Are Selective Serotonin Reuptake Inhibitors 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. They seem to be as effective as older antidepressants but have a different adverse effect profile. Despite their favorable safety profile, little is known about their influence on traffic safety.

Objective: To conduct a literature review to summarize the current evidence on the role of SSRIs in traffic safety, particularly concerning undesirable effects that could potentially impair fitness to drive, experimental and pharmacoepidemiologic studies on driving impairment, 2 existing categorization systems for driving-impairing medications, and the European legislative procedures for assessing fitness to drive before issuing a driver’s license and driving under the influence of medicines.

Methods: The article search was performed in the following electronic databases: MEDLINE, PsycINFO, ScienceDirect, and SafetyLit. The 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, refer to possible driving-related adverse effects, and be experimental or pharmacoepidemiologic studies on SSRIs and traffic accident risks. No restrictions concerning publication year were applied.

Results: Ten articles were selected as background information on driving-related adverse effects, and 15 articles were selected regarding experimental and pharmacoepidemiologic work. Regarding SSRI adverse effects, the most reported undesirable effects referring to driving impairment were anxiety, agitation, sleep disturbances, headache, increased risk of suicidal behavior, and deliberate self-harm. Regarding the remaining issues addressed in this article, inconsistencies were found between the outcomes of the selected experimental and epidemiologic studies and between the 2 existing categorization systems under evaluation. Some pitfalls of the current legislative scenario were identified as well.

Conclusions: Based on the current evidence, it was concluded that more experimental and epidemiologic research is needed to elucidate the relationship between SSRI use and traffic safety. Furthermore, a revision of the existing categorization systems and harmonized European legislation in the field of medication use and driving were highly recommended. (Clin Ther. 2012;34:1070–1083) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: adverse effect, automobile driving, experimental research, pharmacoepidemiologic studies, selective serotonin reuptake inhibitors, traffic accident.

INTRODUCTION

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

Although SSRIs are associated with a different adverse effect profile compared with other antidepressant
medications (eg, tricyclic antidepressants [TCAs]).\(^4\)–\(^6\) they can also affect psychomotor and cognitive functions and, consequently, have the potential to impair fitness to drive.\(^1\),\(^7\)

The relationship between SSRI use and traffic safety has been studied by means of experimental and epidemiologic studies. In general, experimental studies evaluate volunteers’ performance after intake of a single or multiple doses of the study medication through the use of laboratory tests, driving simulator tasks, and on-the-road experiments.\(^8\) Epidemiologic studies usually explore the risk of having a traffic accident by comparing exposure to the study medications in drivers who sustained injuries (case group) and drivers who were not involved in accidents (reference or comparison group). Afterward, relative risks, or odds ratios, or standardized incidence ratios are calculated to estimate the risk of being involved in a traffic accident while under the influence of a certain medication.\(^9\)–\(^12\)

To date, several experimental and epidemiologic studies have been performed investigating the role of SSRIs in traffic safety. Yet, an initial reading of these studies seems to indicate that their outcomes are inconsistent and inconclusive.

In addition, incongruities also seem to emerge from existing categorization systems of driving-impairing medications. In the European Union (EU), it is mandatory to perform studies to assess the effect of a medication on fitness to drive before its commercialization. The outcomes of these studies have to be used to write the medication Summary of Product Characteristics and the package insert, which mentions the medication’s possible effects on fitness to drive.\(^13\) As reported in the most recent Summary of Product Characteristics guideline, a medicinal product can be classified according to 4 levels of impairment, ranging from no influence to major influence on fitness to drive.\(^14\) Following the aforementioned guideline, in the past few decades, several categorization systems of potentially driving-impairing medicines have been developed or implemented at a national level in Europe.\(^15\) To our knowledge, no standardized and harmonized criteria were used to categorize commonly used medications. Therefore, the currently available categorization systems differ significantly from each other, often resulting in divergent categories being assigned to the same active substance, especially with reference to the SSRIs.\(^13\)

In 2006, the EU launched the project “Driving under the Influence of Drugs, Alcohol and Medicines (DRUID)” with the purpose of obtaining scientific support for a European transport policy and establishing guidelines and measures that combat impaired driving.\(^16\) The DRUID Work Package (WP4) was assigned the task of establishing standardized and harmonized criteria for a European classification system and developing a categorization system for relevant therapeutic groups of medications with respect to their effect on driving skills.\(^16\) The WP4 partners decided to adopt a step-by-step procedure; more specifically, a procedure that can evaluate different types of available information and data, such as pharmacodynamic and pharmacokinetic properties, pharmacovigilance data, and experimental and epidemiologic studies.\(^17\) Furthermore, the WP4 partners decided to ask the Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use to participate in the discussions on the DRUID categorization system since patient safety affected by medicines’ adverse reactions was the WP4’s primary focus. In 2011, consensus was reached that a basic 2-level framework would be developed as the basis for issuing warnings in the patient information leaflet. Specific advice for the patient was proposed 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 or major influence). In the case of medicines with a potential relevant influence on driving, a warning was proposed as well. Since the current Summary of Product Characteristics guideline reports 4 descriptions of potential levels of impairment to fitness to drive, an update to the evidence-based approach for supporting the warnings for medicines such as SSRIs was needed.\(^13\)

In the context of the DRUID project and in view of the possible discrepancies between experimental and epidemiologic data and the inconsistencies between the existing categorization systems concerning SSRIs, it was decided to perform a literature 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 the adverse effects that could potentially impair fitness to drive, experimental and pharmacoepidemiologic findings on SSRIs and traffic safety, the discrepancies between 2 well-known categorization systems for medicines and driving, and the European legislation on driving under the influence of medications.
METHODS
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, adverse, or undesirable effects. In addition, the reference lists of relevant articles, books, guidelines, and prescribing information were checked to retrieve other potentially relevant published materials. Owing to the large amount of literature published on undesirable effects of SSRIs, manuscript selection was limited to full-text articles (not abstracts) published in English that referred to adverse effects that could potentially impair fitness to drive and experimental or pharmacoepidemiologic studies on SSRI use and the risk of traffic accidents. Articles were excluded if they did not focus on the previously mentioned topics. Furthermore, letters, commentaries, and articles reporting animal studies, clinical trials, and descriptive studies on the incidence and prevalence of driving under the influence of antidepressants were disregarded. No restrictions concerning publication year were applied.

The search and examination of the references were performed by one of us (S.R.) after having discussed and agreed on the search strategy and the inclusion/exclusion criteria with the article coauthors. When in doubt, references were also evaluated by another author (J.J. dG) to establish whether a particular source could be relevant to the aim of this review. As previously mentioned, eligible publications were examined for direct relevance to one of the following topics (related to SSRIs): (1) pharmacologic properties, (2) therapeutic indications, (3) undesirable effects related to driving impairment, and (4) experimental and pharmacoepidemiologic studies focused on SSRI use and fitness to drive.

RESULTS
In total, 2650 references were retrieved. Based on the previously mentioned criteria, after a title, key word, and abstract screening, 10 articles were selected as background information on driving-related adverse effects and 15 articles were selected regarding experimental and pharmacoepidemiologic work. The remaining retrieved publications were excluded because the primary objective of the study was not related to SSRIs and their possible effect on fitness to drive and, therefore, was not in accordance with the aforementioned inclusion criteria (driving-related adverse effects of SSRIs, experimental and epidemiologic studies on SSRIs and fitness to drive, etc).

Mechanism of Action, Driving-Related Adverse Effects, and Clinical Use of SSRIs
Six SSRIs are currently marketed in Europe: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Despite the structural diversity among the SSRIs, which results in clear variations in their pharmacodynamic and pharmacokinetic profiles, the previously mentioned active substances have a similar mechanism of action and undesired effects. In brief, SSRIs selectively block the reuptake of serotonin (5-hydroxytryptamine 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. Serotonin binds to serotonin receptors located in the central and peripheral nervous system and affect various functions, such as sleep, pain perception, blood vessel regulation, anxiety, mood, and depression. The SSRIs have lower binding affinities for other neurotransmitter receptors (eg, dopaminergic, histaminergic, and muscarinic receptors) and, therefore, are considered better tolerated than TCAs and monoamine oxidase inhibitors.

After oral administration, SSRIs are well-absorbed, have high protein binding, and have 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); SSRIs with longer half-lives need more time to reach the steady-state concentration and to wash out after discontinuation.

In general, SSRIs have milder adverse effects than do older antidepressants, and their adverse effects are often dose related and transient. The most commonly reported undesired effects, which can also play a role in traffic safety, are anxiety, agitation, sleep disturbances, headache, and therapy discontinuation reactions (eg, dizziness, fatigue, and anxiety). Last, 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 adverse effects seem to be limited to particular patient populations (eg, patients with a history of suicide-related events and
children and adolescents <18 years old). The SSRIs are commonly used to treat a variety of psychiatric illnesses, such as depression, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, eating disorders, personality disorders, behavioral symptoms in dementia, and premenstrual dysphoric disorder.

Experimental Studies
The selected experimental studies assessed the performance of healthy and diseased participants by conducting laboratory tests, driving simulator tests, or on-the-road tests. Laboratory tests evaluate cognitive and psychomotor functions and include the critical tracking test, where the subject is asked to control the position of a light bar on a display screen using a steering wheel or joystick, and the choice reaction time (CRT) task, where the individual is asked to respond appropriately and rapidly through hand or foot movements to a series of auditory or visual stimuli. Driving simulator tests, in this case, involve individuals performing a computer simulation of a driving task, and on-the-road tests measure the ability of a person to drive in the presence or absence of normal traffic (Table I). In addition, currently available experimental studies on SSRIs focus on single active substances or on SSRIs as a total group and are mostly performed on healthy volunteers (Table I).

Experimental Studies in Healthy Volunteers
Acute Treatment (Laboratory and Driving Simulator Tests)

Iwamoto et al performed a double-blinded, 3-way crossover trial involving 17 healthy volunteers who received a single dose of paroxetine (10 mg), amitriptyline (25 mg), or placebo. The subjects’ cognitive and driving skills were tested by means of computer tasks and a driving simulator test, respectively. The study found that acute doses of paroxetine or placebo did not affect cognitive function or driving performance, whereas amitriptyline significantly impaired driving performance and caused somnolence.

Acute and Subchronic Treatment (Laboratory and On-the-Road Tests)

One study used attention tests (vigilance, selective, and divided attention assessments) and the Groningen Sleep Quality Questionnaire to evaluate vigilance performance in sertraline, paroxetine, and placebo users. A randomized, double-blind, placebo-controlled, 3-way crossover design was used. Twenty-one healthy middle-aged individuals were tested during 3 treatment periods of 2 weeks each in which sertraline (50 mg on days 1–7 and 100 mg on days 8–14), paroxetine (20 mg on days 1–7 and 40 mg on days 8–14), and placebo were administered. From this study, it was apparent that subchronic administration (ie, daily administration of the active substance during the defined timeframe) of paroxetine decreased vigilance performance, whereas subchronic administration of sertraline did not produce any vigilance impairment. Furthermore, paroxetine use reduced sleep quality in women, whereas sleep quality in men remained unchanged; sertraline use did not have any influence on their sleep quality.

The acute and subchronic 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 authors performed a randomized, double-blind, placebo-controlled, 3-way crossover study. Eighteen healthy subjects were selected and received 10 mg/d of escitalopram on days 1 to 7 followed by 20 mg/d of escitalopram on days 8 to 15; 30 mg/d of mirtazapine on days 1 to 7 followed by 45 mg/d of mirtazapine on days 8 to 15; or placebo. The results of this study suggested that escitalopram use did not impair driving and psychomotor skills after single and repeated doses, but a significantly reduced sleep duration was observed.

Experimental Studies in Depressed Patients
Antidepressant Monotherapy (Laboratory Tests)

Brunnauer et al examined the psychomotor function of 100 depressed patients (diagnosed as having major depressive disorder) using TCAs (40 patients), SSRIs (25 patients), mirtazapine (20 patients), and venlafaxine (15 patients) monotherapy. Dosage and choice of antidepressants were selected on an individual clinical basis by the treating psychiatrist. The authors chose a nonrandomized, comparative clinical study covering a 14-month period (ie, January 2004–March 2005). Computerized psychomotor and visual perception tests revealed that SSRIs and mirtazapine users had better test performances than did TCA users. However, the data also suggested that 16% of the sample was unfit to drive and that 60% of the patients were mildly to moderately impaired.
Table 1. Experimental studies of SSRIs and driving impairment.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Country</th>
<th>Period</th>
<th>Type of Study Methods</th>
<th>Population</th>
<th>Medications</th>
<th>Main Outcomes (Referring to SSRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumont et al44</td>
<td></td>
<td></td>
<td>Literature review of CNS tests (171 variants of neuropsychological tests)</td>
<td>Healthy subjects</td>
<td>SSRIs (56 single doses and 22 multiple doses) Amitriptyline (used as a positive control)</td>
<td>SSRI low single doses: attention and memory stimulation SSRI high doses: impairment of visual/auditory and visuomotor systems and subjective performance but acceleration of motor functions</td>
</tr>
<tr>
<td>Hindmarch41</td>
<td></td>
<td></td>
<td>Literature review of CFFT and CRT tests</td>
<td>Not specified</td>
<td>TCAs SSRIs</td>
<td>SSRIs not associated with an increased accident risk CFFT Sertraline and paroxetine &gt;excitatory effect Fluvoxamine &gt;comparable with placebo CRT Fluvoxamine &gt;better reaction time than placebo Remaining SSRIs &gt;comparable with placebo Therapeutic doses of fluoxetine and paroxetine: no influence on driving performance after acute or repeated doses Interactions between antidepressants and comedications &gt;driving impairment SSRIs and mirtazapine: better performance than TCAs 76% of the study population mildly to severely impaired</td>
</tr>
<tr>
<td>Ramaekers43</td>
<td></td>
<td>1983–2000</td>
<td>Literature review of driving studies (standard on-the-road driving tests)</td>
<td>Mainly healthy subjects</td>
<td>Sedating antidepressants Non sedating antidepressants (including SSRIs)</td>
<td>No differences in performance in the 3 antidepressant groups 88.6% of the study population did not pass all the tests</td>
</tr>
<tr>
<td>Brunnauer et al36</td>
<td>Germany</td>
<td>January 2004–March 2005</td>
<td>ART-90 Wiener Test system HDRS</td>
<td>100 depressed inpatients (mean age, 46.8 y)</td>
<td>Monotherapy regimen: TCAs, SSRIs (25 users), mirtazapine, venlafaxine</td>
<td>Combination therapy regimen: MAOIs, SSRIs (15 users), tricyclic and tetracyclic antidepressants Acute doses of paroxetine, amitriptyline, placebo</td>
</tr>
<tr>
<td>Grabe et al10</td>
<td>Germany</td>
<td>1998</td>
<td>ART-90 HDRS CGI scale</td>
<td>44 depressed inpatients (mean age, 44.4 y)</td>
<td>Combination therapy regimen: MAOIs, SSRIs (15 users), tricyclic and tetracyclic antidepressants</td>
<td>No differences in performance in the 3 antidepressant groups 88.6% of the study population did not pass all the tests</td>
</tr>
<tr>
<td>Iwamoto et al35</td>
<td>Japan</td>
<td>2008</td>
<td>Double-blind trial Driving tests (driving simulator) + cognitive tests (computer tests) + Stanford Sleepiness Scale</td>
<td>17 healthy males (mean age, 35.8 y)</td>
<td>Combination therapy regimen: MAOIs, SSRIs (15 users), tricyclic and tetracyclic antidepressants</td>
<td>Acute doses of paroxetine, amitriptyline, placebo</td>
</tr>
<tr>
<td>Schmitt et al16</td>
<td>The Netherlands</td>
<td>2002</td>
<td>RCT Attentions tests + GSQS</td>
<td>21 healthy volunteers (mean age, 37.8 y)</td>
<td>Paroxetine (2 different dosages) sertraline (2 different dosages) Placebo</td>
<td>Paroxetine: Subchronic administration &gt;negative effect on vigilance performance Reduction of women’s sleep quality Sertraline No impairment of vigilance performance Possible increase of response speed No influence on sleep quality CFFT Fluvoxamine and fluoxetine &gt;no effects Zimelidine, paroxetine, and sertraline &gt;increased scores CBT: SSRIs &gt;performances comparable with placebo Sedation: sertraline (100 mg) &gt;sedation sensation Escitalopram: no influence on driving performance, psychomotor function, subjective mood, decrease in sleep duration</td>
</tr>
<tr>
<td>Sherwood42</td>
<td>United Kingdom (Human Psychopharmacology Research Unit)</td>
<td>Before 1995</td>
<td>Overview of CFFT, CRT tests, and subjective ratings of sedation</td>
<td>Healthy volunteers</td>
<td>Different SSRIs TCAs (amitriptyline and dothiepin) Placebo</td>
<td>Clinical Therapeutics 1074 Volume 34 Number 5 (continued)</td>
</tr>
<tr>
<td>Wingen et al17</td>
<td>The Netherlands</td>
<td>2004</td>
<td>RCT Driving test (on the road) Psychometric tests (computer tests) Subjective mood measurement GSQS</td>
<td>18 healthy subjects (mean age, 31.4 y)</td>
<td>Escitalopram (2 different dosages) Mirtazapine (2 different dosages) Placebo</td>
<td>Escitalopram: no influence on driving performance, psychomotor function, subjective mood, decrease in sleep duration</td>
</tr>
</tbody>
</table>
Antidepressant Monotherapy in Depressed Patients Compared with Controls (Laboratory and On-the-Road Tests)

Wingen et al\(^3^9\) also investigated driving performance and cognition in 24 depressed patients (diagnosed as having unipolar disorder with an active depressive episode) treated with SSRIs or venlafaxine and in 24 controls. Healthy participants did not take any medication. Depressed patients received treatment with citalopram (\(n = 4\); average dose, 25 mg), sertraline (\(n = 4\); average dose, 87.5 mg), paroxetine (\(n = 8\); average dose, 28.8 mg), or venlafaxine (\(n = 8\); average dose, 134.4 mg) but no other psychoactive medications. Standardized on-the-road tests, laboratory cognition tests, and subjective measures were performed. These tests revealed statistically significant impairment of driving performance in depressed patients compared with controls. In particular, driving impairment was evident from increments in weaving and time to speed adaptation on the on-the-road driving tests in medicated patients relative to controls. Moreover, time to speed adaptation and critical flicker fusion threshold were also impaired in medicated patients. Last, Hamilton Depression Rating Scale scores in medicated patients turned out to be significantly higher than those in control patients.\(^3^9\)

Antidepressants Combined with Other Central Nervous System Medications (Laboratory Tests)

Results similar to those found in the study by Wingen et al\(^3^9\) were also reported in a German study.\(^4^0\) The influence of 3 antidepressant types (ie, SSRIs, monoamine oxidase inhibitors, and TCAs) and common comediations (eg, lorazepam, zopiclone, and lithium) were evaluated in 44 depressed inpatients recovering from moderate to severe depression. Different types of computer-based tests were performed to evaluate the patients’ visual perception, reaction time, and attention. The outcomes of the examinations suggested that 88.6% of the patients did not pass all the tests. No remarkable differences were seen in the users of the 3 types of antidepressants, although there was a non–statistically significant tendency to perform better on time and error variables in the case of SSRI users.\(^4^0\)

Review Articles Focusing on Experimental Studies in Healthy Volunteers

Acute Treatment (Laboratory Tests)

A review by Hindmarch\(^4^1\) focusing on critical flicker fusion threshold and CRT tests suggested that sertraline and paroxetine produced a dose-related elevation of critical flicker fusion threshold, whereas fluvoxamine was comparable with placebo. Fluvoxamine also had a better effect on CRT than did placebo, whereas no difference in CRT was noted between placebo users and the remaining SSRIs studied.\(^4^1\)

Analogous results were also presented in another review in which SSRIs were considered comparable with placebo regarding critical flicker fusion threshold, CRT, and compensatory tracking task tests. In addition, the article pointed out that paroxetine and sertraline increased central nervous system activation and excitation.\(^4^2\)
Acute and Subchronic Treatment, Combined with Benzodiazepines (On-the-Road Tests)

In 2003, Ramaekers published a review that compiled the outcomes of standard on-the-road tests performed between 1983 and 2000. The article reported that nonsedating antidepressants (which include 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 with benzodiazepines or with other medicines with incompatible pharmacokinetic profiles.

Low and High Dosage (Laboratory Tests)

Another Dutch research group also performed a literature review covering all SSRI studies conducted on healthy volunteers. Seventy-eight studies were identified, published since 1983 and reporting 171 neuropsychological tests. The results of these studies suggested that at low single doses, SSRIs caused slight stimulation of central nervous system functions. However, at high doses, SSRIs seemed to impair visual/auditory and visuomotor skills and subjective performance.

Pharmacoepidemiologic Studies

Few pharmacoepidemiologic data are currently available on SSRI use and the risk of having a traffic accident. Barbone et al performed a case-crossover study to investigate the risk of having a traffic accident if exposed to psychotropic medications, including SSRIs. This study did not find any association between SSRI exposure and the risk of experiencing a traffic accident.

Bramness et al performed a study of population-based registry data in Norway and found that there was a slight increase in traffic accident risk for drivers who received a newer antidepressant (including SSRIs).

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 (ie, SSRIs and other newer antidepressants) were associated with a higher risk of motor vehicle crashes than were older antidepressants (ie, cyclic antidepressants and irreversible monoamine oxidase A inhibitors).

A statistically significant association was also observed between exposure to SSRIs and traffic accident risk in a case-control study performed in the Netherlands. As in the previously mentioned study, the traffic accident risk was also found to be higher in the case of SSRI exposure than in the case of older antidepressant exposure.

Last, Rapoport et al recently performed a population-based, case-only, time-to-event analysis to evaluate whether antidepressant drug treatment was associated with an increase in the risk of a motor vehicle crash in older adults (≥65 years old). The study outcomes suggested a significant increase in crash risk for the later-generation antidepressants (ie, SSRIs and other newer antidepressants), yet there was no statistically significant association with increased risk for the first-generation antidepressants (ie, TCAs, monoamine oxidase inhibitors, and other cyclic antidepressants). However, the increased traffic accident risk in newer antidepressant users was found to be significant only for crashes in which the patient was deemed to be at fault and for patients concurrently receiving benzodiazepines or strong anticholinergic drugs.

DISCUSSION

Clinical Particulars of SSRIs

Ten studies were included in this review that elucidate the pharmacologic properties, therapeutic indications, and undesirable effects of SSRIs related to driving impairment. The selected studies indicated that 6 SSRIs are currently available on the European market. These antidepressants have similar mechanisms of action and, at the moment, are widely used to treat several psychiatric disorders (eg, depression, eating disorders, and posttraumatic stress disorders). Furthermore, the selected studies pointed out that despite the likelihood that the older antidepressants have a greater effect on fitness to drive than do the newer antidepressants, the ability of SSRIs to impair psychomotor and cognitive skills could represent a hazard to traffic safety.

Outcomes of Experimental and Epidemiologic Studies

Fifteen studies reporting the relationship between SSRI use and driving impairment or accident risk were included in the current literature review. Based on the outcomes of the evaluation of the literature, it
Table II. Pharmacoepidemiologic studies of SSRIs and driving impairment.

<table>
<thead>
<tr>
<th>Study Country Period</th>
<th>Type of Study Methods</th>
<th>Population</th>
<th>Medications</th>
<th>Main Outcomes (Referring to SSRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbone et al45</td>
<td>Case-crossover</td>
<td>≥18 years old 19,386 accidents</td>
<td>Benzodiazepines, Tricyclic and related antidepressants, SSRIs as a total group (84 users), Other psychoactive drugs</td>
<td>SSRIs: OR = 0.85 (95% CI, 0.55–1.33) (no association found)</td>
</tr>
<tr>
<td>United Kingdom August 1992–June 1995</td>
<td></td>
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</tr>
<tr>
<td>Bramness et al46</td>
<td>Cohort</td>
<td>18–69 years old 20,494 accidents</td>
<td>Cyclic sedating antidepressants, Newer antidepressants (including SSRIs, 884 users)</td>
<td>Newer antidepressants: SIR = 1.6 (95% CI, 1.5–1.7) (statistically significant association)</td>
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<tr>
<td>Norway April 2004–September 2006</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rapoport et al47</td>
<td>Case-crossover</td>
<td>Adults with dementia ≥65 years old 8690 accidents</td>
<td>Benzodiazepines, Antidepressants (among which are SSRIs), Antipsychotics</td>
<td>Later-generation antidepressants (SSRIs and newer agents): OR = 2.15 (95% CI, 1.78–2.60) (statistically significant association)</td>
</tr>
<tr>
<td>Canada April 1997–March 2005</td>
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<tr>
<td>Ravera et al48</td>
<td>Case-control</td>
<td>≥18 years old 3963 accidents</td>
<td>Antipsychotics, Anxiolytics, Hypnotics and sedatives, SSRIs (344 users), Other antidepressants</td>
<td>SSRIs: OR = 2.03 (95% CI, 1.31–3.14) (statistically significant association)</td>
</tr>
<tr>
<td>The Netherlands January 2000–December 2007</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rapoport et al49</td>
<td>Population-based only time-to-event</td>
<td>≥65 years old 159,678 accidents</td>
<td>First-generation antidepressants (TCAs, MAOIs, and other cyclic antidepressants, Second-generation antidepressants (SSRIs and other newer antidepressants), Benzodiazepines and antipsychotics = concomitant medications used as positive control, Proton pump inhibitors and topical antifungals = concomitant medications used neutral controls</td>
<td>Second-generation antidepressants (SSRIs and other newer antidepressants): Hazard ratio = 1.10 (95% CI, 1.07–1.13) (statistically significant association)</td>
</tr>
<tr>
<td>Canada January 2007–October 2007</td>
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</table>

MAOI = monoamine oxidase inhibitor; OR = odds ratio; SIR = standardized incidence ratio; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
can be stated that the role of SSRIs in traffic safety seems to be unclear and conflicting.

Regarding the selected experimental studies, it could be argued that experimental data suggest 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, are compatible with impaired driving performance.

Finally, it is important to underline that experimental studies are not free of limitations. First, these studies are usually performed on healthy and young volunteers who can differ from the actual patients. Second, tests are often performed on an alcohol-, smoke-, and drug-free population, which is often different from real clinical populations, which have high degrees of substance and other psychiatric comorbidity. Third, the frequent use of small numbers of participants could result in the nondetection of existing effects and a lack of statistical power. Fourth, experimental studies often evaluate the acute effects of the medication; for this reason, there is often a lack of information on the effects of a medicine after its long-term use. Last, it can be questioned whether the tests actually represent facets of real driving, which is a much more complex and multifactorial task.

In light of the previous considerations, it seems reasonable to conclude that experimental and epidemiologic studies can provide valuable information on the risk of experiencing a traffic accident while exposed to SSRIs. But caution must be applied while interpreting the outcomes of each research study because they might not be directly comparable and generalizable since every investigation has its unique methods and nuances.

**Discrepancies Between 2 Categorization Systems for Medications and Driving**

In 1993, the European Commission developed the first action program on road safety and highlighted the influence of medicines on road safety in an official communication. The EU action programs that followed also underlined the role of medicines in traffic safety. Particularly, 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 that affect driving ability.” As previously mentioned, no standard European classification and labeling system is available, but there are several examples of categorization systems that were mainly developed at a national level.

Regarding the classification of SSRIs, it is interesting to examine the discrepancies between 2 existing categorization systems, namely, the French system and the International Council on Alcohol, Drugs, and Traffic Safety (ICADTS) system. 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.57,58 Three levels of impairment were proposed and 3 different pictograms were associated with the medication level of impairment: level 1 medicinal products do not generally affect the ability to drive but require patient information; patients have to read the leaflet carefully before driving; level 2 medicinal products could affect the ability to drive and require medical advice from a physician or a pharmacist before use; and level 3 medicinal products affect the ability to drive during their use, and patients should not drive; before starting to drive again, patients must 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 that affect driving performance also published a list with a categorization of medications according to their driving impairment.59 This list was based on the Belgian, Spanish, and French categorization lists, and 3 categories were proposed to define the level of impairment of commonly prescribed medications: category I medications are presumed to be tolerable or unlikely to produce an effect; category II medications are likely to produce minor or moderate adverse effects; and category III medications are likely to produce severe effects or are 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, with the latter belonging to either category II or III. It is difficult to explain the discrepancies between these 2 categorization systems, but they could be because the French experts might have also considered the role of depression, whereas the ICADTS working group solely focused on the medication effects and on the outcomes of the experimental research.

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

**Legislation in the EU**

The EU Council Directive 91/439/EEC of July 1991 on driving licenses 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 and 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 that affect the ability to drive."60 The application of this directive is mandatory for all EU Member States, but there are differences in its implementation across EU countries.61

It is noteworthy that, on the one hand, the EU directive clearly indicates that driving under the influence of psychotropic medications can hamper traffic safety and, consequently, that individuals using these medications should not be allowed to drive a car. However, on the other hand, the current legislation is general, and it does not refer to any specific psychoactive substances that can impair the ability to drive safely. Finally, it is also important to underline that there is still no general consensus on factors that are strictly related to the enforcement of the directive, 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 on the individual’s ability to drive, and the individual’s liability.62–64

Regarding driving impairment related to SSRI use, it is interesting to note that according to the literature, there are few case reports focusing on the relationship between SSRIs and cognitive impairment.65,66 Rohrig and Goodson65 reported a case of a car accident after sertraline intoxication. The medication was probably taken alone, at a high dosage, and it caused confusion, eye disorders, and sleepiness, which could have played a role in the involvement in an accident.65 Another example of possible impairment caused by SSRI use was examined in an American study that investigated the presence of these antidepressants in fatal civil aircraft accidents. The number of SSRI-involved accidents was low, but the possible contributory role of these medicines (alone or combined with alcohol or other medications) could not be ruled out.66 Taken together, these 2 examples suggest that there could be a connection between the use of SSRIs and involvement in an accident. Therefore, we can conclude that in Europe and in other developed countries, there is a defi-
nite need for specific legislation covering enforcement of the directive and the individual’s general liability in cases of driving under the influence of SSRIs.

FUTURE STEPS
The results of this study indicate that SSRIs are commonly used medications that carry an unclear risk of driving impairment. In particular, this research points out that based on the available knowledge, the role of SSRIs in traffic safety is still doubtful, and the results of experimental and pharmacoepidemiologic studies were often contradictory. Furthermore, discrepancies were also found in 2 existing categorization systems, which should support prescribers choosing a tolerable medication with respect to its potential hazard to a patient’s ability to drive. Finally, regarding the current EU legislation, this article highlighted that, to date, the issue of driving under the influence of medications is not clearly and fully covered.

Further epidemiologic work is needed to investigate the effects of these active substances on the ability to drive in different types of users (eg, new and long-term users, young and old individuals, depressed patients, and anxious patients) and combined with other illegal and legal substances (ie, drugs, alcohol, and medications).67 Moreover, additional experimental investigations that focus on larger and representative groups of depressed patients are needed to determine the impact of each SSRI on psychomotor and cognitive functions and to better understand the different levels of impairment caused by available SSRIs. In addition, future research should also concentrate on the role of the comorbidities and the diseases that are treated with SSRIs, which can also affect cognitive and psychomotor skills if not properly managed.1,7,10 Last but not least, synchronization of epidemiologic and experimental studies on driving under the influence of medications is also required. This will enable better comparisons between study results and lead to a proper estimation of the risks associated with driving under the influence of SSRIs. Generally, this is especially true for new medications that have been recently approved or introduced to the market (eg, new antidepressants).

The present research also suggests that physicians and HCPs in general have to be aware of the possible risks associated with SSRI treatment and driving. Consequently, HCPs should counsel their patients individually and should monitor them during their therapy, including considering potential adverse effects, the patient’s response to the treatment, the patient’s medical conditions and disease (not only depression itself but also its heterogeneity of presentations), and the concomitant use of other medications. Last, patients should be adequately informed about their therapy and, if needed, be able to individually or in consultation with an HCP evaluate their clinical conditions with respect to driving.7,56 In this respect, a consensus-based revision of the existing categorization systems would be highly recommended. This would provide HCPs and patients with consistent information about SSRIs and their impact on fitness to drive and be a trustworthy tool for determining the correct use of driving-impairing medications.

Finally, this work also supports the need for harmonized and clear regulations against driving under the influence of impairing medications. Specifically, more effective methods for identifying and measuring medication impairment would be indispensable. Furthermore, detailed directives on medical assessment of fitness to drive in the case of psychotropic medication users would also prove highly useful.

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

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CONFLICTS OF INTEREST
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