Road traffic accidents and psychotropic medication use in the Netherlands: Results from a case-control and a case-crossover study

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Abstract

Background
The consumption of psychoactive medications can influence people’s motor and cognitive performances and, therefore, impair the ability to drive safely.

Aims
To evaluate the risk of having a motor vehicle accident (MVA) while exposed to psychotropic medications by means of a case-control and a case-crossover study, and to compare the outcomes of these two studies in order to evaluate the effects of different study designs on the MVA risk estimate.

Methods
A record-linkage database was used to perform a case-control and a case-crossover study, in the Netherlands, between 2000 and 2007. The data came from three sources: a pharmacy prescription database, a police traffic accident database, and a driving license database. The following psychotropic medicine groups were examined: antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants stratified into selective serotonin reuptake inhibitors (SSRIs) and other antidepressants.

Results
3963 cases and 18828 controls were included in the case-control analysis. A significant association was found between MVA risk and exposure to anxiolytics [Adj. odds ratio (OR) = 1.54 (95%CI: 1.11-2.15)], and SSRIs [Adj. OR=2.03 (95%CI: 1.31-3.14)]. In the case-crossover analysis, 3786 cases were included. This latter did not show any statistically significant association between psychotropic medication exposure and MVA 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)].

Discussion and conclusions
Case-control and case-crossover analyses showed different results. 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, it can be concluded that this approach is probably not the most suitable one to investigate the relation between MVA risk and psychotropic medications, which, on the contrary, are often used chronically.

Introduction
Driving a motor vehicle is a complex task that involves several psychomotor and cognitive skills (de Gier, Alvarez, Mercier-Guyon, & Verstraete, 2009). Some commonly prescribed medications can influence cognitive and psychomotor functions and, therefore, impair the ability to drive safely (de Gier et al., 2009; Drummer, 2008).
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 (Orriols et al., 2009). The results of these studies have frequently shown a positive association between the risk of having a motor vehicle accident (MVA) and the exposure to certain groups of psychoactive medications (e.g., benzodiazepines, benzodiazepine-like substances, tricyclic antidepressants) (Orriols et al., 2009; Raes, van den Neste, & Verstraete, 2008; Walsh, de Gier, Christopherson, & Verstraete, 2004) 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 MVA within the first week of BZD use (Hemmelgarn, Suissa, Huang, Boivin, & Pinard, 1997), but, on the contrary, in 1998, the case-crossover study of Barbone et al. found no increased traffic accident risk associated to BZD use in individuals ≥ 65 years old (Barbone et al., 1998). A similar discrepancy was also described in the study of Hebert et al. which showed an increased MVA risk 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 (Hebert, Delaney, Hemmelgarn, Levesque, & Suissa, 2007). The divergences in the outcomes of the above-mentioned pharmacoepidemiological studies could be explained by the use of different study designs, namely the case-control and the case-crossover designs.

**Aims**
The aim of this study was to evaluate the risk of having an MVA while exposed to some psychotropic medication groups (which are known to be related to driving impairment (Barbone et al., 1998; Movig et al., 2004; Orriols et al., 2009; Walsh et al., 2004)) by means of a case-control as well as a case-crossover study, and to compare the results in order to evaluate whether the outcomes of these two pharmacoepidemiological designs would lead to analogous traffic accident risk estimates.

**Methods**

**Data sources**
A record-linkage database was used to perform a case-control and case-crossover study in the Netherlands, between 2000 and 2007. In brief, a Trusted Third Party performed the linkage between the PHARMO (PHARMO Institute), the Dutch Traffic and Navigation Authority (DVS) (Dienst Verkeer en Scheepvaart - DVS), and the Dutch Road Transport Authority (RDW) (Rijks Dienst Wegverkeer - RDW) databases, which provided pharmacy prescription data (in particular, the following details were available: dispensing date, the prescribed dosage, the dispensed quantity and the estimated duration of use), traffic accident data, and driving license records, respectively.

**Case-control study – Definition, and inclusion and exclusion criteria**
Cases were defined as adults (≥ 18 years), who had a traffic accident between 2000 and 2007 and were driving, and received medical assistance. Cases were restricted to those subjects who were found negative for alcohol use (if no data on alcohol use was available, cases were excluded). Controls were defined as adults (≥ 18 years), who had a driving license and had no traffic accident during the study period. Four controls were matched for each case; the matching was by sex, age within five years, postcode, and date of the accident.
**Case-crossover study – Definition, and inclusion and exclusion criteria**

Cases were defined as drivers who had an MVA attended by the Dutch police during the above-mentioned 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 was available. Lastly, subjects were excluded if their medication history in the 18 months preceding the index date was not available. 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 in order to control for possible seasonal and weather variations which could play a causal role in traffic accidents.

**Selected medication groups**

The following psychotropic medication groups were included: antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics and sedatives (ATC code: N05C), antidepressants stratified in selective serotonin re-uptake inhibitors (SSRIs) (ATC code: N06AB) and other antidepressants [i.e., non-selective monoamine re-uptake inhibitors (ATC code: N06AA); monoamine oxidase A inhibitors (MAOs) (ATC code: N06AG); other antidepressants (ATC codes: N06AF and N06AX)].

**Medication exposure**

Cases and controls (controls: case-control study only) were considered to be exposed if the medication was used during the week before the accident date (i.e., index date). Exposure was considered to start the day after the dispensing date. If the medication exposure ended 2 days before the index date, the subjects were still considered as exposed. Mono-therapy 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.

In order to evaluate the effects of the user type on the results of the case-crossover design, 2 types of exposure were examined: 1) All exposed individual: subjects who were exposed to a driving impairing medication in the week before the index date and also used the same medication in the 6 months before the index date (i.e., subjects who used a psychotropic medicine on a regular basis during the 6 months preceding the traffic accident); 2) Acute users: subjects who used a driving impairing medication in the week before the index date, but did not receive any prescriptions for the same medication in the 6 months before the initiation of the therapy (i.e., subjects who initiated their therapy in the week before the MVA and were not exposed to this medication in the 6 months before the initiation of the therapy).

**Statistical analysis**

The statistical analysis was performed by using the statistical package SPSS (SPSS 16.0 for Windows and SPSS 18.0 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 ratio (OR) of a traffic accident after exposure to the study medications. 95% confidence intervals (CIs) were calculated for all ORs to establish whether the findings were statistically significant. ORs were adjusted for psychotropic drug poly-pharmacy 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 MVA risk (Drummer, 2008; Movig et al., 2004; Ravera, Visser, de Gier, & de Jong-van den Berg, 2010).
Results
The study population of the case-control study consisted of 3963 cases and 18828 controls whereas the study population of the case-crossover study consisted of 3786 cases. The results of the case-control study are reported in Table 1 whereas the outcomes of the case-crossover study are reported in Table 2 (NB: the outcomes of descriptive statistics analyses are not reported here).

Table 1. Exposed subjects [cases (N=3963) and controls (N=18828)], crude and adjusted ORs for road-traffic accident in different psychotropic medicine group users.

<table>
<thead>
<tr>
<th>MEDICINE GROUP</th>
<th>CASES (Exposed) (%)</th>
<th>CONTROLS (Exposed) (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adj. OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td></td>
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</tr>
<tr>
<td>All exposed individuals</td>
<td>20 (0.50)</td>
<td>96 (0.51)</td>
<td>1.01 (0.62-1.63)</td>
<td>1.31 (0.71-2.42)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>94 (2.37)</td>
<td>310 (1.65)</td>
<td>1.46 (1.16-1.85)</td>
<td>1.54 (1.11-2.15)</td>
</tr>
<tr>
<td>Hypnotics</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>76 (1.92)</td>
<td>273 (1.45)</td>
<td>1.34 (1.04-1.74)</td>
<td>1.39 (0.94-2.07)</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
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<tr>
<td>All exposed individuals</td>
<td>92 (2.32)</td>
<td>252 (1.34)</td>
<td>1.76 (1.38-2.24)</td>
<td>2.03 (1.31-3.14)</td>
</tr>
<tr>
<td>Other antidepressants</td>
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<tr>
<td>All exposed individuals</td>
<td>40 (1.01)</td>
<td>146 (0.78)</td>
<td>1.32 (0.93-1.88)</td>
<td>1.45 (0.81-2.58)</td>
</tr>
</tbody>
</table>

Table 2. Exposed subjects (N=3786) in the case and control windows, crude and adjusted ORs for road-traffic accident in different psychotropic medicine group users, stratified by all exposed individuals and acute users.

<table>
<thead>
<tr>
<th>MEDICINE GROUP</th>
<th>CASE WINDOW (Exposed) (%)</th>
<th>CONTROL WINDOW (Exposed) (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adj. OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>18 (0.50)</td>
<td>23 (0.60)</td>
<td>0.76 (0.41-1.41)</td>
<td>0.68 (0.34-1.35)</td>
</tr>
<tr>
<td>Acute users</td>
<td>1 (0.02)</td>
<td>1 (0.002)</td>
<td>0.97 (0.06-15.52)</td>
<td>0.97 (0.06-15.52)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>92 (2.40)</td>
<td>94 (2.50)</td>
<td>0.95 (0.71-1.27)</td>
<td>0.95 (0.68-1.31)</td>
</tr>
<tr>
<td>Acute users</td>
<td>13 (0.34)</td>
<td>11 (0.29)</td>
<td>1.15 (0.51-2.56)</td>
<td>0.97 (0.40-2.33)</td>
</tr>
<tr>
<td>Hypnotics</td>
<td></td>
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</tr>
<tr>
<td>All exposed individuals</td>
<td>75 (2.00)</td>
<td>85 (2.20)</td>
<td>0.86 (0.63-1.17)</td>
<td>0.89 (0.63-1.25)</td>
</tr>
<tr>
<td>Acute users</td>
<td>6 (0.16)</td>
<td>11 (0.29)</td>
<td>0.53 (0.20-1.43)</td>
<td>0.39 (0.12-1.24)</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>92 (2.40)</td>
<td>87 (2.30)</td>
<td>1.03 (0.76-1.38)</td>
<td>1.00 (0.69-1.46)</td>
</tr>
<tr>
<td>Acute users</td>
<td>7 (0.18)</td>
<td>5 (0.13)</td>
<td>1.36 (0.43-4.28)</td>
<td>1.29 (0.29-5.79)</td>
</tr>
<tr>
<td>Other antidepressants</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All exposed individuals</td>
<td>40 (1.10)</td>
<td>45 (1.20)</td>
<td>0.86 (0.56-1.33)</td>
<td>0.88 (0.53-1.46)</td>
</tr>
<tr>
<td>Acute users</td>
<td>3 (0.08)</td>
<td>3 (0.08)</td>
<td>0.97 (0.20-4.81)</td>
<td>0.97 (0.20-4.81)</td>
</tr>
</tbody>
</table>

Discussion and conclusion
To the best of our knowledge, this is one of the few studies that evaluated and highlighted the possible impact of two different epidemiologic study designs (i.e., case-control and case-crossover) on the association between MVA risks and psychototropic medication exposure in the same study population. The outcomes of the case-control study indicated that there was a statistically significant association between the risk of having a road traffic accident and the 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)] whereas the results of the case-crossover study did not show any significant increase in MVA risk associated with the exposure to the selected psychotropic medicine groups [e.g., All exposed individuals: Anxiolytics: Adj. OR=0.95 (95% CI: 0.68 – 1.31); SSRIs: Adj. OR=1.00 (95% CI: 0.69 – 1.46)]

The discrepancies between the outcomes of the case-control and case-crossover studies could be attributed to the choice of the 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 (Maclure & Mittleman, 2000). The case-crossover is a matched case-control study, but it only involves cases and each case serves as its own control (Maclure & Mittleman, 2000). Because of this peculiarity, the case-crossover design controls for stable subject-specific covariates and it overcomes control selection bias (Maclure, 1991). However, this type of design requires that the exposures are brief and their effects transient (Maclure, 1991; Strom, 1994). Considering that psychotropic medications are often used on a regular and chronic basis (Del Rio & Alvarez, 1996; Hebert et al., 2007; Ravera et al., 2010), 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 (i.e., acute users) were more similar to the ORs obtained by applying the case-control technique, it can be speculated that our study did not have adequate statistical power to detect the association between incidental psychotropic medication users and MVA risks (Hennekens & Buring, 1987; Strom, 1994).

Besides the above-mentioned points, there could also be other possible explanations for the discrepancies among the findings of the two designs that were used. As some authors have also pointed out (Hebert et al., 2007; Hernandez-Diaz, Hernan, Meyer, Werler, & Mitchell, 2003; Maclure, 1991; Maclure, 2007; Schneeweiss, Sturmer, & Maclure, 1997), 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 (no information was available on what medical condition the psychotropic medications were prescribed for, and, consequently, we could not account for the confounding effect of the disease), different effects of the medication at different points in time (e.g., different estimates in relation to therapy duration and/or prior exposures (Guess, 2006)), time-varying within-subject confounding factors (e.g., fluctuations in disease severity, comorbidities, etc.), and time trend bias (i.e., changes in the prescribing patterns of the medications of interest).

In conclusion, our investigation showed that different study designs gave different answers to the same research hypothesis, in the same population. Considering that every study design has design-specific assumptions, and strengths and limitations, it could be assumed that our analyses actually tested distinctive causal hypotheses and focused on different aspects of psychoactive medication use and MVA risk (Hebert et al., 2007; Hernandez-Diaz et al., 2003; Maclure, 2007). As a consequence, it seems reasonable to conclude that each pharmacoepidemiological design may be appropriate only in certain settings and under specific assumptions (Hernandez-Diaz et al., 2003). 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.
Disclaimers
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