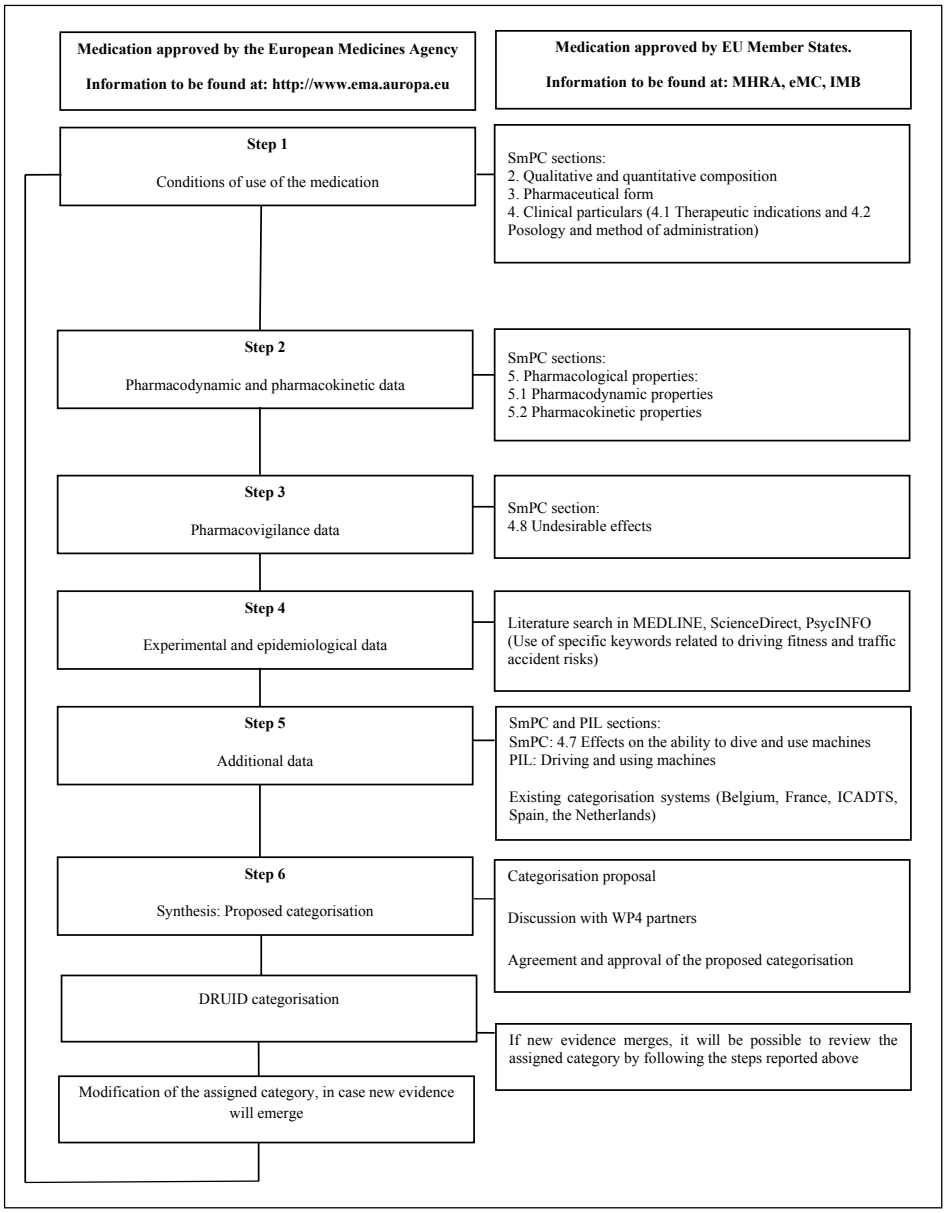

Figure 2. Flowchart representing the methodology that was followed during the DRUID categorisation process.

Table 1. Relationship of the undesirable effects category in the SmPC with the DRUID categorisation system.

DECLARATION of UNDESIRABLE EFFECTS THAT CAN POTENTIALLY IMPAIR FITNESS to DRIVE	DRUID Category
Very common (> 1/10)	Category II or III
Common (>1/100, <1/10)	Category I
Rare (>1/10000, <1/1000) or very rare (<1/10000)	Category 0

Table 2 lists the undesirable effects that could impair the ability to dive, and, therefore, were taken into account in the categorisation process.

Data sources for the scientific literature evaluation included the electronic databases MEDLINE, ScienceDirect, and PsycINFO.

Table 2. List of side effects that can impair driving ability that were considered for the categorisation of active substances based on their level of driving impairment.

System organ class	SELECTION of SIDE EFFECTS THAT CAN IMPAIR FITNESS TO DRIVE
Nervous system disorders	Somnolence, dizziness, drowsiness Confusion - cognitive disorder - disorientation Involuntary movement disorders: ataxia, tremor, parkinsonism, acute dystonic (dyskinesia) and dyskinetic reactions (dystonia) Convulsions - seizures
Psychiatric disorders	Perception disturbances (hallucination, visual hallucination, auditory hallucination, illusion) Psychotic reactions and psychotic disorder (including paranoia psychosis) [Other: emotional lability, mood swings, aggression, nervousness, irritability, personality disorders, thinking abnormal, abnormal behaviour, euphoric mood, restlessness (emotional state of excitement), depersonalisation]
Eye disorders	Diplopia or double vision Blurred vision Accommodation disorders Visual acuity reduced Photophobia [Other: visual field defect, peripheral vision loss, altered visual depth perception, oculogyric crisis]
Ear and Labyrinth disorders	Vertigo Hearing loss [Other: buzzing, tinnitus]
Metabolism and nutrition disorders	Hypoglycaemia
Vascular disorders	Hypotension

The search was performed by using these combinations of keywords: "active substance name and psychomotor performance", "active substance name and automobile driving", and "active substance name and traffic accidents". The final data selection was limited to full text articles published in English and other languages that included references to side effects, experimental and pharmacoepidemiological studies, and case reports on each active substance to be categorised and its possible driving impairment. No restrictions concerning the publication year were applied.

Additional steps consisted of reviewing section 4.7 of the SmPC "Effects on ability to drive and use machines" and the PIL section on "Driving and using machines" as well as reviewing the previous categorisation (if available) of the medicine in Belgium, France, the Netherlands, Spain and the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) list.

In the cases of severely impairing medicines, recently approved medications, or medicines belonging to the ATC groups N and R06, all the collected data were compiled in fact sheets with a standardized lay-out, which were used during the active substance evaluation procedure and the approval of its final category.

After evaluating all the available data, a provisional category was assigned to each active substance. The provisional category was proposed and discussed during WP4 meetings, where a final and definitive category was assigned and approved by all WP4 partners.

It is important to note that the DRUID methodology on the categorisation of medicines affecting driving fitness allows not only to categorise an active substance but also to revise a previously assigned category, in cases where new evidence emerges, by following the same 5 step approach (Figure 2).

Medicines to be categorised

The following ATC groups were considered in the categorisation process:

A - Alimentary tract and metabolism
B - Blood and blood forming organs
C - Cardiovascular system
D - Dermatologicals
M - Musculo skeletal system
N - Nervous system
R - Respiratory system
S - Sensory organs

RESULTS

Three-thousand fifty-four medicines were considered for inclusion into the categorisation process. Of these 3054 medicines, 1513 were not categorised because they were not available on the EU market.

The distribution of the 1541 categorised medicines was as follows (Figure 3): Category 0 - 51%; Category I - 26%; Category II - 11%; Category III - 6%; Multiple categories - 4%; and Depending on the medicine in combination - 2%. This figure shows that the majority of medications belong to either category 0 or category I (Figure 3).

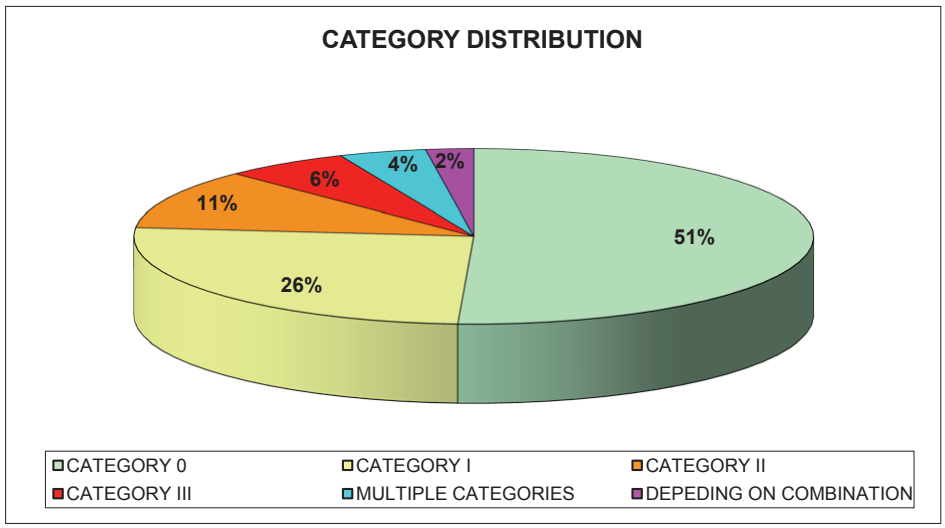

Figure 3. Percentage of active substances within each DRUID category.

It is important to note that the term "multiple categories" refers to the fact that a certain medication could be included in more than 1 category. There could be several reasons for this, such as different routes of administration of the same active substances (e.g., topical, oral, parenteral, etc.), different pharmaceutical formulations (e.g., aqueous-vehicle, cream, drops or ointment, etc.), different dosages administered, etc.

With respect to the terminology "depending on medicines in combination", it is relevant to observe that this approach was used when the categorisation depended on the combination of the medication under evaluation with another active substance. In these cases, since the ATC classification [18] often did not report the medicine used in combination, it was decided not to use a final category but to follow the above-mentioned approach.

Table 3 gives an overview of the distribution of the medicines in each category, stratified by ATC group. It is apparent from this table that the N group contains the highest number of category III medications. A detailed description of the category distribution within the N group is depicted in Table 4. The N05 sub-group shows the highest number of category III medicines, followed by the N01 sub-group. The N05 sub-group also contains the highest number of medications assigned to more than one category.

Table 3. Distribution of the active substances within each category, stratified by ATC group.

ATC GROUP	NOT EVALUATED	CATEGORY 0	CATEGORY I	CATEGORY II	CATEGORY III	MULTIPLE CATEGORIES	DEPENDING ON COMBINATION	TOTAL
A - ALIMENTARY TRACT AND METABOLISM	243	234	69	8	1	4	4	563
B - BLOOD AND BLOOD FORMING ORGANS	86	135	1	1	-	-	2	225
C - CARDIOVASCULAR SYSTEM	246	90	200	11	-	1	-	548
D - DERMATOLOGICALS	156	192	1	-	-	4	-	353
M - MUSCULO-SKELETAL SYSTEM	88	22	44	28	15	-	-	197
N - NERVOUS SYSTEM	346	9	30	86	53	36	-	560
R - RESPIRATORY SYSTEM	195	62	24	32	10	5	14	342
S - SENSORY ORGANS	153	31	31	6	11	18	16	266

Table 4. Distribution of the active substances within each category, in the N group.

NERVOUS SYSTEM	NOT EVALUATED	CATEGORY 0	CATEGORY I	CATEGORY II	CATEGORY III	MULTIPLE CATEGORIES	TOTAL
N01 ANESTHETICS	31	3	3	1	12	10	60
N02 ANALGESICS	93	2	7	10	3	7	122
N03 ANTIEPILEPTICS	23	-	-	14	4	2	43
N04 ANTI-PARKINSON DRUGS	16	-	3	16	-	1	36
N05 PSYCHOLEPTICS							
N05A ANTIPSYCHOTICS	31	-	-	13	8	9	65
N05B ANXIOLYTICS	23	-	1	3	7	1	35
N05C HYPNOTICS AND SEDATIVES	53	-	3	-	11	2	69
N06 PSYCHOANALEPTICS							
N06A ANTIDEPRESSANTS	37	1	7	12	7	1	65
N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS	22	-	3	4	-	-	29
N06C PSYCHOLEPTICS	2	-	-	-	-	-	2
N06D ANTI-DEMENTIA DRUGS	1	1	-	4	-	-	6
N07 OTHER NERVOUS SYSTEM DRUGS	14	2	3	9	1	3	32

DISCUSSION

The current DRUID categorisation system establishes and defines standardized and harmonized criteria to categorise commonly prescribed medicines based on their influence on fitness to drive. To date, this system nearly embraces the full ATC index and it intends to provide a complete coverage of the most commonly prescribed medications in Europe. This categorisation procedure is developed by a European group of experts and is meant to go beyond the national context to address a broader European scenario and involve different facets of health care practice.

The categorisation system could be seen as a tool to improve prescribing and dispensing procedures both at a national and European level and, therefore, as an instrument to better inform and involve HCPs [11, 30]. In this respect, it is important that HCPs know the fundamentals of the categorisation system and use it properly in order to fully inform their patients about the risks of driving under the influence of impairing medicines. Furthermore, HCPs should be able to distinguish between the four levels of impairment and, if possible, choose the least impairing medication within the same therapeutic group. Moreover, this system should encourage HCPs to update their knowledge on medicines and driving in order to be prepared to answer questions that patients might have on this topic [8, 11].

The DRUID categorisation system should also be used as a tool to motivate HCPs to provide patients with clear information, communicate to patients the risk associated with driving under the influence of medicines, and catalyse health care professional-patient discussions, leading to both safer prescriptions and patients who are more contentious about their decision on whether or not to drive [8, 11, 30].

This classification could be a useful tool in helping patients be more involved in the decision-making process, understand the hazards of some medications to traffic safety, and remind them to use caution while driving until their individual responses to their therapy have been well established.

To our knowledge, this is the first time that the European Commission assigned an expert group in the field of medicines and driving the task of establishing the criteria for a European classification system and developing a categorisation system for relevant therapeutic groups of medications with respect to their impact on driving skills. The categorisation efforts were carried out by an international group of DRUID partners, coming from 6 different institutions in Europe, and gathered all their scientific competence, knowledge, expertise, and experience in the field of road safety research and practice. All the available data from multiple sources were collected according to a standardized step-by-step procedure, which allows for the future maintenance and/or revision of the current DRUID categorisation system as new evidence emerges in the future, and, on the other hand, it also allows for the constitution of a consistent evidence-based classification methodology to categorise new medications prior to their market authorization. Last but not least, as reported above, the DRUID categorisation

system encompasses the entire ATC list. Therefore, it is the first categorisation system to provide a nearly complete overview of the influence of frequently prescribed medications on the ability to drive. Additionally, in the cases of severely impairing medications (e.g., medicines from the N group), the system is integrated with fact sheets which concisely emphasize the key-points of the categorisation and can be easily used as a support mechanism in HCPs' daily practice [24].

Lastly, some limitations of the DRUID categorisation system should be considered. In particular, special attention should be paid to the fact that a category is attributed to the single medicine, given to an adult, for its main indication, in a normal dosage, and at the start of the treatment [7, 8, 17]. Therefore, if a medication is not prescribed according to these conditions, it is crucial to bear in mind that the categorisation system can only be used as background information, and it is necessary to carefully assess all the individual risk factors and avoid strict adherence to the medication classification. Furthermore, the system is focused on the effects of medications on fitness to drive and, consequently, the role of the disease, which could also influence fitness to drive, is not considered and certainly needs further attention while counselling the patient [7, 8].

Finally, the categorisation system should always be associated with proper patient counselling in order to avoid any misunderstandings from the patient's side and to ensure that the patient receives adequate information allowing him/her to make a consistent decision with the message given by the medication category.

NEXT STEPS and RECOMMENDATIONS

The categorisation system presented in this manuscript was developed within the DRUID project and, therefore, in a European context. As a consequence, the DRUID partners agreed that the European regulatory authorities should to be informed about this categorisation process. This should lead to discussion and consensus on the criteria hereby proposed and special efforts should be carried out to implement the current system at both international and national level, with consideration country specific circumstances.

In this respect, it is important to underline that the DRUID consortium [31] previously approached the EMA Pharmacovigilance Working Party (PhVWP) in order to obtain its contribution in relation to the development of the categorisation/labelling system for driving impairing medicines [32]. In June 2011, the PhVWP agreed that any information on the influence of medicines on driving ability should be simple and helpful to the patient and, therefore, be reflected in the package leaflet. Furthermore, the PhVWP recommended including in the package leaflet a two-tier risk classification system differentiating between medicinal products with a potential for relevant influence on driving (moderate or major influence) and medicinal products without a potential for relevant influence (no or minor influence). Finally, the PhVWP recognised that this two-tier risk classification system could be further divided to include a maximum of

four categories at the discretion of Member States [32]. This consensus is an important step in the harmonization of information on the potential for a medicine's impairing effects on fitness to drive. However, it would be desirable for Member States to be provided with further discretionary activities, which could be used to reinforce the awareness of HCPs and patients on the effects of medicines on fitness to drive.

Since the categorisation requires constant revision, it is also advised that an expert working group on medicines and driving be established to keep the system functional, up-to-date, and reliable.

Furthermore, it is recommended that special attention be paid to educating those who might play an active role in traffic safety. In this respect, medical and pharmacy schools should develop targeted educational programs covering the issue of medication use and driving. Police officers and driving instructors should be adequately trained on this topic so that they are able to transfer knowledge about the effects of certain medications on a person's ability to drive to potential patients who may participate in traffic.

Finally, a guideline should be developed to explain the use of the categorisation system to HCPs and to serve as a support mechanism in the decision making process. On the other hand, since the patient information leaflet is the most accessible source of information for patients, it would also be advisable to develop an effective strategy to communicate the risk related to the use of medicines and driving. For instances, a straightforward grading system could be included in the patient package leaflet and warning labels in the form of pictograms could be printed on the medication box to provide clear instructions about the use of the medication and driving to patients.

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REFERENCES

1. Kelly E, Darke S, Ross J (2004) A review of drug use and driving: Epidemiology, impairment, risk factors and risk perceptions. Drug Alcohol Rev 23:319-344
2. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS (2002) Can patients taking opioids drive safely? A structured evidence-based review. J Pain Palliat Care Pharmacother 16:9-28
3. Hogan DB (2005) Which older patients are competent to drive? Approaches to office-based assessment. Can Fam Physician 51:362-368
4. Drummer OH (2008) The role of drugs in road safety. Australian Prescriber 31:33-35
5. Augsburger M, Rivier L (1997) Drugs and alcohol among suspected impaired drivers in Canton de Vaud (Switzerland). Forensic Sci Int 85:95-104
6. European Council Directive 83/570/EEC (1983). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31983L0570:EN:HTML. Accessed: 15 July 2011
7. Alvarez FJ, del Rio MC (1994) Drugs and driving. Lancet 344:282
8. de Gier JJ, Alvarez FJ, Mercier-Guyon C, Verstraete AG (2009) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 121-134
9. Alvarez FJ, del Río MC (2002) Medicinal drugs and driving: From research to clinical practice. Trends Pharmacol Sci 23:441-445
10. European Commission - Enterprise and Industry Directorate - General (2009) A guideline on summary of product characteristics (SmPC). Available at: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm. Accessed: 10 September 2011
11. de Gier JJ (1998) Drugs and driving research: Application of results by drug regulatory authorities. Human psychopharmacology: Clinical and Experimental 13: S133-S136
12. Pil K, Raes E, van den Neste T, Goessaert AS, Veramme J, Verstraete AG (2008) Review of existing classification efforts - DRUID Deliverable 4.1.1. Available at: http://www.druid-project.eu. Accessed: 12 July 2011
13. Wolschrijn H, de Gier JJ, de Smet PAGM (1991) Drugs and driving: A new categorization system for drugs affecting psychomotor performance. Institute for Drugs, Safety and Behavior, University of Limburg, the Netherlands. Tech Report
14. Toxicological Society of Belgium and Luxembourg asbl (1999) Influence des médicaments sur les capacités de conduire (in French). Bruxelles: Toxicological Society of Belgium and Luxembourg asbl
15. del Río MC, Alvarez FJ, González-Luque JC (2002) Guía de prescripción farmacológica y seguridad vial (The Pharmaceutical Prescription Guidelines and Road Safety) (in Spanish), Madrid: Dirección General de Tráfico
16. Anonymous (2006) Rules on labelling of medicinal products and on the packaging leaflet - Official Journal of the Republic of Slovenia, No. 54/06 and the Medicinal Products Act (Official Journal of the Republic of Slovenia, No. 31/06)
17. ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance. The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) categorization list. Available at: http://www.icadts.nl/medicinal.html. Accessed: 12 September 2011
18. Arrêté du 18 juillet 2005 pris pour l'application de l'article R. 5121-139 du code de la santé publique et relatif l'apposition d'un pictogramme sur le conditionnement extérieur de certains médicaments et produit. Available at: http://admi.net/jo/20050802/SANP0522726A.html. Accessed: 12 October 2011
19. Real Decreto 1345/2007, de 11 de octobre, por el que se regula el procedimiento de autorización, registro y condiciones de dispensación de los medicamentos de uso humano fabricados industrialmente (in Spanish). BOE de 7 de Noviembre de 2007, pp 45652-45698
20. Contra-indicatie Verkeersdeelname - Contra-indication "Participation in traffic" (in Dutch). Available at: www.geneesmiddeleninhetverkeer.nl. Accessed: 15 July 2011

21. Agence française de sécurité sanitaire des produits de santé - AFSSAPS (2009) Medicinal products and driving (02/07/2009). Available at: http://www.afssaps.fr/Afssaps-media/Publications/Information-in-English. Accessed: 12 September 2011
22. Agencia Española de Medicamentos y Productos Sanitarios. Medicamentos y Conduccion. Available at: http://www.aemps.gob.es/industria/etiquetado/conduccion/home.htm. Accessed: 15 July 2011
23. Driving under the Influence of Drugs, Alcohol and Medicines - DRUID. Available at: http://www.druid-project.eu. Accessed: 10 July 2011
24. Gómez-Talegón T, Fierro I, del Río MC, Alvarez FJ (2011) Establishment of framework for classification/categorisation and labelling of medicinal drugs and driving - DRUID Deliverable 4.3.1. Available at: http://www.druid-project.eu. Accessed: 10 October 2011
25. WHO Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/ddd/definition_and_general_considera. Accessed: 15 July 2011
26. Medicines and Healthcare Products Regulatory Agency - MHRA. Available at: http://www.mhra.gov.uk/index.htm. Accessed: 12 July 2011
27. Electronic Medicines Compendium - eMC. Available at: http://www.medicines.org.uk/EMC/default.aspx. Accessed: 12 July 2011
28. Irish Medicines Board - IMB. Available at: http://www.imb.ie. Accessed: 12 July 2011
29. European Medicines Agency - EMA. Available at: http://www.ema.europa.eu/ema/index.jsp. Accessed: 12 July 2011
30. Talbot J, Stephens MDB (2004) Clinical trials - Collection of safety data and establishing the adverse drug reaction profile. In: Talbot J and Stephens MDB (eds) Stephens' Detection of New Adverse Drug Reactions. Chichester, West Sussex, John Wiley and Sons, Ltd, pp 167-242
31. de Gier JJ, Ravera S, Monteiro SP, DRUID Work Package 4 Partners (2011) Establishment of criteria for a European categorization system for medicines and driving - DRUID Deliverable 4.2.1. Available at: http://www.druid-project.eu. Accessed: 10 July 2011
32. Anonymous (2011) Monthly Report Issue number 1106. Pharmacovigilance Working Party (PhVWP). June 2011 plenary meeting. EMA/CHMP/PhVWP/486894/2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/06/WC500108098.pdf. Accessed: 10 October 2011

CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

MAIN GOALS OF THE DISSERTATION

This thesis addressed the association of psychotropic medication use and traffic safety.

To date, the available research has shown that exposure to some psychoactive medication classes can impair driving related skills (e.g., cognitive, visual and psychomotor performance) and, therefore, increase the risk of being involved in a traffic accident [1-5]. However, with the exception of a few medicine groups (e.g., benzodiazepines, tricyclic and tetracyclic antidepressants, sedating antihistamines), the evidence for the role of prescribed medications in traffic safety is still uncertain and several questions remain unanswered [3, 5, 6].

The current dissertation explores the use of driving impairing medications in the general population, evaluates the potential traffic accident risk associated with the exposure to these medications, and proposes a categorisation system as a source for developing tools to improve prescribing, dispensing and use of psychotropic medicines that can be a hazard to traffic safety.

This general discussion summarizes and evaluates the main results of our research as presented in this thesis, and, in addition, gives some general recommendations for future perspectives.

PSYCHOTROPIC MEDICATION USE IN THE GENERAL POPULATION (Chapter 2 and Chapter 3)

Chapter 2 and 3 examined the use of psychotropic medications in the general population in Europe and in the northern part of the Netherlands, respectively.

Twelve EU countries provided national utilization data, aggregated at the level of the active substance and presented in defined daily doses (DDDs) per 1000 inhabitants per day. Trends within countries indicated that, in the years 2000 - 2005, there was slight to no increase in the consumption of the medication groups of interest, except for the antidepressants and, specifically, the SSRIs, which showed an increased use in almost all the countries included in the study. Due to different data collection techniques and data collection bias, it was not possible to compare the use of the selected medication groups among EU countries and, consequently, to obtain a general and comprehensive overview of the psychotropic medication utilization patterns across Europe. Lastly, not all the invited EU countries participated in our survey and, therefore, the European map of psychotropic medicine use remained incomplete.

The outcomes of the European survey referred to the Netherlands were in line with those of the drug utilization study regarding the Dutch driving population, which showed that the yearly prevalence and cumulative incidence of prescriptions for psychoactive medications were relatively stable in the period 2000 - 2005. Additionally, this study showed that combination therapy was common among subjects aged 30 to 59 years, and that, generally speaking, psychoactive medications were used for relatively

long periods (e.g., median treatment duration of anxiolytics: approximately 1.7 years; median treatment duration of antipsychotics: approximately 5 years).

Based on the outcomes of these two studies, it can be stated that, in general, in the time-frame of interest, the consumption of driving impairing medications remained rather constant and did not show a significant decrease, in spite of the fact that several public information campaigns were launched in different EU countries with the aim of increasing the awareness of the risks associated with driving under the influence of some medicines [7]. Given that the selected medication groups could be a contributory factor to road traffic accidents [2, 8], special attention should be paid when prescribing and dispensing these medications in order to reduce the motor vehicle accident risks related to psychotropic medication therapies, and, when conceivable, the safest alternatives within each therapeutic class should be preferred to severely impairing active substances.

Our research also underlined that the administration of more than one psychotropic medication is relatively common among the Dutch driving population. It is well known that combination therapy can expose patients to a higher risk of adverse effects, drug interactions, and noncompliance [9], and, therefore, it can be argued that it might also play a role in traffic safety [8]. Thus, it seems reasonable to stress that, if possible, combination therapy should be avoided or, at least, restricted to special circumstances [9, 10].

The results of our research also pointed out that, in case of anxiolytics and hypnotics, treatment duration seemed to be much longer than that recommended by clinical guidelines. The active substances of these two medication classes are mainly benzodiazepines, which are well known to increase the risk of motor vehicle accidents [1-4], and, therefore, it is strongly advised to prescribe and use these medicines according to the current medical recommendations in order to minimize the negative effects that might derive from their chronic use and their hazards to traffic safety [11-13].

Lastly, our drug utilization studies showed that it is still difficult to perform cross-national comparisons of psychotropic medication use in Europe and that, even at national levels, different shortcomings could limit the study outcomes (e.g., availability of pharmacy dispensing data only, not covering over-the-counter medication use, and medications prescribed in hospital settings, etc.). For these reasons, the use of standard methodological approaches, guidelines, and international collaboration between countries would be of great value and highly recommended.

TRAFFIC ACCIDENT RISK ASSOCIATED TO PSYCHOTROPIC MEDICATION EXPOSURE (Chapter 4, Chapter 5 and Chapter 6)

In Chapter 4 and 5 we studied the relationship between psychotropic medication exposure and the risk of experiencing a motor vehicle accident, by means of a case-control study, and case-crossover and case-time-control studies, respectively. The case-control analyses revealed a statistically significant increased risk in subjects exposed to anxiolytics [Adj. OR = 1.54 (95% CI: 1.11 - 2.15)], and SSRIs [Adj. OR = 2.03 (95% CI: 1.31 - 3.14)]. These findings were not confirmed by the case-crossover study, which did not show any significant increase in motor vehicle accident risk associated with the exposure to the above-mentioned psychotropic medication groups [Anxiolytics: Adj. OR = 0.95 (95% CI: 0.68 - 1.31); SSRIs: Adj. OR = 1.00 (95% CI: 0.69 - 1.46)], but, on the other hand, the case-time-control analysis partially supported the outcomes of the case-control study and showed a borderline statistically significant increased motor vehicle accident risk in SSRI users [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)]. These rather contradictory findings could be explained by the use of three different study designs which probably relied on distinctive assumptions and had different interpretations, and, consequently, led to divergent final answers [14-16]. In particular, considering that case-crossover and case-time-control studies are especially useful for studying intermittent exposures with transient effects [17, 18], it can be speculated that these two approaches were probably not the most suitable ones to investigate the relation between traffic accident risk and psychotropic medications, which are often used chronically (Chapter 3).

In view of the fact that different epidemiological designs could produce different results, it seems reasonable to stress that special attention should be paid to the assumptions about the exposures and the outcomes that we intend to investigate, and that the final choice of the study design should be made accordingly [15, 16]. Lastly, our findings also indicated that it could be difficult to choose an appropriate research method and, therefore, the development and adoption of guidelines and structured, standardized protocols for research into medication use and driving is highly recommended [4]. With this respect, for instance, the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [19] or the example reported by Walsh *et al.* [20] could be used as a starting point to elaborate more specific recommendations in the field of epidemiological studies on driving under the influence of medications, and, as a consequence, harmonize the research methods in this area.

In spite of the aforementioned divergent results, our research pointed out that SSRIs could represent a risk to traffic safety. The results of our case-control and case-time-control studies were consistent with two other recent epidemiological studies [21, 22] and also confirmed the findings of some experimental research that was performed

on depressed patients [23-25] (Chapter 6). In contrast, the above-mentioned findings differed from Barbone's work [1] and the majority of the published experimental studies, which showed that SSRIs did not constitute a hazard to traffic safety [26-28] (Chapter 6). It is difficult to explain the discrepancies and inconsistencies on the role of SSRIs in traffic safety that were observed between the experimental and epidemiological studies that were included in our literature review. However, it is important to bear in mind that experimental and epidemiological researches are performed in different settings (e.g., study population, medication selection, medication administration/ exposure, outcome definition, study designs and methodologies, etc.) and have their own specific limitations (e.g., sample size, use of databases as the only source of information, confounding by indication, validity of the tests - it is not always the case that tests measure what they are meant to measure, etc.), which often make the comparison or combination of their results rather difficult and controversial [4, 29]. Once more, it is advised to develop standards or guidelines to enable the comparability and the combination of the results of epidemiological and experimental studies with the purpose of obtaining a more reliable estimate of the impact of certain medications on fitness to drive and traffic safety [4, 29, 30]. Lastly, more knowledge is needed about the actual effects of SSRIs and depression on fitness to drive and, furthermore, it is also suggested to properly inform health care professionals and patients about the potential driving impairment related to both depression and its therapeutic treatments.

In contrast to earlier findings [1, 31-33], our pharmacoepidemiological studies did not find a strong association between motor vehicle accidents and anxiolytics and hypnotics, both known to increase the risk of experiencing a traffic accident [1-3]. It seems possible that our results could be due to the growing perception of the role of these medications in road trauma as a result of the numerous scientific publications on this topic [5, 34, 35], guidelines on prescribing and dispensing driving impairing medications [10, 36, 37], and public campaigns [7], which all encouraged the prescription of less impairing or safer active substances, proper patient counselling on the cautious use of these potentially driving impairing medications, and the importance of avoiding driving while taking such medicines [7, 10, 37]. Considering that anxiolytics and hypnotics are two of the most frequently used psychoactive medication groups in several European countries [38] (Chapter 2), it is strongly advised to continue to inform both health care professionals and drivers about the motor vehicle accident risks associated with these medicines and to combat the scourge of driving under their influence in order to eventually prevent as many road traffic accidents as possible.

Finally, the findings of our pharmacoepidemiological research and our inventory of the existing literature on SSRIs and driving impairment highlighted that there is still a need for further studies in order to improve our current knowledge on the impact of psychotropic medications on traffic safety. In particular, it is recommended that future research be undertaken to clarify the following points: the effects of different aspects of therapeutic treatments (e.g., dose changes, beginning of treatment, withdrawal of

treatment, etc.), the potential driving impairment of new generations of medications (with special attention to SSRIs and newer antidepressants), the hazards of combinations of psychotropic and non-psychotropic therapies, and the role of the diseases on fitness to drive (e.g., depression, insomnia, anxiety, etc.).

A CATEGORISATION SYSTEM FOR POTENTIALLY DRIVING IMPAIRING MEDICATIONS: A SOURCE FOR DEVELOPING TOOLS TO SUPPORT PRESCRIBING AND DISPENSING PRACTICES AND A STEP FORWARD IN EUROPE (Chapter 7)

In Chapter 7 we presented the DRUID methodology for the development and the maintenance of a European classification system for relevant therapeutic groups of medications available on the EU market, and the classification of 1541 active substances, almost covering the full ATC index, based on their potentials to impair fitness to drive. The proposed DRUID categorisation system resulted from a tiered and structured process which involved the evaluation of pharmacological data (pharmacodynamic and pharmacokinetic medication profiles), pharmacovigilance data, experimental and epidemiological literature reviews, and additional data (e.g., information derived from the patient information leaflet, existing categorisation systems, etc.). Furthermore, Chapter 7 also described the 4 categories, ranking from 0 (no or negligible driving impairment) to III (severe driving impairment), which were suggested by the DRUID working group in order to define the influence of commonly prescribed active substances on fitness to drive.

The proposed methodological approach and medication categorisation are an attempt to establish the basis for a pan-European classification system for medicines and driving which can serve the needs of drug regulatory agencies, drug manufacturers, health care professionals and patients [39]. Since the current national categorisation efforts substantially differ from each other [40], the main goal of our work was to elaborate clear instructions as to how a common and consistent categorisation system should be set up and, afterwards, to develop a tool (i.e., the DRUID classification list) which can help manufacturers and regulatory agencies in assessing the driving impairment of medicines that received a marketing authorization, health care professionals in selecting safer alternatives and counselling their patients, and drivers in understanding the risks associated with their therapeutic treatments and deciding whether or not to drive [10, 39].

An important limitation of the DRUID approach for the development and maintenance of the categorisation system is that this methodology is determined by the availability of data that are needed to classify medications into "driving risk" categories and/or to provide a list of "safe" medications with respect to driving [39, 41]. In these circumstances, it is advised to focus on undesirable effects that have the potentials to

impair fitness to drive [39], and to review the assigned category as soon as more data will become available.

Finally, it is fundamental that the proposed methodology will be approved and implemented at both international and national level, in Europe, in order to have a standardized and validated protocol to assess the impairing effects of prescription medications on driving related skills.

With respect to the DRUID classification list, it is important to stress that, as a rule, the proposed four categories are assigned to the active substance at the normal dosage given to an adult for the main indication of the medication [39]. Therefore, the categorisation does not take into account potential dosing restrictions, possible interactions with concomitant medications or illicit drugs or alcohol, tolerance and pharmacokinetic considerations, inter-individual differences and economic issues [41], and, consequently, it is up to health care professionals to evaluate all those factors that can also play a crucial role in traffic safety and make a proper decision based on the appraisal of the above-mentioned circumstances. In addition, it is essential to inform physicians, pharmacists and patients about the existence and the meaning of the categorisation system with the aim of promoting informed prescribing, appropriate patient counselling and safe medication use by patients [41]. Finally, it is also recommended to validate the categorisation system by means of epidemiological studies, to investigate its effects on the prevention of motor vehicle accidents, and to regularly update it with respect to the approval of new medications and the availability of new epidemiological and pharmacovigilance data.

In regard to the DRUID methodology and categorisation system, it is important to underline that, in June 2011, the Pharmacovigilance Working Party at the European Medicines Agency (EMA) in London endorsed the work that was carried out within the DRUID WP 4 (specifically, DRUID Deliverable 4.2.1.). In particular, it was agreed that the DRUID preliminary recommendations on the criteria for medication categorisation were of relevance, and, specifically, the DRUID approach (i.e., examination of pharmacological data, pharmacovigilance data, experimental and epidemiological literature, individual sensitivity, and available additional data) could be accepted for evaluating the medicine overall potentials to impair fitness to drive [39]. Furthermore, consensus was reached that a basic two-tier categorisation system should be developed as the basis for warnings to the patient in the patient information leaflet. The decision of using a two-tier categorisation system, differentiating between medications without the potential for influence and medications for moderate or major influence on fitness to drive, was reached after considering evidence based medicine, as well. Specifically, the outcomes of two recent studies on medication use and motor vehicle accident risks were taken into account, that is to say a French study [42] and a DRUID study (DRUID Deliverable 2.3.1.) [43]. The Orriols' study showed that the risk of accident for patients who had taken a medicine described as having minor influence on fitness to drive was not different from those patients who had taken medicines with no or

negligible influence. Furthermore, the French study also pointed out that, similarly, there was no substantial difference in motor vehicle accident risk between patients taking medicines with moderate influence and patients taking medicines described as having a major influence on driving fitness [42]. The French results were in agreement with the findings reported in DRUID Deliverable 2.3.1. which also showed that the motor vehicle accident risk was only considered significant for categories of level II and above [43]. Consequentially, as stated above, the Pharmacovigilance Working Party concluded that a single warning was required for those patients who had taken medicines described as having major or moderate influence on fitness to drive [39].

Lastly, the Pharmacovigilance Working Party acknowledged that, at the EU Member States level, further discretionary activities could be undertaken in order to reinforce the awareness of patients on the effects of medicines on fitness to drive, such as the use of an alerting pictogram on the product packaging and further stratifications of the number of risk categories to a maximum of four categories [39].

The aforementioned Pharmacovigilance Working Party's consensus can certainly be considered as a first step towards a common approach to medication categorisation with the final aim to harmonize patient information on the potential driving impairment of commonly prescribed medications in Europe [39]. However, it is fundamental that, in the future, more activities will be carried out in order to build on the above-mentioned framework and bring this information to the attention of stakeholders (e.g., pharmaceutical companies, patient representatives, etc.), national regulatory agencies, health care professionals and patients [39].

CONCLUSIONS and FUTURE PERSPECTIVES

The studies presented in the previous chapters of this dissertation evaluated the use of psychotropic medications in the general population in Europe and in the Netherlands, the traffic accident risks associated with their use, and proposed a methodology and a categorisation system to improve the use of driving impairing medications and, consequently, traffic safety.

Our research showed that, in the last years, both in the European Union and the Netherlands, the use of psychoactive medications remained relatively stable, with the exception of a few medication groups. Our results also demonstrated that some commonly prescribed medications could be associated with the risk of experiencing a motor vehicle accident, and that caution must be applied in order to choose the most appropriate epidemiological design to investigate the above-mentioned relation. Lastly, a classification methodology and a four-level categorisation list were made available, with the purpose of delivering more reliable and valid information on the issue of medication use and driving impairment.

On the one hand, our work contributed additional evidence with respect to the role of prescribed medications in road trauma, but, on the other hand, it also threw

up some questions in need of further investigation as well as some recommendations for policy makers and clinical practice. First, international collaboration between countries is required in order to be able to perform reliable drug utilization studies at international and national levels. Second, standardized data collection techniques and study designs, and guidelines are necessary to provide consistent and comparable pharmacoepidemiological data and experimental data. Third, more research is recommended to explore the role of SSRIs as well as new medications that will appear on the market, factors associated with therapeutic treatments (e.g., combination therapy, dose changes, medication withdrawal, etc.), diseases and co-morbidities, groups of drivers at high risk for motor vehicle accidents, and the effects of the categorisation system on the possible decrease of road traffic accidents. Fourth, the proposed DRUID categorisation system for driving impairing medications should be officially adopted and implemented in EU in order to provide reliable and valid information to health care professionals and consumers, and, moreover, this system should be constantly revised and updated to have a trustworthy and efficient classification list. Lastly, on the one hand, physicians and pharmacists should be supported in prescribing and dispensing the least driving impairing medications and providing their patients with adequate advice; on the other hand, patients should be informed about the risks associated with driving under the influence of their medications and should be able to consciously decide whether to drive or not.

REFERENCES

1. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331-1336
2. Walsh JM, de Gier JJ, Christopherson AS, Verstraete AG (2004) Drugs and driving. Traffic Inj Prev 5:241-253
3. Drummer OH (2008) The role of drugs in road safety. Australian Prescriber 31:33-35
4. Raes E, van den Neste T, Verstraete AG (2008) Drug use, impaired driving and traffic accidents - EMCDDA Insights. Available at: http://www.emcdda.europa.eu/publications/insights/driving. Accessed: 24 July 2011
5. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E (2009) The impact of medicinal drugs on traffic safety: A systematic review of epidemiological studies. Pharmacoepidemiol Drug Saf 18:647-658
6. Jones R, Shinar D, Walsh JM (2003) State of knowledge of drug impaired driving (DOT HS 809 642)
7. Raes E, Pil K, van den Neste T, Verstraete AG (2007) Review of guidelines, booklets, and other resources: State of the art - DRUID Deliverable 7.1.1. Available at: http://www.druid-project.eu. Accessed: 24 July 2011
8. del Rio MC, Alvarez FJ (1996) Medication use by the driving population. Pharmacoepidemiol Drug Saf 5:255-261
9. Ananth J, Parameswaran S, Gunatilake S (2004) Antipsychotic polypharmacy. Curr Pharm Des 10:2231-2238
10. de Gier JJ, Alvarez FJ, Mercier-Guyon C, Verstraete AG (2009) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. In: Verster JC, Pandi-

Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 121-134

11. Woods JH, Winger G (1995) Current benzodiazepine issues. Psychopharmacology (Berl) 118:107-115; discussion 118, 120-121
12. Verster JC, Mets MAJ, Leufkens TRM, Vermeeren A (2009) Insomnia, hypnotic drugs and traffic safety. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ (eds) Drugs, Driving and Traffic Safety. Birkaeuser Verlag AG, Basel - Boston - Berlin, pp 233-244
13. Ashton H (1994) Guidelines for the rational use of benzodiazepines. When and what to use. Drugs 48:25-40
14. Hebert C, Delaney JA, Hemmelgarn B, Levesque LE, Suissa S (2007) Benzodiazepines and elderly drivers: A comparison of pharmacoepidemiological study designs. Pharmacoepidemiol Drug Saf 16:845-849
15. Hernandez-Diaz S, Hernan MA, Meyer K, Werler MM, Mitchell AA (2003) Case-crossover and case-time-control designs in birth defects epidemiology. Am J Epidemiol 158:385-391
16. Maclure M (2007) 'Why me?' versus 'why now?' - Differences between operational hypotheses in case-control versus case-crossover studies. Pharmacoepidemiol Drug Saf 16:850-853
17. Schneeweiss S, Sturmer T, Maclure M (1997) Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf 6(3):S51-59
18. Maclure M, Mittleman MA (2000) Should we use a case-crossover design? Annu Rev Public Health 21:193-221
19. STrengthening the Reporting of OBservational studies in Epidemiology - STROBE. Available at: http://www.strobe-statement.org/index.php?id=strobe-home. Accessed: 24 July 2011
20. Walsh JM, Verstraete AG, Huestis MA, Morland J (2008) Guidelines for research on drugged driving. Addiction 103:1258-1268
21. Bramness JG, Skurtveit S, Neutel CI, Morland J, Engeland A (2008) Minor increase in risk of road traffic accidents after prescriptions of antidepressants: A study of population registry data in Norway. J Clin Psychiatry 69:1099-1103
22. Rapoport MJ, Herrmann N, Molnar F, Rochon PA, Juurlink DN, Zagorski B, Seitz D, Morris JC, Redelmeier DA (2008) Psychotropic medications and motor vehicle collisions in patients with dementia. J Am Geriatr Soc 56:1968-1970
23. Brunnauer A, Laux G, Geiger E, Soyka M, Moller HJ (2006) Antidepressants and driving ability: Results from a clinical study. J Clin Psychiatry 67:1776-1781
24. Grabe HJ, Wolf T, Gratz S, Laux G (1998) The influence of polypharmacological antidepressive treatment on central nervous information processing of depressed patients: Implications for fitness to drive. Neuropsychobiology 37:200-204
25. Wingen M, Ramaekers JG, Schmitt JA (2006) Driving impairment in depressed patients receiving long-term antidepressant treatment. Psychopharmacology 188:84-91
26. Dumont GJ, de Visser SJ, Cohen AF, van Gerven JM, Biomarker Working Group of the German Association for Applied Human Pharmacology (2005) Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. Br J Clin Pharmacol 59:495-510
27. Hindmarch I (1995) The behavioural toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 9 Suppl 4:13-17
28. Ramaekers JG (2003) Antidepressants and driver impairment: Empirical evidence from a standard on-the-road test. J Clin Psychiatry 64:20-29
29. European Monitoring Centre for Drugs and Drug Addiction - EMCDDA (1999) An inventory of literature on the relation between drug use, impaired driving and traffic accidents (CT.97.EP.14). Available at: www.drugsandalcohol.ie/5308/1/1366-1591.pdf. Accessed: 24 July 2011
30. Raes E, Pil K, Verstraete AG (2009) The modern trends in alcohol, drugs and driving research. Forensic Science International Supplement Series 1:11-14

31. Dubois S, Bedard M, Weaver B (2008) The impact of benzodiazepines on safe driving. Traffic Inj Prev 9:404-413
32. Movig KL, Mathijssen MP, Nagel PH, van Egmond T, de Gier JJ, Leufkens HG, Egberts AC (2004) Psychoactive substance use and the risk of motor vehicle accidents. Accid Anal Prev 36:631-636
33. Neutel CI (1995) Risk of traffic accident injury after a prescription for a benzodiazepine. Ann Epidemiol 5:239-244
34. Smink BE, Egberts AC, Lusthof KJ, Uges DR, de Gier JJ (2010) The relationship between benzodiazepine use and traffic accidents: A systematic literature review. CNS Drugs 24:639-653
35. van Laar MW, Volkerts ER (1998) Driving and benzodiazepine use - Evidence that they do not mix. CNS Drugs 10:383-396
36. ICADTS Working Group on Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance. The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) categorization list. Available at: http://www.icadts.nl/medicinal.html. Accessed: 24 July 2011
37. The ICADTS Working Group (2001) Prescribing and dispensing guidelines for medicinal drugs affecting driving performance. Available at: http://www.icadts.nl/medicinal.html. Accessed: 24 July 2011
38. de Gier JJ (2003) Problems raised by the use/abuse of psychoactive drugs by drivers - Report on the situation in 24 European countries. In: Proceeding of road traffic and psychoactive substances (Seminar organized by the Pompidou Group, Strassbourg, France)
39. de Gier JJ, Ravera S, Monteiro SP, and the DRUID Work Package 4 Partners (2011) Establishment of criteria for a European categorization system for medicines and driving - DRUID Deliverable 4.2.1. Available at: http://www.druid-project.eu. Accessed: 24 July 2011
40. Pil K, Raes E, van den Neste T, Goessaert AS, Veramme J, Verstraete AG (2008) Review of existing classification efforts - DRUID Deliverable 4.1.1. Available at: http://www.druid-project.eu. Accessed: 24 July 2011
41. Kay GG, Logan BK (2011) Drugged driving expert panel report: A consensus protocol for assessing the potential of drugs to impair driving (DOT HS 811 438)
42. Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B, Laumon B, Salmi LR, Lagarde E, on behalf of the CESIR research group (2010) Prescription medicines and the risk of road traffic crashes: A French registry-based study. PLoS Med 7:e1000366
43. Ravera S, de Gier JJ (2010) Relative accident risk of patients using psychotropic medicines in the Netherlands: A pharmacoepidemiological study - DRUID Deliverable 2.3.1. Available at: http://www.druid-project.eu. Accessed: 12 September 2011

ADDENDUM

SUMMARY
SAMENVATTING
RIASSUNTO DELLA TESI IN ITALIANO
ACKNOWLEDGMENTS
LIST OF PUBLICATIONS
CURRICULUM VITAE
PREVIOUS DISSERTATIONS OF SHARE

SUMMARY

Road traffic accidents constitute a major public health challenge and cause, every year, a large number of losses of life and injuries worldwide (Chapter 1).

In 2003, in its White Paper on European transport policy, the European Commission fixed the target date of 2010 to halve the number of road deaths, and, in 2006 launched the European Union (EU) project Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) with the purpose of obtaining scientific support to its transport policy to reach the 2010th road safety target (Chapter 1).

DRUID aims to study how the use of alcohol, illicit drugs and medicines can affect driving fitness and to establish guidelines and measures to combat impaired driving (Chapter 1).

This PhD dissertation was part of the DRUID project and aimed to assess the impact of psychoactive medications on traffic safety. Based on the main objective of this thesis, the following research questions were developed and answered: 1) The dimension of the use of potentially driving impairing medications in the general driving population (Chapter 2 and 3); 2) The risks of experiencing a road traffic accident while being exposed to psychoactive medicines (Chapter 4, 5 and 6); 3) The development of criteria and methodology for establishing a European classification system for relevant therapeutic medication groups and driving (Chapter 7).

In **Chapter 2** we presented the results of the European survey estimating the use of driving impairing medication in the general population. Questionnaires were distributed through two scientific networks (i.e., European Drug Utilization Research Group and Post-Innovation Learning through Life-events of drugs) or, when possible, data were collected directly through public websites. A total of 30 countries were asked to supply data on the use of psychotropic medication groups, presented in defined daily doses (DDDs) per 1000 inhabitants per day. Twelve European contries provided national utilization data referred to the study time frame 2000 - 2005. Since different types of bias hampered the delivered data, it was not possible to perform a cross-national comparison and the use of the psychotropic medications of interest could only be examined at a national level. Trends within countries indicated a slight to no increase in the consumption of selected medicinal drug groups, with the exception of the antidepressants and the selective serotonin reuptake inhibitors (SSRIs) which showed a remarkable increased use during the period of interest.

Chapter 3 reported the outcomes of a Dutch drug utilization study which estimated the prevalence, cumulative incidence, monotherapy and combination therapy, and treatment duration of frequently used psychoactive medication classes that might impair driving skills, between the years 2000 and 2005. Data were derived from IADB.nl database, which contains pharmacy dispensing data from a population of approximately 500000 inhabitants in the northern part of the Netherlands. Patients aged 18 to 89 years were selected, and prevalence and cumulative incidence were calculated

per 1000 patients per year whereas the treatment duration was analyzed by means of Kaplan-Meier survival analysis. The findings of this study showed that both prevalence and cumulative incidence had stable trends in the selected time frame; furthermore, age and gender stratifications found that prevalence and cumulative incidence were the highest among elderly and female patients. Combination therapy was mainly observed in patients aged 30-59 years. The longest median treatment duration was seen in antipsychotic use (approximately 5 years) whereas the shortest one was seen in anxiolytic use (approximately 1.7 years). Lastly, our results also pointed out that treatment duration was the longest in elderly and female patients.

In **Chapter 4** we studied the association between the exposure to commonly prescribed psychotropic medications and road traffic accident risk. A record-linkage database was used to perform a case-control study, in the Netherlands, covering the years 2000 - 2007, and using data from three different sources: pharmacy prescription data, police traffic accident data, and driving licence data. Cases were defined as drivers, who had a traffic accident that required medical assistance, between 2000 and 2007. Controls were defined as adults, who had a driving licence and had no traffic accident during the study period. Various variables, such as age, gender, medicine half-life, alcohol use were considered for the analysis. Three-thousand nine-hundred sixty-three cases and 18828 controls were included in our case-control analysis. The results of our study supported previous findings, and, in particular, showed a statistically significant association between traffic accident risk and exposure to anxiolytics [Adj. OR = 1.54 (95% CI: 1.11 - 2.15)], and SSRIs [Adj. OR = 2.03 (95% CI: 1.31 - 3.14)]. In addition, our research also demonstrated a statistically significant increased risk in chronic anxiolytic users, females and young anxiolytic users (18 to 29 years old), chronic SSRI users, females and middle-aged SSRI users (30 to 59 years old), and intermediate half-life hypnotic users.

Chapter 5 presented the outcomes of a case-crossover and case-time-control study that investigated the risk of having a motor vehicle accident while exposed to some psychotropic medication groups and compared the results to those of the case-control study. The study was performed by using the same database of the case-control study. Three-thousand seven-hundred eighty-six cases and 18089 controls were included in the case-crossover and case-time-control analyses. The case-crossover design did not show any statistically significant association between psychotropic medication exposure and motor vehicle accident risk [e.g., SSRIs - Adj. OR = 1.00 (95% CI: 0.69 - 1.46); Anxiolytics - Adj. OR = 0.95 (95% CI: 0.68 - 1.31)] whereas the case-time-control design only showed a statistically significant increased traffic accident risk in SSRI users [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)]. Our study found that case-crossover and case-time-control analyses produced different results than those of our recent case-control study (which showed an increased traffic accident risk in anxiolytic and SSRI users). We concluded that, considering that the case-crossover design is only appropriate for short-term exposures and the case-time-control design is an elaboration of this latter,

these two pharmacoepidemiological designs were probably not the most suitable ones to investigate the relation between traffic accident risk and psychotropic medications, which are often use chronically.

Chapter 6 focused on the role of SSRIs in traffic safety. The MEDLINE, PsycINFO, ScienceDirect, and SafetyLit databases were searched in order to retrieve references concerning SSRI driving related side effects, and experimental and pharmacoepidemiological research on SSRIs and fitness to drive impairment. Twenty-four articles were included in the review. Experimental studies showed that SSRIs did not constitute a high risk to traffic safety, unless used at high dosages or combined with other psychotropic substances whereas 3 of the 4 selected epidemiological studies indicated that SSRIs could constitute a hazard to traffic safety. The literature on the relationship between SSRIs and impaired fitness to drive turned out to be rather conflicting, and, therefore, our findings suggested a definite need for harmonized experimental and epidemiological studies as well as more research on the role of depression in traffic safety.

Chapter 7 described the criteria and methodology that were developed within DRUID Work Package 4 in order to assess the driving impairment risk of medications currently available on the EU market. This chapter also presented the DRUID categorisation list, which includes 1541 active substances and, thus, nearly embraces the full ATC index. The DRUID methodology and categorisation system should be used as a tool to provide reliable and consistent information for health care professionals and users regarding the impact of medications on traffic safety; therefore, it was suggested to implement the DRUID categorisation system at European level and to inform and train health care professionals in order to promote the selection of the safest medicines within each therapeutic class and improve patients' awareness on medication use and driving impairment.

Chapter 8 summarized and discussed the main findings of the studies described in the previous chapters. Briefly, our results showed that the use of psychotropic medications remained quite constant in the last years, with the exception of antidepressants and, in particular, SSRIs (increased use over time). This latter medication class was associated with the highest risk of experiencing a motor vehicle accident, even though experimental and epidemiological research did not always consistently report the above-mentioned relationship. Lastly, our work also established the criteria and methodology for the development of a categorisation system for commonly prescribed medications, based on their ability to impair fitness to drive, in order to improve traffic safety and prevent motor vehicle crashes.

We concluded that there is a need for international cooperation between countries and harmonization of data collection techniques, standards or guidelines for research into medications and driving to improve the comparability of experimental and epidemiological studies as well as larger studies to further increase the knowledge of the association between the use of certain medication groups as well as morbidities

and motor vehicle accident risks. At the EU Member States level, continuous efforts are needed among all stakeholders (e.g., pharmaceutical companies, patient representatives, national regulatory agencies, and professional organisations of health care providers) to support the implementation and use of the DRUID categorisation methodology and system in order to promote the choice of the least impairing medicines as well as proper use of driving impairing medications.

SAMENVATTING (DUTCH SUMMARY)

Verkeersongevallen veroorzaken elk jaar wereldwijd een groot aantal doden en gewonden en het is voor de volksgezondheid een uitdaging dit aantal terug te dringen (Hoofdstuk 1).

In 2003 heeft de Europese Commissie in het *White Paper on European transport policy* als doel geformuleerd en vastgesteld om het aantal verkeersdoden in het jaar 2010 te halveren, en in 2006 lanceerde de Europese Unie het EU-project: *Driving under the Influence of Drugs, Alcohol and Medicines* (DRUID), met als doel het gekozen beleid wetenschappelijk te onderbouwen om het gestelde doel in het jaar 2010 te halen (Hoofdstuk 1).

Het doel van DRUID was om te onderzoeken hoe het gebruik van alcohol, (illegale) drugs en geneesmiddelen de rijvaardigheid kan beïnvloeden, en om richtlijnen en maatregelen te ontwikkelen om rijden onder invloed te bestrijden (Hoofdstuk 1).

Dit proefschrift maakt deel uit van het DRUID project en was gericht op het beoordelen van de invloed van psychoactieve medicatie op de verkeersveiligheid. Op basis van de belangrijkste doelstelling van dit proefschrift zijn de volgende onderzoeksvragen opgesteld en beantwoord: 1) De dimensie van het gebruik van geneesmiddelen die potentieel de rijvaardigheid beïnvloeden bij verkeersdeelnemers (Hoofdstuk 2 en Hoofdstuk 3); 2) De risico's om betrokken te zijn bij een verkeersongeval wanneer mensen zijn blootgesteld aan psychoactieve geneesmiddelen (Hoofdstuk 4, Hoofdstuk 5 en Hoofdstuk 6); 3) De ontwikkeling van criteria en een methodologie voor het inrichten van een Europees classificatiesysteem voor relevante groepen geneesmiddelen die de rijvaardigheid kunnen beïnvloeden (Hoofdstuk 7).

In **Hoofdstuk 2** hebben we de resultaten gepresenteerd van een Europees onderzoek naar het gebruik van geneesmiddelen die de rijvaardigheid beïnvloeden in de verschillende landen. Vragenlijsten zijn verspreid met medewerking van twee wetenschappelijke netwerken (i.e., de *European Drug Utilization Research Group* en de *Post-Innovation Learning through Life-events of drugs*) of, indien dat mogelijk was, zijn gegevens verzameld met behulp van openbare websites. In totaal zijn 30 landen gevraagd om data aan te leveren over het gebruik van psychotrope geneesmiddelen uitgedrukt in *Defined Daily Doses* (DDD's) per 1000 inwoners per dag. Twaalf Europese landen verstrekten nationale gebruiksgegevens over de periode 2000 tot en met 2005, het tijdsbestek van deze studie. Aangezien er verschillende soorten bias in de aangeleverde data waren aangetroffen, was het niet mogelijk om een betrouwbare vergelijking tussen de landen uit te voeren en derhalve kon het gebruik van psychotrope geneesmiddelen enkel op nationaal niveau bestudeerd worden. Trends in de verschillende landen duidden op geen, of een zeer lichte toename van het gebruik van de geselecteerde groepen geneesmiddelen, met uitzondering van antidepressiva en de selectieve serotonine heropname remmers (SSRI's), waarvoor een opmerkelijke toename werd gevonden met betrekking tot het gebruik tijdens de onderzoeksperiode.

In **Hoofdstuk 3** zijn de uitkomsten van een Nederlands onderzoek naar geneesmiddelengebruik gerapporteerd, welke de periode van 2000 tot en met 2005 betrof en een indicatie gaf van de geschatte prevalentie, cumulatieve incidentie, monotherapie en combinatietherapie, en de behandelduur van veelgebruikte psychoactieve geneesmiddelen die mogelijk de rijvaardigheid negatief beïnvloeden. De data waren afkomstig uit de *IADB.nl* database, welke gegevens bevat van door apotheken verstrekte geneesmiddelen aan ongeveer 500.000 inwoners in het noorden van Nederland. Patiënten van 18 tot en met 89 jaar werden geselecteerd, en de prevalentie en cumulatieve incidentie werden berekend per 1000 patiënten per jaar, terwijl de duur van de behandeling werd geanalyseerd door middel van Kaplan-Meier overlevingscurve. De bevindingen van deze studie toonden stabiele trends aan voor zowel de prevalentie als de cumulatieve incidentie in het geselecteerde tijdsbestek; bovendien bleek na stratificatie op leeftijd en geslacht, dat de prevalentie en de cumulatieve incidentie het hoogst was bij ouderen en vrouwelijke patiënten. Combinatietherapie werd voornamelijk waargenomen bij patiënten in de leeftijd van 30 tot en met 59 jaar. De langste mediane behandelduur werd geconstateerd bij het gebruik van antipsychotica (ongeveer 5 jaar), terwijl de kortste behandelduur werd geconstateerd bij gebruik van anxiolytica (ongeveer 1.7 jaar). Ten slotte toonden onze resultaten ook aan dat de behandelduur het langst was bij ouderen en vrouwelijke patiënten.

In **Hoofdstuk 4** bestudeerden we het verband tussen de blootstelling aan veel voorgeschreven psychotrope medicatie en het risico op verkeersongevallen in Nederland. Een *record-linkage database* werd gebruikt om een case-controle studie uit te voeren over de jaren 2000 tot en met 2007, waarvoor gebruik werd gemaakt van data uit drie verschillende bronnen: medicatiegegevens van apotheken, politiegegevens over verkeersongevallen en rijbewijsgegevens. Cases werden gedefinieerd als volwassenen die in de periode van 2000 tot en met 2007 als bestuurder van een gemotoriseerd voertuig bij een verkeersongeval waren betrokken, waarbij medische hulp noodzakelijk was. Controles werden gedefinieerd als volwassenen die tijdens de periode van 2000 tot en met 2007 in het bezit waren van een geldig rijbewijs en die in diezelfde periode geen verkeersongeluk hadden. Verschillende variabelen zoals leeftijd, geslacht, halfwaardetijd van de geneesmiddelen en alcoholgebruik werden gebruikt voor de analyse. Drieduizendnegenhonderddrieënzestig cases en 18.828 controles werden geïncludeerd in onze case-controle analyse. De resultaten van onze studie ondersteunen eerdere bevindingen, en toonden een statistisch significant verband aan tussen het risico op verkeersongevallen en de blootstelling aan anxiolytica [Adj. OR = 1.54 (95% CI: 1.11 - 2.15)], en SSRI's [Adj. OR = 2.03 (95% CI: 1.31 - 3.14)]. Bovendien werd een statistisch significant verhoogd risico aangetroffen bij personen die anxiolytica langdurig gebruiken, vrouwen en gebruikers in de leeftijd van 18 tot en met 29 jaar; personen die langdurig SSRI's gebruiken, vrouwen en gebruikers van middelbare leeftijd (30 tot en met 59 jaar) en personen die hypnotica met een middellange eliminatiehalfwaardetijd gebruiken.

In **Hoofdstuk 5** worden de uitkomsten gepresenteerd van een *case-crossover* en *case-time-control* studie, waarmee wij het risico op het betrokken zijn bij een verkeersongeval tijdens blootstelling aan sommige psychotrope geneesmiddelen hadden onderzocht en waarvan de resultaten werden vergeleken met die van de traditionele *case-control* studie. Het onderzoek werd uitgevoerd door gebruik te maken van dezelfde database. Drieduizendzevenhonderdzesentachtig cases en 18.089 controles werden opgenomen in de *case-crossover* en *case-time-control* analyses. Het *case-crossover* design liet geen statistisch significant verband zien tussen de blootstelling aan psychotrope geneesmiddelen en het risico op verkeersongevallen [e.g., SSRI's - Adj. OR = 1.00 (95% CI: 0.69 - 1.46); anxiolytica - Adj. OR = 0.95 (95% CI: 0.68 - 1.31)], het *case-time-control* design daarentegen, toonde enkel een statistisch significante toename van het risico op verkeersongevallen bij gebruikers van SSRI's [Adj. OR = 1.16 (95% CI: 1.01 - 1.34)]. Uit ons onderzoek bleek dat de *case-crossover* en *case-time-control* analyses andere resultaten geven dan de resultaten van onze traditionele *case-control* studie (welke een verhoogd risico op verkeersongevallen aantoonde voor gebruikers van anxiolytica en SSRI's). Wij concludeerden dat deze twee farmaco-epidemiologische designs waarschijnlijk niet het meest geschikt waren om de relatie tussen het risico op verkeersongevallen en het gebruik van psychotrope geneesmiddelen, welke vaak langdurig worden gebruikt, te onderzoeken, aangezien het *case-crossover* design enkel geschikt is voor korte termijn blootstelling en het *case-time-control* design een verfijnde uitwerking is van de laatstgenoemde.

Hoofdstuk 6 richt zich op de rol van SSRI's voor de verkeersveiligheid. De MEDLINE, PsycINFO, ScienceDirect, en SafetyLit databases werden gebruikt om artikelen te vinden die betrekking hadden op de effecten van SSRI's op het vermogen om een gemotoriseerd voertuig te besturen. Er is gezocht naar experimentele en farmaco-epidemiologische studies. Vierentwintig artikelen werden geselecteerd voor de review. Experimentele studies hebben aangetoond dat gebruik van SSRI's geen verhoogd risico vormt voor de verkeersveiligheid, tenzij er hoge doseringen worden gebruikt of indien er sprake is van een combinatie met andere psychotrope stoffen. Drie van de vier geselecteerde epidemiologische studies toonden daarentegen aan, dat SSRI's een gevaar voor de verkeersveiligheid kunnen vormen. De literatuur bleek nogal tegenstrijdig te zijn wat betreft de relatie tussen het gebruik van SSRI's en verminderde rijvaardigheid, en daarom concluderen we dat er enerzijds een duidelijke behoefte bestaat voor meer geharmoniseerde experimentele en epidemiologische studies, alsmede voor meer onderzoek naar de betekenis van depressie voor de verkeersveiligheid.

Hoofdstuk 7 beschrijft de criteria en methodologie zoals die zijn ontwikkeld binnen DRUID Work Package 4 om het beoordelen van de risico's van de thans op de Europese markt beschikbare geneesmiddelen op het vermogen een gemotoriseerd voertuig te kunnen besturen mogelijk te maken. In dit hoofdstuk wordt ook de DRUID categorisatielijst gepresenteerd, die 1541 werkzame stoffen bevat, en derhalve bijna de volledige ATC-index behelst. De DRUID methodologie en het categorisatiesysteem

dienen te worden gebruikt als een middel om professionals in de gezondheidszorg en personen die geneesmiddelen gebruiken te voorzien van betrouwbare en consistente informatie over de invloed van geneesmiddelen op de verkeersveiligheid. Daarom werd voorgesteld om het categorisatiesysteem van DRUID op Europees niveau te implementeren en om professionals in de gezondheidszorg te informeren over en te trainen in het gebruik van het systeem om op die manier de selectie van de meest veilige geneesmiddelen binnen elke therapeutische klasse te bevorderen en om de bewustwording van patiënten over de invloed van het gebruik van geneesmiddelen op de rijvaardigheid te verbeteren.

Hoofdstuk 8 vat en bediscussieert de meest belangrijke bevindingen van de verschillende studies uit de hoofdstukken samen. Uit onze resultaten bleek dat het gebruik van psychotrope geneesmiddelen de afgelopen jaren vrij constant is gebleven, met uitzondering van antidepressiva, en SSRI's in het bijzonder. Deze laatste groep geneesmiddelen werd geassocieerd met het hoogste risico op het krijgen van een verkeersongeval met een gemotoriseerd voertuig, hoewel experimenteel en epidemiologisch onderzoek deze relatie niet altijd consistent aan het licht heeft gebracht. Tot slot heeft ons onderzoek ook bijgedragen aan de ontwikkeling van een categorisatiesysteem om geneesmiddelen die veel worden voorgeschreven te ordenen in risicocategorieën. De categorieën zijn gebaseerd op de invloed die geneesmiddelen hebben op het vermogen om een gemotoriseerd voertuig te besturen. Op deze manier kan de verkeersveiligheid worden bevorderd en kunnen verkeersongevallen worden voorkomen.

We kwamen tot de conclusie dat er behoefte is aan internationale samenwerking tussen landen en harmonisatie van technieken betreffende gegevensverzameling, richtlijnen voor onderzoek naar geneesmiddelen en het besturen van een gemotoriseerd voertuig die de vergelijkbaarheid van de experimentele en epidemiologische studies verbeteren. Meer onderzoek is nodig, om meer kennis te krijgen over de relatie tussen het gebruik van geneesmiddelen of het hebben van ziektes en de risico's op verkeersongevallen met gemotoriseerde voertuigen. Op het niveau van de Europese lidstaten zijn tussen alle betrokken partijen (e.g., farmaceutische bedrijven, vertegenwoordigers van patiënten, de nationale regelgevende instanties en beroepsorganisaties van zorgverleners) continue inspanningen nodig om de implementatie en het gebruik van de DRUID categorisatie methodiek en -systeem te ondersteunen, om zo de keuze voor de minst rijgevaarlijke geneesmiddelen te bevorderen, en tevens het correct gebruik van geneesmiddelen die de rijvaardigheid negatief beïnvloeden te ondersteunen.

RIASSUNTO DELLA TESI IN ITALIANO (ITALIAN SUMMARY)

Gli incidenti stradali rappresentano una vera e propria emergenza sanitaria in quanto causano, ogni anno, in tutto il mondo, un alto numero di eventi mortali e invalidanti (Capitolo 1).

Nel 2003, nel *White Paper on European Transport Policy*, l'Unione Europea ha fissato un traguardo europeo di riduzione del 50% delle vittime della strada entro l'anno 2010, e, successivamente, nel 2006, ha lanciato il progetto *Driving under the Influence of Drugs, Alcohol and Medicines* (DRUID) con lo scopo di ottenere un sostegno concreto nell'ambito della politica europea dei trasporti e di raggiungere quindi l'obiettivo di sicurezza stradale previsto per il 2010 (Capitolo 1).

In linea generale, DRUID si propone di studiare l'influenza di alcol, droghe e medicinali sull'idoneità alla guida e di stabilire linee guida e misure di sicurezza per combattere la guida sotto l'effetto di sostanze stupefacenti o psicotrope (Capitolo 1).

Questa tesi di dottorato fa parte del progetto DRUID ed è finalizzata a valutare l'impatto di alcune classi di medicinali sulla guida sicura. Le seguenti problematiche sono state prese in considerazione nell'ambito del nostro lavoro di ricerca: 1) L'utilizzo, da parte della popolazione generale, di farmaci potenzialmente pericolosi per la guida (Capitolo 2 e Capitolo 3); 2) Il rischio di essere coinvolti un incidente stradale in seguito all'utilizzo di farmaci psicoattivi (Capitolo 4, Capitolo 5 e Capitolo 6); 3) Lo sviluppo di una metodologia e criteri standard al fine di stabilire un sistema europeo di classificazione di medicinali in merito a possibili effetti negativi sull'idoneità alla guida (Capitolo 7).

Nel **Capitolo 2** vengono presentati i risultati di uno studio europeo riguardante l'uso di farmaci potenzialmente pericolosi per la guida da parte della popolazione generale. Lo studio si è avvalso di questionari che sono stati svilippati e quindi distribuiti attraverso due reti scientifiche (i.e., l'*European Drug Utilization Research Group* ed il *Post-Innovation Learning through Life-events of drugs*) o, quando possibile, i dati sono stati raccolti direttamente tramite siti web pubblici (es, Paesi Scandinavi). Trenta paesi europei sono stati invitati a fornire i loro dati nazionali riguardanti l'uso farmaci psicotropi, presentati in D*efined Daily Doses* (DDD), per 1000 abitanti, per giorno, e riferiti al periodo compreso tra il 2000 ed il 2005. I dati richiesti sono stati forniti da docidi dei trenta paesi inizialmente contattati. Dal momento che diversi tipi di bias hanno influenzato la validità dei dati forniti, non è stato possibile fare un confronto approfondito tra i diversi paesi europei riguardante l'uso delle categorie terapeutiche selezionate e, di conseguenza, i trend di utilizzo di questi medicinali sono stati esaminati solamente a livello nazionale. In generale, l'analisi dei dati forniti ha dimostrato che, nella maggior parte dei paesi europei, non è avventuto alcun aumento significativo del consumo dei farmaci presi in considerazione, ad eccezione degli antidepressivi (gruppo totale) e degli inibitori selettivi della ricaptazione della

serotonina (SSRI) che sono stati caraterizzati da incrementato utilizzo durante tutto il periodo preso in considerazione.

Il **Capitolo 3** riporta i risultati di uno studio riferito alla prevalenza, incidenza cumulativa, monoterapia e politerapia, e durata media della prescrizione di farmaci psicoattivi che possono compromettere la capacità di guida. Il periodo preso in considerazione è compreso tra il 2000 e il 2005 ed i dati sono riferiti ai Paesi Bassi. In particolare, i dati sono stati ottenuti dal database *IADB.nl* che si basa sulla distribuzione di farmaci da prescrizione tramite farmacie aperte al pubblico ed ha una copertura pari ad una popolazione di circa 500000 abitanti, residenti nella parte nord dei Paesi Bassi. In questo studio sono stati inclusi tutti i pazienti di età compresa tra i 18 e 89 anni e, di conseguenza, tutti quei soggetti che, teoricamente, sono in possesso di una patente di guida. La prevalenza e l'incidenza cumulativa sono state calcolate per 1000 pazienti all'anno mentre la durata del trattamento è stata analizzata tramite il metodo di Kaplan-Meier (analisi della sopravvivenza). I risultati di questo studio hanno dimostrato che, nel periodo 2000-2005, la prevalenza e l'incidenza cumulativa hanno seguito un andamento stabile. Per quanto concerne le stratificazioni della popolazione per fasce d'età e sesso, i dati hanno invece evidenziato che la prevalenza e l'incidenza cumulativa sono state tra le più alte nel caso di pazienti anziani e di sesso femminile. La politerapia è stata principalmente osservata in pazienti di età compresa tra i 30 ed i 59 anni. Per quanto riguarda la durata media delle prescrizioni, gli antipsicotici hanno evidenziato la più lunga durata di trattamento (circa 5 anni) mentre la più breve è stata osservata nel caso degli ansiolitici (circa 1.7 anni). Per finire, i nostri risultati hanno anche rivelato che i pazienti anziani e di sesso femminile sono le fasce che si avvalgono più spesso di trattamenti farmacologici di lunga durata.

Nel **Capitolo 4** abbiamo studiato l'associazione tra l'esposizione a farmaci psicotropi comunemente prescritti ed il rischio di subire un incidente stradale. Il metodo d'indagine utilizzato è stato il caso-controllo. Lo studio si è basato su dati olandesi, relativi agli anni 2000 - 2007, e provenienti da tre diverse fonti: dati di distribuzione di farmaci da prescrizione tramite farmacie aperte al pubblico (fonte: PHARMO database), dati relativi ad incidenti stradali registrati dalla polizia (fonte: database del ministero olandese delle infrastrutture e dell'ambiente - DVS) e, da ultimo, dati riferiti al possesso della patente di guida (fonte: database della motorizzazione civile olandese - RDW). I dati provenienti dalle tre fonti precedentemente citate sono stati raccolti in un unico database, ottenuto tramite la tecnica del record linkage deterministico. Il gruppo dei casi è stato rappresentato da soggetti coinvolti in incidenti stradali che hanno necessitato di assistenza medica e che sono avvenuti tra il 2000 e il 2007. Il gruppo dei controlli è stato rappresentato da soggetti adulti, in possesso di una patente di guida, che non hanno subito alcun incidente stradale durante il periodo preso in considerazione. Variabili quali età, sesso, emivita del farmaco ed uso di alcol sono state prese in considerazione durante l'analisi statistica dei dati. 3963 casi e 18828 controlli sono stati inclusi in questo studio. I risultati emersi dalla nostra analisi

statistica hanno confermato i risultati riportati dalla letteratura scientifica in materia e, in particolare, hanno evidenziato un'associazione statisticamente significativa tra il rischio di essere coinvolti in incidenti stradali in seguito all'esposizione a farmaci ansiolitici [OR aggiustati = 1.54 (IC 95%: 1.11 - 2.15)] e agli inibitori selettivi della ricaptazione della serotonina [OR aggiustati = 2.03 (IC 95%: 1.31 - 3.14)]. Da ultimo, la nostra ricerca ha anche dimostrato un maggiore rischio di incidenti stradali nel caso di utilizzo cronico di ansiolitici nonché nel caso di pazienti di sesso femminile e pazienti di giovane età trattati con farmaci ansiolitici (18 ai 29 anni), nel caso di utilizzo cronico di SSRI, pazienti di sesso femminile e pazienti di giovane età trattati con questo tipo di antidepressivi (età compresa tra i 30 ed i 59 anni) ed infine nel caso di pazienti esposti ad ipnotici ad emivita intermedia.

Il **Capitolo 5** presenta i risultati di uno studio *case-crossover* e di uno studio *case-time-control* che hanno esaminato il rischio di essere coinvolti in un incidente automobilistico in seguito all'esposizione ad alcuni gruppi di farmaci psicotropi. I risultati di entrambi gli studi sono stati poi confrontati con quelli ottentuti tramite lo studio caso-controllo presentato nel Capitolo 4. Entrambi gli studi sono stati eseguiti utilizzando lo stesso database impiegato nello studio caso-controllo. 3786 casi e 18089 controlli sono stati inclusi nel *case-crossover* e *case-time-control*. Il *case-crossover* non ha mostrato alcuna associazione statisticamente significativa tra l'esposizione a farmaci psicotropici ed il rischio di essere coinvolti in un incidente stradale [es, SSRI - OR aggiustati = 1.00 (IC 95%: 0.69 - 1.46); Ansiolitici - OR aggiustati = 0.95 (IC 95%: 0.68 - 1.31)]. Per quanto riguarda invece lo studio *case-time-control*, un aumento statisticamente significativo del rischio di incidenti stradali è stato osservato solo nel caso di pazienti esposti ad SSRI [OR aggiustati = 1.16 (IC 95%: 1.01 - 1.34)]. Per finire, la nostra ricerca ha evidenziato che le analisi statistiche effettuate con i metodi *case-crossover* e *case-time-control* hanno prodotto risultati diversi rispetto a quelli osservati nello studio caso-controllo (che, in linea generale, ha evidenziato un maggior rischio di incidenti stradali in pazienti esposti ad ansiolitici e SSRI). Di conseguenza, la nostra ricerca si è conclusa osservando che, dal momento che il disegno statistico degli studi *case-crossover* è appropriato solo se riferito ad esposizioni di breve durata mentre il disegno statistico degli studi *case-time-control* può essere considerato un'elaborazione del *case-crossover*, queste due tipologie di studi epidemiologici non sono probabilmente appropriate al fine di studiare la relazione tra il rischio di incidenti stradali e l'utilizzo di farmaci psicotropi, che, come riportato nel Capitolo 3, sono spesso usati in maniera cronica.

Il **Capitolo 6** illustra la relazione tra gli SSRI e la guida sicura. Database quali MEDLINE, PsycINFO, ScienceDirect eSafetyLit sono stati presi in considerazione al fine di ottenere publicazioni scientifiche relative agli effetti collaterali potenzialmente pericolosi per la guida causati da questo gruppo di antidepressivi ed i risultati principali della ricerca sperimentale ed epidemiologica relativi all'uso degli SSRI e l'idoneità alla guida. Ventiquattro articoli sono stati esaminati in questo capitolo. In

linea generale, gli studi sperimentali hanno dimostrato che gli SSRI non costituiscono un rischio elevato per la sicurezza stradale, tranne nel caso in cui vengano utilizzati ad alti dosaggi o in combinazione con altre sostanze psicotrope mentre, al contrario, 3 dei 4 studi epidemiologici selezionati hanno indicato che gli SSRI possono rappresentare un pericolo reale per la guida sicura. In conclusione, la letteratura scientifica in merito agli SSRI e l'idoneità alla guida si è rivelata piuttosto conflittuale, e, di conseguenza, la nostra ricerca ha sottolineato sia la necessità di standardizzare la metodologia utilizzata in studi sperimentali ed epidemiologici sia l'importanza di portare a termine ricerche più approfondite sul ruolo di questi antidepressivi e della depressione nell'ambito della sicurezza viaria.

Il **Capitolo 7** descrive i criteri e la metodologia che sono stati sviluppati dal DRUID *Work Package 4* al fine di valutare l'influenza sull'idoneità alla guida della maggior parte dei farmaci attualmente disponibili sul mercato europeo. Questo capitolo presenta anche la categorizzazione di 1541 principi attivi che è stata sviluppata dal gruppo di lavoro del DRUID *Work Package 4* seguendo i criteri e la metodologia precedentemente citati. Lo scopo ultimo del lavoro presentato in questo capitolo è stato quello di fornire uno strumento scientifico atto a dispensare informazioni affidabili e coerenti circa il ruolo dei farmaci sulla sicurezza stradale rivolte agli operatori sanitari ed ai pazienti. Di conseguenza, gli esperti coinvolti nel *Work Package 4* hanno sottolineato l'importanza di implementare a livello europeo il sistema di categorizzazione proposto dal progetto DRUID, di informare ed educare gli operatori sanitari al fine di promuovere la selezione di farmaci più sicuri all'interno di ogni classe terapeutica e di migliorare la consapevolezza dei pazienti circa l'uso di tutti quei farmaci che possono avere un'influenza negativa sull'idoneità alla guida.

Nel **Capitolo 8** vengono riassunti e discussi i principali risultati degli studi descritti nei capitoli precedenti. In breve, la nostra ricerca ha dimostrato che l'utilizzo di farmaci psicotropi è rimasto relativamente costante negli ultimi anni, con l'eccezione degli antidepressivi e, in particolare, degli SSRI. Questa classe di farmaci è risultata essere associata ad un maggior rischio di subire un incidente automobilistico, anche se è opportuno ricordare che i risultati di studi sperimentali ed epidemiologici non hanno dimostrato in modo coerente la relazione da noi osservata. Da ultimo, il nostro lavoro ha proposto una metodologia standard per lo sviluppo di un sistema di classificazione relativo ai farmaci da prescrizione ed alla loro capacità di influenzare l'idoneità alla guida al fine di migliorare la sicurezza stradale e prevenire il maggior numero possibile di incidenti automobilistici.

La nostra ricerca si è conclusa sottolineando l'importanza di istituire una solida cooperazione internazionale ed armonizzare le tecniche di raccolta dati, norme e linee guida per la ricerca sull'uso di farmaci e guida sicura al fine di migliorare la comparabilità di studi sperimentali ed epidemiologici nonché di portare a termine studi più approfonditi circa il ruolo di farmaci e disturbi psichiatrici in tema di sicurezza stradale. Per quanto concerne lo scenario europeo, la nostra ricerca ha sottolineato

che, a livello degli Stati Membri, l'impegno delle varie parti coinvolte (ad esempio, aziende farmaceutiche, associazioni nazionali di pazienti, agenzie regolatorie nazionali ed ordini professionali di operatori sanitari) sarebbe decisamente fondamentale ed auspicabile al fine di implentare la metodologia ed il sistema di categorizzazione proposti dal progetto DRUID e quindi di promuovere la scelta di farmaci più sicuri ed il corretto utilizzo di quelle categorie terapeutiche che possono compromettere l'idoneità alla guida.

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"I determined never to stop until I had
come to the end and achieved my purpose"
Dr. Livingstone

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LIST OF PUBLICATIONS - INTERNATIONAL

Ravera S, Hummel SA, Stolk P, Heerdink RE, de Jong-van den Berg LTW, de Gier JJ. The use of driving impairing medicines: A European survey. European Journal of Clinical Pharmacology 2009; 65:1139-1147.

Ravera S, Visser ST, de Gier JJ, de Jong-van den Berg LTW. Prevalence, cumulative incidence, monotherapy and combination therapy, and treatment duration of frequently prescribed psychoactive medications in the Netherlands: Retrospective database analysis for the years 2000 to 2005. Clinical Therapeutics 2010; 32(14):2457-2466.

Ravera S, van Rein N, de Gier JJ, de Jong-van den Berg LTW. Road traffic accidents and psychotropic medication use in the Netherlands: A case-control study. British Journal of Clinical Pharmacology 2011; 72(3): 505-513.

Ravera S, van Rein N, de Gier JJ, de Jong-van den Berg LTW. A comparison of pharmacoepidemiological study designs in medication use and traffic safety research. (*Submitted*)

Ravera S, Ramaekers JG, de Jong-van den Berg LTW, de Gier JJ. Are SSRIs safe for drivers? What is the evidence? (*Submitted*)

Ravera S and Monteiro SP, de Gier JJ, Van der Linden T, Gómez-Talegón T, Alvarez FJ, and the DRUID WP4 Partners. A European approach to categorizing medicines for fitness to drive: Outcomes of the DRUID project. *(Accepted for publication in British Journal of Clinical Pharmacology)*

LIST OF PUBLICATIONS - DRUID DELIVERABLES

Ravera S, de Gier JJ. Prevalence of psychoactive substances in the general population - DRUID Deliverable 2.1.1.

Ravera S, de Gier JJ. Relative accident risk of patients using psychotropic medicines in the Netherlands - DRUID Deliverable 2.3.1.

De Gier JJ, Ravera S, Monteiro SP, Alvarez FJ, in cooperation with Work Package 4 Partners. Establishment of criteria for a European categorisation system for medicines and driving - DRUID Deliverable 4.2.1.

Gómez-Talegón T, Fierro I, Del Río C, Alvarez FJ, Ravera S, Monteiro SP, de Gier JJ, Van der Linden T, Mallaret M, Mercier-Guyon C, in cooperation with Work Package 4 Partners. Establishment of framework for classification/categorisation and labelling of medicinal drugs and driving - DRUID Deliverable 4.3.1.

Margaritis D, Touliou K, Ravera S, Monteiro S, de Gier JJ, Boets S, Meesman U, Alvarez FJ, in cooperation with Work Package 7 Partners. Training manual for physicians and pharmacists on medicinal drugs and driving - DRUID Deliverable 7.4.1.

Touliou K, Margaritis D, Spanidis P, Monteiro S, Ravera S, de Gier JJ, Boets S, Meesman U, Tant M, Legrand SA, Van der Linden T, Verstraete A, Fierro I, Gómez-Talegón MT, Martín Lara L, Alvarez FJ, in cooperation with Work Package 7 Partners. Report on the implementation, evaluation and new technologies of practice guidelines and information materials - DRUID Deliverable 7.4.2.

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2011

Mookhoek, EJ. Patterns of somatic disease in residential psychiatric patients.
Supervisors: Prof. dr. AJM Loonen, Prof. dr. JRBJ Brouwers, Prof. dr. JEJM Hovens.

Vehof, J. Personalized pharmacotherapy of psychosis - Clinical and pharmacogenetic approaches.
Supervisors: Prof. dr. H Snieder, Prof. dr. RP Stolk;
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2010

De Smedt, RHE. Patients' perceptions of adverse drug events and their management in heart failure - Towards a better understanding of the perspectives of the patients.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. T Jaarsma, Prof. dr. K van der Meer;
Co-supervisor: Dr. P Denig.

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Supervisor: Prof. dr. JRBJ Brouwers;
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Van Vliet-Ostaptchoul, JV. Revealing the genetic roots of obesity and type 2 diabetes.
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Connolly, MP. The economics of assisted reproduction; costs and consequences of fertility treatments.
Supervisors Prof. dr. MJ Postma, Prof. dr. W Ledger.

Voorham, J. Assessing cardiometabolic treatment quality in general practice.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. BHR Wolffenbuttel;
Co-supervisor: Dr. P Denig.

De Vries, R. Health-economics of interventions aimed at infectious diseases: Dynamic modeling inevitable for reliable medical decision making.
Supervisors: Prof. dr. MJ Postma, Prof. dr. LTW de Jong-van den Berg.

Schorr, SG. Drug safety in patients with psychotic disorders.
Supervisors: Prof. dr. K Taxis, Prof. dr. JRBJ Brouwers;
Co-supervisors: Dr. R Bruggeman, Dr. CJ Slooff.

2009

Van Doormaal, JE. Medication errors and adverse drug events in hospitalised patients - Methodological issues and computerised intervention.
Supervisor: Prof. dr. FM Haaijer-Ruskamp;
Co-supervisors: Dr. PGM Mol, Dr. JGW Kosterink, Dr. PLA van den Bemt.

Beinema, MJ. The optimalization of coumarin anticoagulant therapy: Pharmacogenetics and computer assisted dose finding.
Supervisors: Prof. dr. JRBJ Brouwers, Prof. dr. J van der Meer;
Co-supervisor: Dr. B Wilffert.

Boersma, C. Health economics of cardiovascular and renal disease prevention.
Supervisors: Prof. dr. MJ Postma, Prof. dr. LTW de Jong-van den Berg, Prof. dr. PE de Jong;
Co-supervisor: Dr. T Gansevoort.

Vroom, F. Drug use in pregnancy - Exploring the field of DMARDs in pregnancy.
Supervisors: Prof. dr. LTW de Jong-van den Berg, Prof. dr. JRBJ Brouwers, Prof. dr. MAFJ van de Laar;
Co-supervisor: Dr. HEK de Walle.

2008

Van Hulst, M. Health economics of blood transfusion safety.
Supervisors: Prof. dr. MJ Postma, Prof. dr. CTh Smit Sibinga.

2007

Grigoryan, L. Self-medication with antibiotics in Europe and its determinants.
Supersvisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. JE Degener.

Sturm, HB. Influencing physician prescribing in an international context: The role of systems, policies and patients.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. WH van Gilst.

Greving, J. Trends in cardiovascular drug prescribing in Dutch general practice: Role of patient and physician related characteristics.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. D de Zeeuw;
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De Roos, MAJ. Diagnostics and prognostics in ductal carcinoma in situ of the breast.
Supervisor: Prof. dr. T Wiggers;
Co-supervisor: Dr. GH de Bock.

2006

Dobre, D. Treatment of heart failure and patient outcomes in real life.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. R Sanderman, Prof. dr. DJ van Veldhuisen;
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2005

Houweling, ST. Taakdelegatie in de eerste en tweedelijns diabeteszorg - Resultaten van de DISCOURSE studies.
Supervisor: Prof. dr. B Meyboom-de Jong;
Co-supervisor: Dr. HJ Bilo.

Mol, PGM. The quest for optimal antimicrobial therapy.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. ROB Gans, Prof. dr. JE Degener.

Bergman, GJD. Manipulative therapy for shoulder complaints in general practice.
Supervisors: Prof. dr. B Meyboom-de Jong, Prof. dr. K Postema;
Co-supervisors: Dr. JS Winters, Dr. GJMG van der Heijden.

2004

Baarveld, F. Sportgerelateerde problemen in de huisartspraktijk.
Supervisor: Prof. dr. B Meyboom-de Jong;
Co-supervisors: Dr. J Schuling, Dr. GC van Enst.

Ubink-Veltmaat, LJ. Type 2 diabetes mellitus in a Dutch region - Epidemiology and shared care.
Supervisor: Prof. dr. B Meyboom-de Jong;
Co-supervisor: Dr. HJG Bilo.

Kasje, WN. Implementing joint treatment guidelines to improve prescribing in general practice.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. PA de Graeff;
Co-supervisor: Dr. P Denig.

Groenier, KH. Empirical classification of shoulder complaints.
Supervisor: Prof. dr. B Meyboom-de Jong;
Co-supervisors: Dr. WH van Schuur, Dr. JC Winters.

Wachters-Kaufmann, CSM. Voorlichting aan CVA-patiënten en hun centrale verzorgers.
Supervisors: Prof. dr. B Meyboom-de Jong;
Co-supervisor: Dr. J Schuling.

2002

Pont, LG. Assessing the quality of prescribing in general practice.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. WH van Gilst, Prof. dr. T van der Molen.

2001

Bemelmans, WJE. Prevention of coronary heart disease by nutritional interventions. Impact of nutritional education in groups and supplementation with alpha-linolenic acid.
Supervisor: Prof. dr. B Meyboom-de Jong;
Co-supervisors: Dr. JF May, Dr. J Broer, Dr. EJM Feskens, Dr. FW Siero, Dr. AJ Smit.

2000

Veninga, CCM. Improving prescribing in general practice.
Supervisor: Prof. dr. FM Haaijer-Ruskamp;
Co-supervisor: Dr. P Denig.

1999

Veehof, LJG. Polypharmacy in the elderly.
Supervisors: Prof. dr. B Meyboom-de Jong, Prof. dr. FM Haaijer-Ruskamp.

1998

De Vries, SO. Management strategies for intermittent claudication.
Supervisor: Prof. dr. MGM Hunink;
Co-supervisor: Dr. JB Wong.

1997

Bosch, JL. Outcome assessment of the percutaneous treatment of iliac artery occlusive disease.
Supervisors: Prof. dr. MGM Hunink, Prof. dr. WPTM Mall, Prof. dr. L Koopmans.

Dijkers, FW. Repeat prescriptions: a study in general practice in the Netherlands.
Supervisors: Prof. dr. B Meyboom-de Jong, Prof. dr. FM Haaijer-Ruskamp, Prof. dr. AF Casparie.

1995

Van Trigt, AM. Making news about medicines.
Supervisors: Prof. dr. TFJ Tromp, Prof. dr. FM Haaijer-Ruskamp.

Boerkamp, E. Assessing professional services quality: An application in health care.
Supervisors: Prof. dr. JC Reuijl, Prof. dr. FM Haaijer-Ruskamp.

1994

Denig, P. Drug choice in medical practice: Rationales, routines, and remedies.
Supervisors: Prof. dr. FM Haaijer-Ruskamp, Prof. dr. H Wesseling.

1992

De Jong-van den Berg, LTW. Drug utilization studies in pregnancy: What can they contribute to safety assessment?
Supervisors: Prof. dr. MNG Dukes, Prof. dr. H Wesseling;
Co-supervisor: Dr. FM Haaijer-Ruskamp.

1991

Zijlstra, IF. De regionaal klinisch farmacoloog.
Supervisors: Prof. dr. H Wesseling, Prof. dr. FWJ Gribnau, Prof. dr. C van Weel;
Co-supervisors: Dr. FM Haaijer-Ruskamp, Dr. H Wollersheim.